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DIRECTOR and CEO – Professor Brendan Crabb AC PhD
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Pregnant women and COVID-19 in the NSW prison system
18 October 2021

This report is provided at the request of Legal Aid New South Wales (NSW). The request was to provide an expert report regarding the risk that COVID-19 poses to pregnant women, in particular incarcerated women.

Qualifications and experience of expert

Professor Caroline Homer (RM MN MscMed(ClinEpi) PhD FAAHMS) is a leading midwifery researcher in Australia and has an international reputation as a scholar and leader in maternal and newborn health care and service delivery. She is the Co-Program Director: Maternal and Child Health at the Burnet Institute and an Emeritus Professor of Midwifery at the University of Technology Sydney.

Caroline obtained her PhD in 2001 (UTS) and since then has led research and development projects in Australia and internationally especially in relation to health services delivery, reproductive, maternal and newborn care, human resources for health workforce development and midwifery education. She has more than 25 years of experience in the sector – as a clinician, educator, researcher and leader. Caroline is a past President of the Australian College of Midwives and worked continually as a clinical midwife from 1996 to 2016.

In 2017, she was awarded an Order of Australia (AO) for distinguished service to medicine in the field of midwifery as a clinician, researcher, author and educator, through the development of worldwide education standards, and to professional organisations. Caroline has more than 280 publications in peer reviewed journals and 15 book chapters. She has supervised to completion 49 PhD, Masters by Research and Honours students.

Since the COVID-19 pandemic was declared she has worked on a number of projects and advocacy in relation to COVID-19 and the impact especially on pregnant women. She has published more than 10 papers, commentaries and editorials on the indirect impact on pregnant women and have given numerous presentations on COVID-19 in pregnancy and the need for vaccination.

The Burnet Institute

The Macfarlane Burnet Institute for Medical Research and Public Health ('The Burnet') is an Australian, unaligned, not-for-profit, independent organisation that links public health and

medical research with practical action to achieve better health for vulnerable communities. We have proven expertise in systematic reviews in the area of SRMNCAH.

Burnet's mission is to achieve better health for vulnerable communities in Australia and internationally by accelerating the translation of research, discovery and evidence into sustainable health solutions. The Institute has four major thematic programs: Maternal, Child and Adolescent Health, Disease Elimination, Behaviour and Health Risks, and Health Security.

The Burnet Institute has played a key role in Australia's response to the COVID-19 pandemic. The Burnet Institute has been at the forefront of COVID-19 including vaccine and test development, direct and indirect impacts and modelling the path forward for both NSW and Victorian governments. We have hosted the Know-C19 Hub is a COVID-19 Knowledge Hub gateway to our research findings, actively seeking to address gaps in knowledge, and to collate and provide novel strategic information on COVID-19 to inform the Australian and International response.

Materials received
The following documents was provided by NSW Legal Aid:

- Australian Government, COVID-19 Vaccination discussion guide for women who are pregnant, breastfeeding or planning pregnancy, 19 August 2021
- Report on COVID-19 and the impact on NSW prisoners (16 April 2020)
- Supplementary Report on COVID-19 and the impact on NSW prisoners (22 May 2020)
- Updated report on the impact of the COVID-19 virus on the New South Wales prisoner population (09 September 2021)
- Report of Dr Andrew Ellis dated 9 April 2020
- Report of Dr Andrew Ellis dated 29 August 2021

Specific questions to address

1. ***What is the risk of adverse health outcomes/serious illness if a pregnant woman contracts COVID-19?***

a) The evidence has mounted over the last 20 months as to the increased risks for pregnant women who contract COVID-19. A synthesis of the best available evidence shows that women who contract COVID-19 whilst pregnant have a higher risk of certain complications compared to those who are not pregnant with COVID-19 of the same age, including:
    - An increased risk (about 5 times higher) of needing admission to hospital.

- An increased risk (about 2-3 times higher) of needing admission to an intensive care unit.
- An increased risk (about 3 times higher) of needing invasive ventilation (breathing life support).

b) COVID-19 during pregnancy also increases the risk of complications for the newborn, including:
    - A slightly increased risk (about 1.5 times higher) of being born prematurely (before 37 weeks of pregnancy).
    - An increased risk (about 3 times higher) of needing admission to a hospital newborn care unit.

c) These data are based on a number of papers including a highly regarded living systematic review published in the British Medical Journal (**Annex 1**) and cited in the Australian Government's COVID-19 vaccination decision guide for women who are pregnant, breastfeeding or planning pregnancy which was most recently updated on 15 September 2021 (**Annex 2**). These data are not in women with the COVID-19 Delta variant specifically but cover all variants.

d) A recent pre-print (meaning it has not gone through peer review as yet) paper from the UK has shown that SARS-CoV-2 infection during Alpha and Delta dominant periods was associated with more severe infection and worse pregnancy outcomes compared to the Wildtype infection (the original virus from China), which itself shows an increased risk compared to women without SARS-CoV-2 infection (**Annex 3**). This means that there are concerns that the impact of the Delta variant could be worse.

e) In summary, there are significant concerns for the health of pregnant women and their unborn baby if they were to contract COVID-19 infection.

2. Are there particular health conditions/factors that impact on these risks for some women?

f) Some women who are pregnant are more likely to have severe illness from COVID-19 compared to those who are pregnant *without* these conditions. The conditions are:
    - Being older than 35 years
    - Being overweight or obese (body mass index above 30 kg/m^2)
    - Having pre-existing (pre-pregnancy) high blood pressure
    - Having pre-existing (pre-pregnancy) diabetes (type 1 or type 2)

3. ***Are there any particular times during pregnancy that someone would be at greater risk of contracting the virus or of serious health complications if they were to contract the virus?***

g) The available studies indicate that the risk seems to be greater later in pregnancy. A key study from the United Kingdom has shown that most pregnant women admitted to hospital with COVID-19 were in the late second or third trimester, that is from 28 weeks of pregnancy onwards (**Annex 4**). This study highlighted the need for continued social distancing measures in later pregnancy.

4. ***What is the impact of vaccination on that risk?***

h) Vaccination reduced the risk of becoming unwell from COVID-19 considerably. Advice from the Australian government states that:

> *'Real-world' evidence from other countries has accumulated and reports show that the mRNA COVID-19 vaccines Pfizer and Moderna are safe to use in pregnancy. Emerging research also demonstrates there is a similar immune response to mRNA vaccines in pregnancy compared to those who are not pregnant. Therefore, it is likely there is similar protection from the vaccines against COVID-19 during pregnancy. Results from the vaccine program in Israel have suggested that Pfizer is effective in preventing COVID-19 in pregnancy. Furthermore, research shows that the antibodies produced by vaccination cross the placenta and may provide some protection to newborn babies (**Annex 2**).*

i) **Annex 5** provides a table on the vaccine effectiveness. This Annex is an update published monthly by the Melbourne Children's Campus – COVID-19 Weekly Vaccine Update (14 October 2021)[1]. Table 1 below is a summary of the vaccine effectiveness in the two vaccines recommended for pregnant women in Australia. Both Moderna and Pfizer vaccines are highly effective, especially after two doses. Individuals may not be fully protected until 7-14 days after their second dose of the Pfizer vaccine.

[1] https://medicine.unimelb.edu.au/__data/assets/pdf_file/0006/3933159/Melbourne-Childrens-Campus-Weekly-COVID-19-Vaccine-Updates-14-October-2021.pdf

Table 1: Vaccine Effectiveness Summary at-a-glance – Vaccines recommended in pregnancy

Vaccine	Any infection	Symptomatic Infection	Hospitalisation or severe disease	Death
Moderna	76-87% Single dose: 72%	82-95% Single dose: 72%	92-98% Single dose: 96%	98%
Pfizer/BioNTech	63-95% Single dose: 36-57%	72-97% Single dose: 49-61%	85-98% Single dose: 85-94%	91-100%

Adapted from: Melbourne Children's Campus - Weekly COVID-19 Vaccine Updates Number 29, 14 October 2021 (Annex 5)

j) Vaccination is essential and confers significant benefits. However, the protection against illness is not 100% and use of other measures such as masks, physical distancing and adequate ventilation (safe air) is still important.

5. How does imprisonment impact on the risk of adverse health outcomes/serious illness of a pregnant woman who contracts COVID-19?

k) If a woman did contract COVID-19 while in prison, it is possible that she would be unable to receive the immediate care to which she may need. The clinical course of COVID-19 in pregnant women is a little unpredictable and some women become sick very quickly and require immediate access to medical care.

l) Careful monitoring of people with COVID-19 infection through Hospital in the Home systems are in operation in NSW but this would not be possible in a prison situation.

m) An ability to quickly transfer to hospital is important in pregnant women with COVID-19 as they can deteriorate quickly.

6. Can you comment on the impact of measures Corrective Services NSW has put in place to prevent COVID-19 spreading within the prison population on a pregnant woman, in particular any relevant mental health impacts of such measures on a woman who is pregnant or recently pregnant?

By way of background, these measures include:

- ***COVID positive inmates are housed in isolation areas away from the main population***
- ***All new inmates are quarantined for 14-days, either by themselves or in a cell with one other person***
- ***if an inmate develops cold or flu like symptoms, they are immediately isolated in-situ***
- ***female inmates who test positive for COVID-19 are transferred and managed at Silverwater Women's Correctional Centre***
- ***in person family visits have been suspended since 24 June 2021***

Further detail is provided here: Corrective Services \| COVID-19 (coronavirus) response (nsw.gov.au)

n) These factors are all important. The issue of compliance with all of the above measures is unclear in all correctional centres across NSW.

o) There are additional complexities for pregnant women as they can deteriorate very quickly. I would like to comment on a number of factors which I believe occur in prison facilities and would be of concern in relation to pregnant women. Many of these have also be raised by the *Updated report on the impact of the COVID-19 virus on the New South Wales prisoner population (9 September 2021).*

p) The risk of shared spaces with those in a small unit – that is, the laundry, kitchen and bathroom and during lockdowns, sharing the same space for extended periods of time, with limited opportunities to socially distance or get fresh air. I understand that masks are not worn in the unit during lockdown periods which increases the risk of transmission.

q) I believe that there is a lack of access to hand sanitiser and no additional cleaning some units since the first identified case of COVID-19 in the NSW prison population in 2021.

r) Poor ventilation especially not enough to allow consistent air flow, and in warmer weather I believe that there is reportedly very little movement in the air at all.

s) I understand that the use of masks amongst prisoners is not actively encouraged at some centres.

t) In some prisons, I believe that women who work move between different areas of the prison regularly and mix with prisoners who are housed in other areas of the gaol. This movement within the gaol increases the risk of the spread of COVID-19 within a Correctional Centre if a positive case is identified.

u) When women are released from their units for exercise, I understand that in some centres, up to 300 inmates can mix in the yard at one time. Given inmates are not wearing masks on a regular basis this mixing of the prison population increases the

risk of COVID-19 spreading within the population very quickly if there is an outbreak.

b) It is highly likely that there is a limited ability to practice physical distancing, a lack of face mask use, inadequate ventilation. Physical distancing, masks and adequate ventilation are all essential public health measures to reduce transmission of COVID-19, especially the Delta variant. I would have significant concerns that a Delta variant would spread very quickly through this population.

7. Any view you may have on the medical intervention available to a pregnant inmate in prison as compared to what would be available in the community, and the impact that this could have on positive pregnancy outcomes.

v) Another key issue to ensure a positive pregnancy outcome is access to social support and the importance of reduced stress. The COVID-19 era has been very stressful for pregnant women and many have reported increased stress and anxiety from lockdown. A suspension of in person family visits and limitations on access to calls to family, in some cases, as a result of prison lockdowns are likely to be stressful for many women and add to the lack of support from family or friends.

w) Distress, fear and isolation are significant concerns and likely to impact on her mental health during pregnancy and into the postpartum period after the baby is born. Mental health issues for pregnant and recently pregnant women is a significant concern with suicide being the third leading indirect cause of maternal death in Australia.

I hope this information has been of assistance to you.

Yours sincerely

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END OF REPORT – 7 pages in total

Annex 1: Allotey et al - Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis

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Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis

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ABSTRACT

OBJECTIVE

To determine the clinical manifestations, risk factors, and maternal and perinatal outcomes in pregnant and recently pregnant women with suspected or confirmed coronavirus disease 2019 (covid-19).

DESIGN

Living systematic review and meta-analysis.

DATA SOURCES

Medline, Embase, Cochrane database, WHO COVID-19 database, China National Knowledge Infrastructure (CNKI), and Wanfang databases from 1 December 2019 to 6 October 2020, along with preprint servers, social media, and reference lists.

STUDY SELECTION

Cohort studies reporting the rates, clinical manifestations (symptoms, laboratory and radiological findings), risk factors, and maternal and perinatal outcomes in pregnant and recently pregnant women with suspected or confirmed covid-19.

DATA EXTRACTION

At least two researchers independently extracted the data and assessed study quality. Random effects meta-analysis was performed, with estimates pooled as odds ratios and proportions with 95% confidence intervals. All analyses will be updated regularly.

RESULTS

192 studies were included. Overall, 10% (95% confidence interval 7% to 12%; 73 studies, 67 271 women) of pregnant and recently pregnant women attending or admitted to hospital for any reason were diagnosed as having suspected or confirmed covid-19. The most common clinical manifestations of covid-19 in pregnancy were fever (40%) and cough (41%). Compared with non-pregnant women of reproductive age, pregnant and recently pregnant women with covid-19 were less likely to have symptoms (odds ratio 0.28, 95% confidence interval 0.13 to 0.62; I^2=42.9%) or report symptoms of fever (0.49, 0.38 to 0.63; I^2=40.8%), dyspnoea (0.76, 0.67 to 0.85; I^2=4.4%) and myalgia (0.53, 0.36 to 0.78; I^2=59.4%). The odds of admission to an intensive care unit (odds ratio 2.13, 1.53 to 2.95; I^2=71.2%), invasive ventilation (2.59, 2.28 to 2.94; I^2=0%) and need for extra corporeal membrane oxygenation (2.02, 1.22 to 3.34; I^2=0%) were higher in pregnant and recently pregnant than non-pregnant reproductive aged women. Overall, 339 pregnant women (0.02%, 59 studies, 41 664 women) with confirmed covid-19 died from any cause. Increased maternal age (odds ratio 1.83, 1.27 to 2.63; I^2=43.4%), high body mass index (2.37, 1.83 to 3.07; I^2=0%), any pre-existing maternal comorbidity (1.81, 1.49 to 2.20; I^2=0%), chronic hypertension (2.0, 1.14 to 3.48; I^2=0%), pre-existing diabetes (2.12, 1.62 to 2.78; I^2=0%), and pre-eclampsia (4.21, 1.27 to 14.0; I^2=0%) were associated with severe covid-19 in pregnancy. In pregnant women with covid-19, increased maternal age, high body mass index, non-white ethnicity, any pre-existing maternal comorbidity including chronic hypertension and diabetes, and pre-eclampsia were associated with serious complications such as admission to an intensive care unit, invasive

WHAT IS ALREADY KNOWN ON THIS TOPIC

Pregnant women are considered to be a high risk group for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and the potential adverse effects of the virus on maternal and perinatal outcomes are of concern

In non-pregnant populations admitted to hospital with coronavirus disease 2019 (covid-19) the most common symptoms are fever, cough, and dyspnoea, reported in more than two thirds of individuals

Advancing age, high body mass index, non-white ethnicity, and pre-existing comorbidities are risk factors for severe covid-19 in the general population

WHAT THIS STUDY ADDS

Pregnant and recently pregnant women with covid-19 diagnosed in hospital are less likely to have or manifest symptoms of fever, dyspnoea, and myalgia than non-pregnant women of reproductive age

Pregnant and recently pregnant women are at increased risk of admission to an intensive care unit, receiving invasive ventilation and extra corporeal membrane oxygenation treatment, compared with non-pregnant women of reproductive age

Risk factors for severe covid-19 in pregnancy include increasing maternal age, high body mass index, non-white ethnicity, pre-existing comorbidities, and pregnancy specific disorders such as gestational diabetes and pre-eclampsia

Pregnant women with covid-19 are more likely to experience preterm birth and their neonates are more likely to be admitted to a neonatal unit

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ventilation and maternal death. Compared to pregnant women without covid-19, those with the disease had increased odds of maternal death (odds ratio 2.85, 1.08 to 7.52; I^2=0%), of needing admission to the intensive care unit (18.58, 7.53 to 45.82; I^2=0%), and of preterm birth (1.47, 1.14 to 1.91; I^2=18.6%). The odds of admission to the neonatal intensive care unit (4.89, 1.87 to 12.81, I^2=96.2%) were higher in babies born to mothers with covid-19 versus those without covid-19.

CONCLUSION

Pregnant and recently pregnant women with covid-19 attending or admitted to the hospitals for any reason are less likely to manifest symptoms such as fever, dyspnoea, and myalgia, and are more likely to be admitted to the intensive care unit or needing invasive ventilation than non-pregnant women of reproductive age. Pre-existing comorbidities, non-white ethnicity, chronic hypertension, pre-existing diabetes, high maternal age, and high body mass index are risk factors for severe covid-19 in pregnancy. Pregnant women with covid-19 versus without covid-19 are more likely to deliver preterm and could have an increased risk of maternal death and of being admitted to the intensive care unit. Their babies are more likely to be admitted to the neonatal unit.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42020178076.

READERS' NOTE

This article is a living systematic review that will be updated to reflect emerging evidence. Updates may occur for up to two years from the date of original publication. This version is update 1 of the original article published on 1 September 2020 (*BMJ* 2020;370:m3320), and previous updates can be found as data supplements (https://www.bmj.com/content/370/bmj.m3320/related#datasupp). When citing this paper please consider adding the update number and date of access for clarity.

Introduction

Since the first report (December 2019) of the novel coronavirus disease 2019 (covid-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the number of confirmed cases and associated mortality and morbidity have increased rapidly.[1 2] Pregnant women are considered a high risk group because of concerns about the effect of covid-19 on them during and after pregnancy, and on their neonates.[3] Quantification of the rates of covid-19, its risk factors, clinical manifestations, and outcomes is key to planning clinical maternal care and management in an evolving pandemic scenario.[4]

Publications on covid-19 in pregnancy have risen steeply through individual case reports, case series, observational studies, and systematic reviews. Since the publication of our first version of the living systematic review on covid-19 in pregnancy,[5] over 150 reviews have been published in this area,[6-11] with many more registered in PROSPERO.[9 12] Early reviews mostly included case reports and case series that were often inappropriately meta-analysed providing biased estimates.[13] Subsequent reviews differed little from each other, often including similar primary studies, many with duplicate data. These reviews became quickly outdated as new evidence emerged. Moreover, the sampling frames in primary studies have varied, ranging from universal SARS-CoV-2 testing for all pregnant women admitted to hospital[14 15] to symptom based testing.[16 17] Testing strategies have also differed within and between countries, with diagnosis in many early studies based on epidemiological risk assessment and clinical features without confirmed SARS-CoV-2 infection, which need to be considered in the analysis.[18] Limitations in the external and internal validity of studies make it challenging for guideline developers and policy makers to make evidence based recommendations for the management of pregnant and recently pregnant women with covid-19.

We started this living systematic review in April 2020 to determine the clinical manifestations of covid-19 in pregnant and recently pregnant women, identify the risk factors for complications, and quantify maternal and perinatal outcomes. The systematic review is being updated on a regular basis.

Methods

Our systematic review is based on a prospectively registered protocol (PROSPERO CRD42020178076; registered 22 April 2020)[19] to evaluate a series of research questions on covid-19 during and after pregnancy. We report our findings on the rates, clinical manifestations, risk factors, and maternal and perinatal outcomes in women with covid-19 in line with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) recommendations (see appendix 1). As more relevant data become available, we shall address the research questions in our published protocol.[20] Each cycle of our living systematic review involves weekly search updates (rounds), with analysis performed every 2-4 months for reporting through a dedicated website, with early analysis if new definitive evidence emerges. We are regularly reviewing the planned frequency of updates.

Literature search

For the first publication of the review, we performed a systematic search of major databases: Medline, Embase, Cochrane database, WHO (World Health Organization) COVID-19 database, China National Knowledge Infrastructure (CNKI), and Wanfang databases from 1 December 2019 to 26 June 2020 for relevant studies on covid-19 in pregnant and recently pregnant women.[5] For this first update of the review, we searched databases up to 6 October 2020. To identify potential studies, we coordinated our search efforts with the Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre), the WHO Library, and the Cochrane Gynaecology and Fertility group. Additional searches were conducted of preprint servers, blogs, websites that serve as repositories

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for covid-19 studies, social media, guidelines, and reference lists of included studies and unpublished data. We also searched the Living Overview of the Evidence (LOVE) platform from June 2020.[21] We contacted established groups that were coordinating or conducting surveillance and studies in pregnant women with covid-19, such as the WHO Maternal, Newborn, Child and Adolescent health (MNCAH) covid-19 research network, the International Network of Obstetric Survey Systems (INOSS), the United States Centers for Disease Control and Prevention (CDC), and the European Centre for Disease Prevention and Control for information on published and upcoming data. No language restrictions were applied. Appendix 2 provides details of the search strategies and databases searched.

Study selection

Two reviewers independently selected studies using a two stage process: they first screened the titles and abstracts of studies and then assessed the full text of the selected studies in detail for eligibility. A total of 10 reviewers contributed to study selection. Disagreements were resolved through discussion with a third reviewer (ST or JA). We excluded studies if the duplicated data for all outcomes of interest were published elsewhere, as reported by the study authors, or when the characteristics of the mother or neonate matched the setting, characteristics, and duration of another study from the same geographical location. When we suspected an overlap of data between studies, the study that provided comparative data was included. If there was an overlap of data or suspicion of duplicates of participants in studies between the previous and current versions of the living systematic review, we included studies based on their study design (prioritising comparative cohorts), and sample size (larger study prioritised). When there was uncertainty about duplicate data, we contacted the authors of primary studies.

We defined women as having confirmed covid-19 if they had laboratory confirmation of SARS-CoV-2 infection irrespective of clinical signs and symptoms.[22] Women with a diagnosis based only on clinical or radiological findings were defined as having suspected covid-19. The recently pregnant group comprised women in the postpartum and post-abortion period. We included studies that compared covid-19 rates, clinical manifestations (symptoms, laboratory and radiological results), risk factors, and associated mortality and morbidity between pregnant and recently pregnant and non-pregnant women of reproductive age, and those that compared maternal and perinatal outcomes in pregnant women with and without covid-19. In studies comparing maternal and perinatal outcomes of pregnant women with covid-19 to those without, we classified the comparative controls as being historical if the cohort of pregnant women without covid-19 were pregnant before December 2019. Studies on non-comparative cohorts with a minimum of 10 participants were included if they reported on the rates and clinical manifestations of covid-19 and relevant outcomes in pregnant and recently pregnant women. We defined cohort studies as those that sampled participants on the basis of exposure, followed-up participants over time, and ascertained the outcomes.[23] The PROSPERO protocol provides a full list of the risk factors, clinical features, and outcomes evaluated.[19]

The sampling frames for detecting covid-19 included universal screening and testing, when all women were assessed for covid-19 using reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 or chest computed tomography; risk based testing on the basis of epidemiological history and clinical manifestations by National Health Commission of China (NHCC) guidelines[18]; and symptom based when testing was performed on women with symptoms and those with a history of contact with affected individuals. We defined the population as being selected when only specific groups of women were included, such as those undergoing caesarean section or in the third trimester. We categorised studies as a high risk group if only women with any pre-existing medical or obstetric risk factors were included, low risk if women did not have any risk factors, and any risk if all women were included.

Study quality assessment and data extraction

The quality of the comparative cohort studies was assessed for selection, comparability, and outcome ascertainment bias using the Newcastle Ottawa scale.[24] Studies achieving four stars for selection, two for comparability, and three for ascertainment of the outcome were considered to have a low risk of bias. Studies achieving two or three stars for selection, one for comparability, and two for outcome ascertainment were considered to have a medium risk of bias, and any study achieving one star for selection or outcome ascertainment, or zero for any of the three domains, was regarded as having a high risk of bias. We assessed the quality of studies reporting on the prevalence of clinical manifestations or outcomes for internal and external validity using an existing tool.[25] The following were considered as low risk of bias for external validity: representative of national population for relevant variables (population), representative of target population (sampling frame), random selection (selection bias), and more than 75% response rate in individuals with and without the outcome (non-response bias).[25] Two independent reviewers extracted data using a pre-piloted form.

Statistical analysis

We pooled the comparative dichotomous data using random effects meta-analysis and summarised the findings as odds ratios with 95% confidence intervals. To combine comparative continuous data with dichotomous data we transformed standardised mean differences to logarithm odds ratios, assuming a normal underlying distribution.[26] We pooled the dichotomous non-comparative data for rates of clinical manifestations and maternal and perinatal outcomes

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as proportions with 95% confidence intervals using Dersimonian and Laird random effects meta-analysis after transforming data using Freeman-Tukey double arcsin transformation. Heterogeneity was reported as I^2 statistics. We undertook subgroup analysis by country status (high income *v* low and middle income), sampling frame (universal, risk based, and symptom based testing, including not reported), and risk status of women in the studies (high, low, any). Sensitivity analysis was performed by restricting the analysis to women with confirmed covid-19, study quality (high, low), and population (unselected, selected). All analyses were done with Stata (version 16).

Patient and public involvement

The study was supported by Katie's Team, a dedicated patients and public involvement group in Women's Health. The team was involved in the conduct, interpretation, and reporting of this living systematic review through participation in virtual meetings.

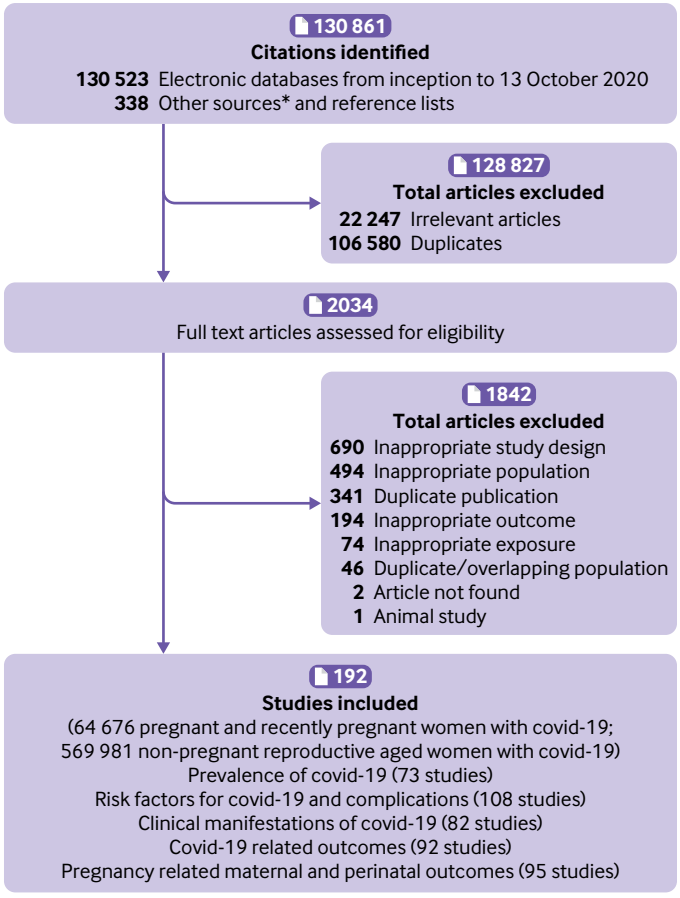

Fig 1 | Study selection process. *Twitter, national reports, blog by J Thornton, ObG Project, COVID-19 and Pregnancy Cases, www.obgproject.com/2020/04/07/covid-19-research-watch-with-dr-jim-thornton/; EPPI-Centre, COVID-19: a living systematic map of evidence, http://eppi.ioe.ac.uk/cms/Projects/DepartmentofHealthandSocialCare/Publishedreviews/COVID-19Livingsystematicmapoftheevidence/tabid/3765/Default.aspx; Norwegian Institute of Public Health, NIPH systematic and living map on COVID-19 evidence, www.nornesk.no/forskningskart/NIPH_mainMap.html; Johns Hopkins University Center for Humanitarian Health; COVID-19, Maternal and Child Health, Nutrition, http://hopkinshumanitarianhealth.org/empower/advocacy/covid-19/covid-19-children-and-nutrition/; ResearchGate, COVID-19 research community, www.researchgate.net/community/COVID-19; and Living Overview of the Evidence, Coronavirus disease (COVID-19), https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?population=5d062d5fc80dd41e58ba8459

Results

In the original review, 20 625 unique citations were identified after removing duplicates from 49 684 citations, with 77 cohort studies included in the review.[5] After removing duplicates from 130 861 citations, 24 281 unique citations were identified and 192 cohort studies (131 comparative, 61 non-comparative) were included in this update of the systematic review (fig 1). Two studies included in the original systematic review were excluded from the update because the information reported in those studies were reported in more recent and larger studies.[27 28]

Characteristics of included studies

Of 192 studies, 58 (30%) were from the United States; 31 from China (16%); 17 from Italy; 15 from Spain; eight from Turkey; seven each from the United Kingdom and India; five each from Brazil, France, and Mexico; three each from Iran and Portugal; two each from Belgium, Denmark, the Netherlands, Peru, and Sweden; and one each from Bangladesh, Chile, Estonia, Israel, Japan, Germany, Ireland, Kuwait, Pakistan, Qatar, Romania, Russia, and Switzerland. Most studies tested respiratory samples using RT-PCR to confirm the presence of SARS-CoV-2 (97%, 187/192); five studies tested for SARS-CoV-2 antibodies to confirm the diagnosis of covid-19; 43 studies additionally diagnosed covid-19 based only on clinical suspicion. Fourteen studies (602 565 women) compared pregnant populations with non-pregnant populations,[29-42] and 47 studies (26 017 women) compared pregnant women with covid-19 versus pregnant women without covid-19.[43-89] Eighty two cohort studies reported on clinical manifestations (41 396 pregnant, 434 348 non-pregnant women), 92 studies reported on covid-19 related maternal outcomes (49 443 pregnant, 568 386 non-pregnant women), and 95 studies reported on pregnancy related maternal (54 943 women) and perinatal outcomes (9466 neonates) (see appendix 3). The sampling frames included universal testing (89 studies), risk based NHCC guidelines (25 studies), and symptom based (32 studies) strategies. Forty six studies did not report the sampling strategy.

Quality of included studies

Overall, 56% (73/131) of the comparative cohort studies evaluated using the Newcastle Ottawa scale had an overall low risk of bias (see appendix 4a). Most (93%, 122/131) had a low risk of bias for study selection and nine (7%) had a medium risk. The risk of bias for comparability of cohorts was low in 59 of the studies (45%), medium in 71 (54%), and high in one (1%). For outcome assessment of the cohorts, 47 (36%) studies had a low risk of bias, 82 (63%) a medium risk, and two (2%) a high risk. Quality assessment of the prevalence studies for external validity showed a low risk of bias for representativeness in 15% (28/192) of

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the studies, sampling in 30% (57/192), selection in 82% (157/192), and non-response in 99% (191/192). For internal validity, there was low risk of bias for data collection in 96% (184/192) of the studies, case definition in 56% (108/192), measurement in 98% (189/192), differential verification in 95% (182/192), adequate follow-up in 35% (67/192), and appropriate numerator and denominator in 92% (177/192) (see appendix 4b).

Rates of covid-19 in pregnant and recently pregnant women

The overall rate of covid-19 diagnosis in pregnant and recently pregnant women attending or admitted to hospital for any reason was 10% (95% confidence interval 7% to 12%; 73 studies, 67 271 women; fig 2 and fig 3). Rates varied by sampling strategy: of the women sampled by universal screening, 7% (5% to 8%; 60 studies, 57 144 women) were diagnosed as having covid-19 compared with 28% (15% to 43%; 11 studies, 2436 women) of women sampled on the basis of symptoms. Most studies with a prevalence rate for covid-19 greater than 15% were from the US, except for two studies from the UK, and one each from Mexico, Turkey, France, and Iran.[90-95] One in 20 asymptomatic women (4%, 3% to 7%; 26 studies) attending or admitted to hospital had a diagnosis of covid-19 (see appendix 5a). Three quarters (73%, 62% to 82%; 38 studies) of the 906 pregnant women with covid-19 in the universal screening population were asymptomatic (see appendix 5b). Non-white ethnicity was associated with a diagnosis of covid-19 in pregnancy (odds ratio 1.66, 95% confidence interval 1.01 to 2.72; 11 studies; 8691 women); none of the other maternal factors assessed were associated with a diagnosis of covid-19 in pregnant women (see appendix 6a).

Clinical manifestations of covid-19 during pregnancy and after delivery

The most common symptoms reported by pregnant and recently pregnant women with suspected or confirmed covid-19 were fever (40%) and cough (41%); raised white cell count (26%), lymphopaenia (33%) and raised C reactive protein levels (49%) were the most common laboratory findings (fig 4). Compared with non-pregnant women of reproductive age with covid-19, pregnant and recently pregnant women with the disease were less likely to have symptoms (odds ratio 0.28, 95% confidence interval 0.13 to 0.62; 4 studies; 462 051 women), or manifest symptoms of fever (0.49, 0.38 to 0.63; 11 studies, 240 324 women), dyspnoea (0.76, 0.67 to 0.85; 11 studies; 240 324 women) and myalgia (0.53, 0.36 to 0.78; 8 studies, 240 105 women) (fig 5). Pregnant women with covid-19 had increased body mass index compared to non-pregnant women with the disease (1.98, 1.74 to 2.26; 2 studies, 461 897 women), and were more likely to have pre-existing diabetes (1.35, 1.24 to 1.46; 5 studies, 462 262 women) (see appendix 6b). Sensitivity analysis restricted to various sampling frames showed lower estimates of reported symptoms in the universal screening population and higher estimates of fever, cough, and dyspnoea in the symptom-based population (see appendix 7). The rates of clinical manifestations varied when the analysis was restricted to only women with RT-PCR confirmed covid-19, unselected populations, and women with any risk (see appendix 7).

Outcomes related to covid-19 in pregnant and recently pregnant women

Overall, 339 pregnant women (59 studies, 41 664 women) with confirmed covid-19 died from any cause (0.02%, 95% confidence interval 0.00% to 0.42%). Severe covid-19 infection as defined by the authors, was diagnosed in 10% (6% to 15%; 39 studies, 5621 women) of pregnant and recently pregnant women with suspected or confirmed covid-19; 4% (2% to 7%; 50 studies, 41 288 women) of pregnant women with covid-19 were admitted to an intensive care unit, 3% (1% to 5%; 31 studies, 42 026 women) required invasive ventilation, and 0.2% (0.0% to 0.7%; 13 studies, 33 521 women) required extracorporeal membrane oxygenation (ECMO) (fig 4). Appendix 8 provides the rates of complications by sampling strategy. Compared with non-pregnant women of reproductive age with covid-19, the odds of admission to the intensive care unit (odds ratio 2.13, 95% confidence interval 1.53 to 2.95; seven studies, 601 108 women) and need for invasive ventilation (2.59, 2.28 to 2.94; six studies, 601 044 women) and ECMO (2.02, 1.22 to 3.34; two studies, 461 936 women) were higher in pregnant and recently pregnant women (table 1).

Maternal risk factors associated with severe covid-19 were increasing age (odds ratio 1.83, 95% confidence interval 1.27 to 2.63; seven studies, 3561 women), high body mass index (2.37, 1.83 to 3.07; five studies, 3367 women), any pre-existing maternal comorbidity (1.81, 1.49 to 2.20; 3 studies; 2634 women), chronic hypertension (2.0, 1.14 to 3.48; two studies, 858 women), pre-eclampsia (4.21, 1.27 to 14.0; 4 studies; 274 women), and pre-existing diabetes (2.12, 1.62 to 2.78; 3 studies, 3333 women) (fig 6). Increasing maternal age (2.11, 1.69 to 2.63; 7 studies, 31 710 women), high body mass index (2.71, 1.10 to 6.63; 4 studies, 31 456 women), non-white ethnicity (1.66, 1.20 to 2.29; 4 studies, 31 543 women), pre-existing maternal comorbidity (1.70, 1.34 to 2.15; 5 studies, 31 512 women), chronic hypertension (4.72, 2.37 to 9.41; 5 studies, 31 433 women), pre-existing diabetes (4.67, 1.94 to 11.22; 6 studies, 31 473 women), and gestational diabetes (3.27, 1.55 to 6.89; 2 studies, 777 women), were associated with admission to an intensive care unit. Risk factors associated with maternal death and the need for invasive ventilation included: non-white ethnicity (1.61, 1.05 to 2.47; 3 studies, 31 469 women; 2.23, 1.25 to 3.97; 1 study, 669 women; respectively), and high body mass index (2.27, 1.20 to 4.31; 3 studies, 31 085 women; 6.61, 1.98 to 22.02; 2 studies, 485 women; respectively; table 2).

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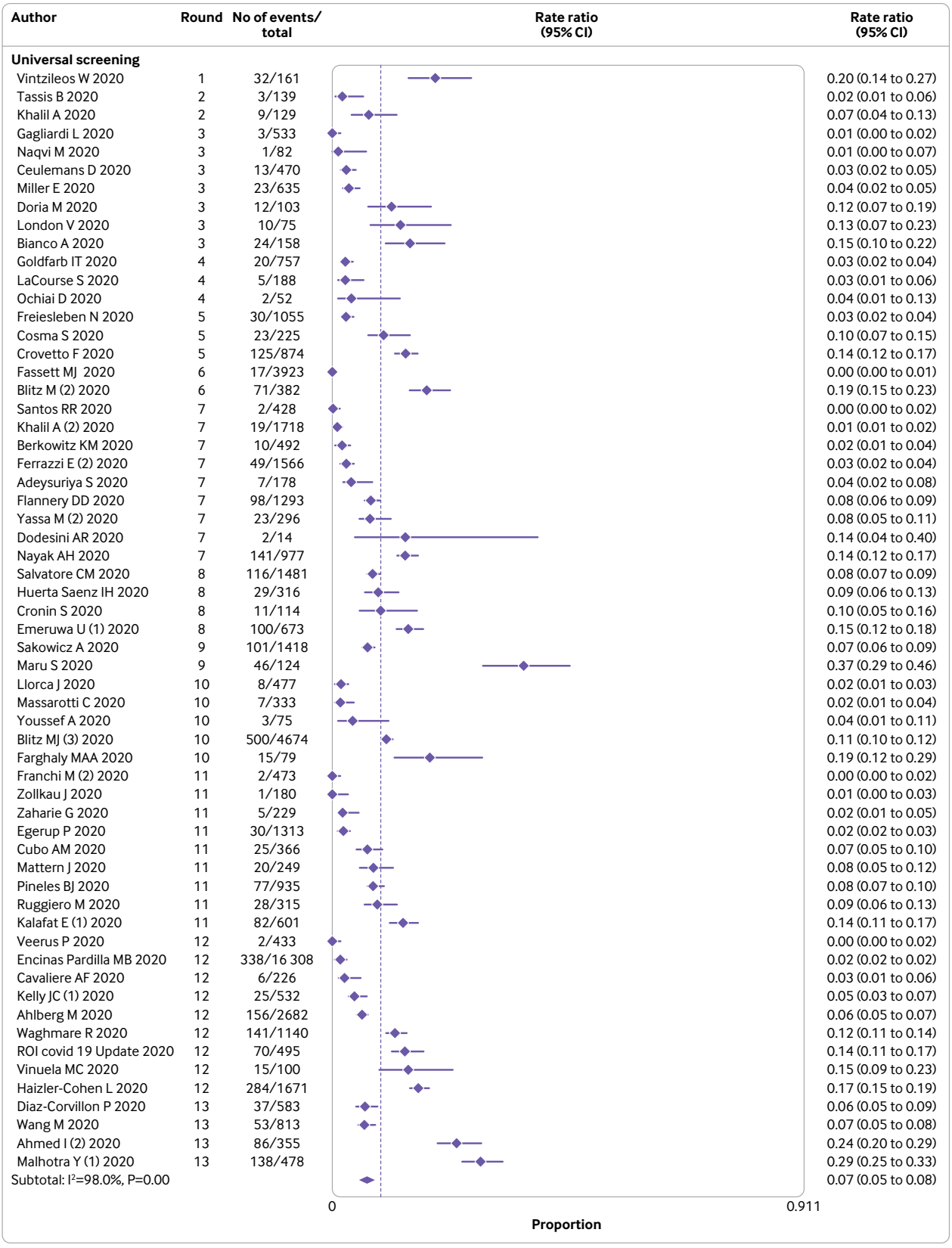

Fig 2 | Prevalence of severe acute respiratory syndrome coronavirus 2 in pregnant and recently pregnant women identified by universal screening. Meta-analysis includes one study (Liao 2020)[46] screened using National Health Commission China criteria with no events. Round number represents search strategy updates in the living systematic review. Overall estimate for sampling strategies can be found in figure 3

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Maternal and perinatal outcomes in pregnant and recently pregnant women with covid-19

In pregnant and recently pregnant women with covid-19 compared with pregnant and recently pregnant women without the disease, the odds of all cause mortality (odds ratio 2.85, 95% confidence interval 1.08 to 7.51; 8 studies, 4820 women), and admission to the intensive care unit (18.58, 95% confidence interval 7.53 to 45.82; 7 studies, 4990 women) were higher (table 1). In pregnant and recently pregnant women with covid-19, the overall rate of preterm birth was 17% (95% confidence interval 14% to 19%; 70 studies, 9369 women) and of spontaneous preterm birth was 6% (4% to 9%; 17 studies, 1629 women) (fig 4). Seventy two stillbirths (47 studies; 9020 offspring) and 41 neonatal deaths (51 studies; 8263 neonates) occurred among these women (fig 4). Compared to pregnant and recently pregnant women without the disease, pregnant women with covid-19 were at higher risk of any preterm birth (odds ratio 1.47, 95% confidence interval 1.14 to 1.91; 18 studies, 8549 women) and stillbirth (2.84, 95% confidence interval 1.25 to 6.45; 9 studies, 5794 women), although the overall number of stillbirth was small (only nine events in the covid-19 group).

Overall, 33% (95% confidence interval 24% to 43%; 41 studies, 3323 women) of neonates born to women with covid-19 were admitted to the neonatal intensive care unit (NICU) (fig 4), with a higher risk of NICU admission (odds ratio 4.89, 95% confidence interval 1.87 to 12.81; 10 studies, 5873 neonates) than neonates born to women without the disease. No differences were observed for other perinatal outcomes. Appendix 9 provides the rates of covid-19 related and pregnancy related outcomes for the individual studies.

Discussion

Compared with the original version of our living systematic review, the findings in this update remain consistent for prevalence of covid-19, rates of clinical manifestations, and outcomes in pregnant and recently pregnant women. One in 10 pregnant or recently pregnant women who are attending or admitted to hospital for any reason were diagnosed as having suspected or confirmed covid-19, although the rates vary by sampling strategy. Pregnant and recently pregnant women were more likely to be asymptomatic than non-pregnant women of reproductive age, and showed covid-19 related symptoms of fever, dyspnoea, and myalgia less often than non-pregnant women with covid-19. Whereas testing for SARS-CoV-2 in non-pregnant women is based on symptoms or contact history, testing in pregnant women is usually done when they are in hospital for reasons that might not be related to covid-19. Pregnant or recently pregnant women with covid-19 seem to be at increased risk of requiring admission to an intensive care unit, invasive ventilation, and extra corporeal membrane oxygenation compared to non-pregnant, reproductive

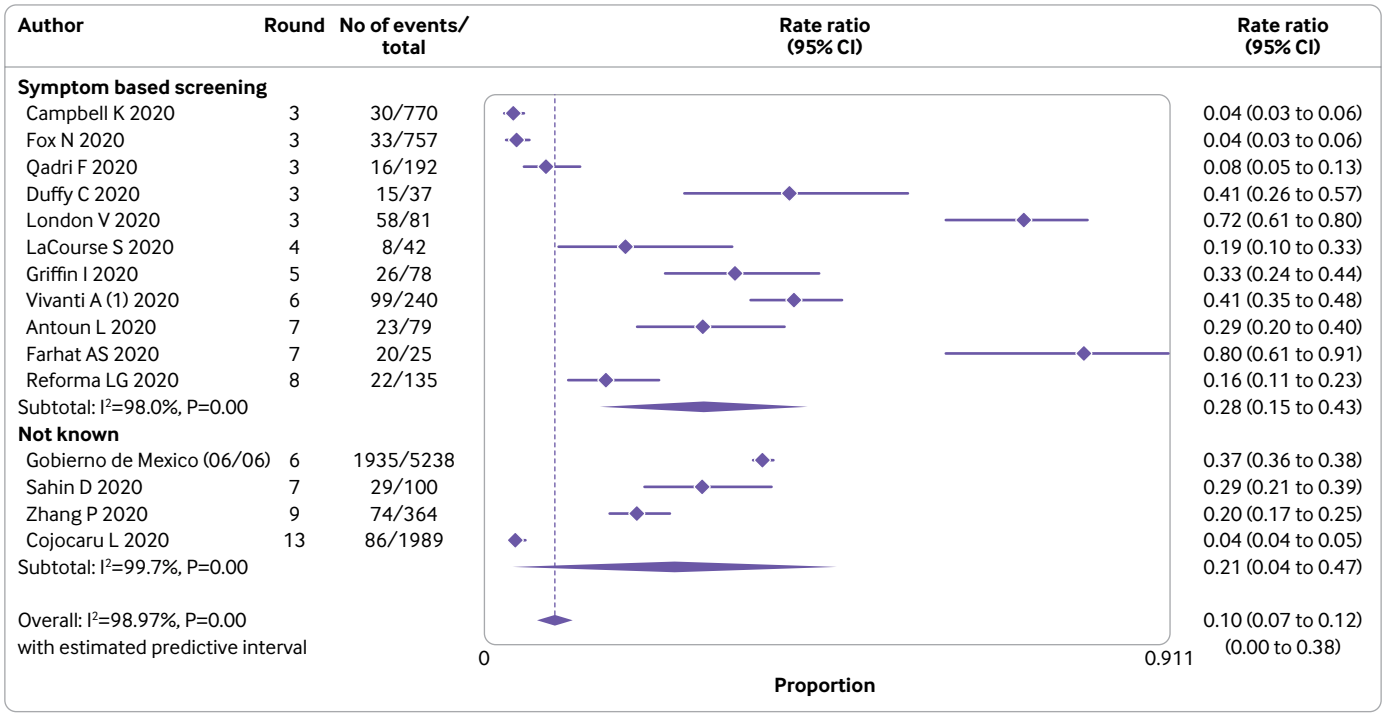

Fig 3 | Prevalence of severe acute respiratory syndrome coronavirus 2 in pregnant and recently pregnant women identified by symptom based screening and unknown sampling strategies. Meta-analysis includes one study (Liao 2020)[46] screened using National Health Commission China criteria with no events. Symptom based screening includes screening based on symptoms or history of contact with individuals with covid-19. Round number represents search strategy updates in the living systematic review. Overall estimate for sampling strategies also includes prevalence data identified by universal screening, which are shown in figure 2

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aged women with covid-19. Increased maternal age, high body mass index, non-white ethnicity, and pre-existing comorbidities are associated with severe disease. Compared to pregnant women without covid-19, pregnant women with covid-19 are at increased risk of death, admission to the intensive care unit, delivering preterm, and their babies being admitted to the neonatal unit. The overall rates of stillbirth and neonatal death are low in women with suspected or confirmed covid-19. Substantial heterogeneity was observed in the estimates for rates of clinical manifestations and outcomes, which varied by sampling frames, participant selection, and risk status of the participants.

This update of the living systematic review includes more than double the number of studies included in the original version, and five times more pregnant women with covid-19. In addition to an increase in precision of the estimates for previously identified risk factors (age, body mass index, and comorbidities such as diabetes and chronic hypertension) for serious complications in pregnant and recently pregnant women with covid-19,

Clinical manifestation	Studies	No of events/ total	Proportion (95% CI)	Proportion (95% CI)	I^2 (%) (P value)	Range
Clinical manifestations						
Symptoms						
Fever	53	8033/39 429		0.40 (0.31 to 0.49)	99.2 (0.00)	(0.05-0.78)
Cough	53	10 379/39 641		0.41 (0.33 to 0.50)	99.1 (0.00)	(0.03-0.83)
Dyspnoea	42	5408/39 014		0.21 (0.15 to 0.28)	98.7 (0.00)	(0.00-0.62)
Myalgia	22	5196/34 663		0.19 (0.12 to 0.27)	98.4 (0.00)	(0.00-0.67)
Ageusia	10	83/776		0.14 (0.06 to 0.24)	89.6 (0.00)	(0.03-0.55)
Diarrhoea	29	2236/38 206		0.08 (0.06 to 0.10)	93.4 (0.00)	(0.00-0.53)
Laboratory findings						
Raised WCC	13	159/580		0.26 (0.14 to 0.40)	90.9 (0.00)	(0.00-0.65)
Lymphopaenia	27	659/1833		0.33 (0.25 to 0.41)	90.4 (0.00)	(0.00-0.90)
Thrombocytopaenia	13	91/1383		0.06 (0.02 to 0.10)	86.3 (0.00)	(0.00-0.35)
Abnormal LFTs	12	99/641		0.13 (0.06 to 0.21)	84.8 (0.00)	(0.00-0.36)
Raised PCT	5	60/261		0.21 (0.00 to 0.59)	96.6 (0.00)	(0.00-0.97)
Raised CRP	10	298/637		0.49 (0.36 to 0.62)	89.5 (0.00)	(0.10-0.71)
Radiological findings						
Ground glass appearance	14	338/569		0.69 (0.46 to 0.87)	96.3 (0.00)	(0.09-1.00)
Any CT abnormality	24	694/2120		0.64 (0.47 to 0.80)	98.2 (0.00)	(0.02-1.00)
Maternal and perinatal outcomes						
Clinical outcomes						
Covid-19 related outcomes						
All cause mortality	59	339/41 664		0.00 (0.00 to 0.00)	91.8 (0.00)	(0.00-0.08)
Admission to ICU	50	1373/41 288		0.04 (0.02 to 0.07)	97.5 (0.00)	(0.00-0.29)
Severe covid-19	39	633/5621		0.10 (0.06 to 0.15)	94.4 (0.00)	(0.00-1.00)
Invasive ventilation	31	668/42 026		0.03 (0.01 to 0.05)	97.5 (0.00)	(0.00-0.13)
ECMO	13	37/33 521		0.00 (0.00 to 0.00)	76.0 (0.00)	(0.00-0.01)
Oxygen/cannula	17	261/1522		0.22 (0.12 to 0.36)	96.2 (0.00)	(0.02-1.00)
ARDS	15	315/2348		0.07 (0.01 to 0.17)	97.8 (0.00)	(0.00-0.51)
Pneumonia	36	1257/7198		0.35 (0.26 to 0.45)	97.9 (0.00)	(0.00-1.00)
Cardiac/liver/renal failure	13	15/2046		0.00 (0.00 to 0.00)	28.3 (0.16)	(0.00-0.13)
Pregnancy related outcomes						
Preterm birth <37 weeks	70	1406/9396		0.17 (0.14 to 0.19)	79.6 (0.00)	(0.00-0.57)
Spontaneous preterm birth	17	104/1629		0.06 (0.04 to 0.09)	67.2 (0.00)	(0.00-0.31)
PPROM <37 weeks	18	58/993		0.05 (0.03 to 0.07)	29.7 (0.11)	(0.00-0.21)
Caesarean section	75	3760/9725		0.54 (0.49 to 0.58)	93.4 (0.00)	(0.00-1.00)
Vaginal delivery	74	5410/9708		0.46 (0.42 to 0.50)	91.8 (0.00)	(0.00-1.00)
Postpartum haemorrhage	15	91/908		0.08 (0.03 to 0.14)	86.7 (0.00)	(0.00-0.30)
Offspring outcomes						
Stillbirth	47	72/9020		0.00 (0.00 to 0.00)	31.2 (0.02)	(0.00-0.24)
Neonatal death	51	41/8263		0.00 (0.00 to 0.00)	33.0 (0.01)	(0.00-0.13)
Admission to neonatal unit	41	934/3323		0.33 (0.24 to 0.43)	96.8 (0.00)	(0.00-1.00)
Neonatal sepsis	6	9/499		0.01 (0.00 to 0.03)	22.6 (0.26)	(0.01-0.06)
Abnormal Apgar score	31	42/1479		0.01 (0.00 to 0.02)	34.8 (0.03)	(0.00-0.26)
Fetal distress	17	65/553		0.11 (0.08 to 0.15)	40.2 (0.04)	(0.04-0.50)

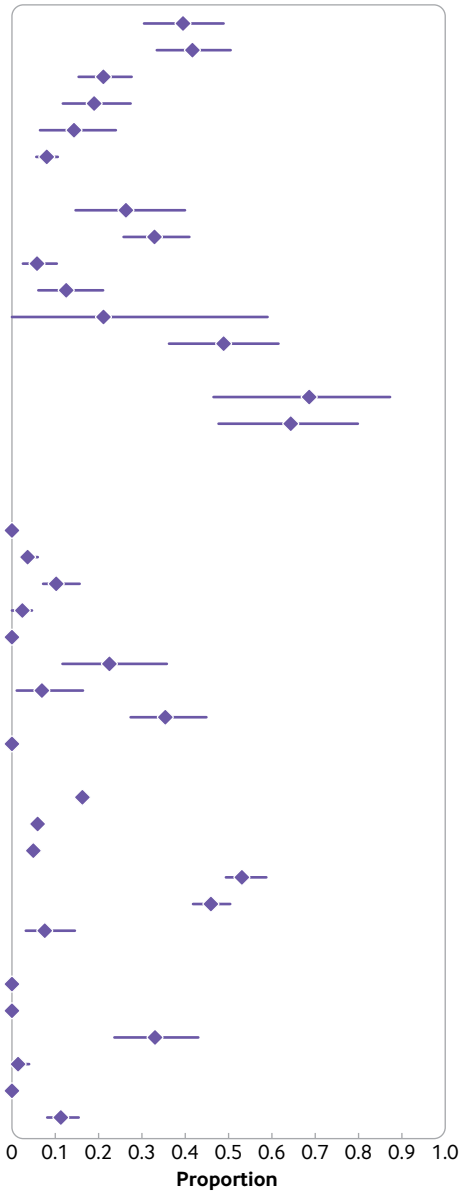

Fig 4 | Rates of clinical manifestations of coronavirus disease 2019 (covid-19) in pregnant women and recently pregnant women with suspected or confirmed covid-19 and associated maternal and perinatal outcomes. ECMO=extracorporeal membrane oxygenation; ARDS=acute respiratory distress syndrome; PPROM=preterm premature rupture of membranes; WCC=white cell count; LFT=liver function test; PCT=procalcitonin; CRP=C reactive protein; CT=computed tomography; ICU=intensive care unit

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in this update, we identified additional risk factors such as non-white ethnicity, and potential association with pregnancy specific conditions such as gestational diabetes and pre-eclampsia, and increased risk of adverse outcomes in pregnant women with covid-19 than without the disease.

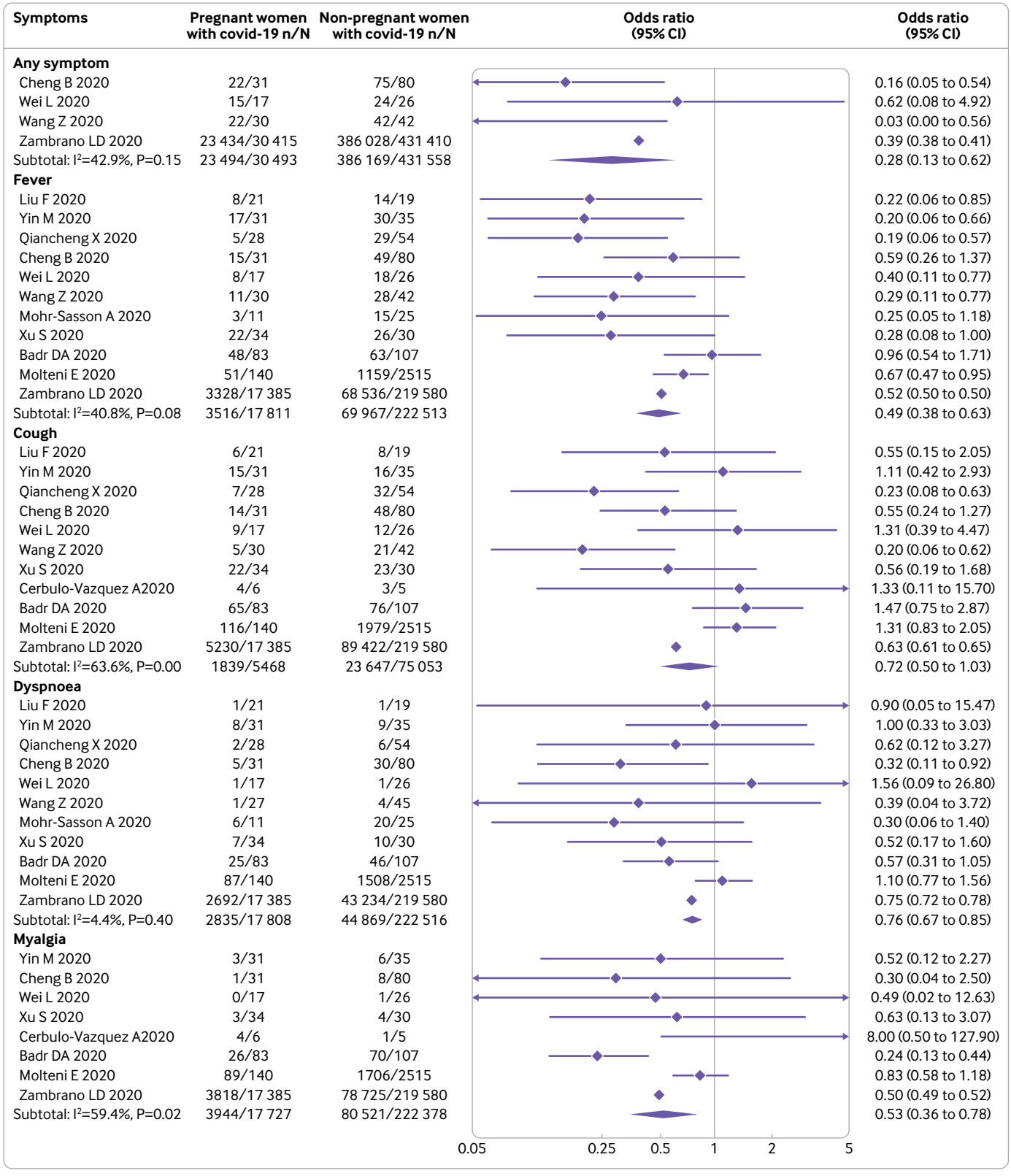

Fig 5 | Clinical manifestations of coronavirus disease 2019 (covid-19) in pregnant and recently pregnant women compared with non-pregnant women of reproductive age with covid-19

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Strengths and limitations of this review

In this unprecedented pandemic situation, where evidence is rapidly produced and published in various formats, our living systematic review underpinned by robust methods and continually updated at regular intervals is relevant for several reasons. Firstly, it addresses important research questions relevant to clinical decision making and policies. Secondly, uncertainties remain for key outcomes that require further evidence. Thirdly, the rapid turnover of evidence in various formats requires assessments of study quality and regular updating of the findings. Finally, our living systematic review is producing strong evidence base for living guidelines on covid-19 and pregnancy.

We undertook a comprehensive search and coordinated our efforts with key organisations and research groups, such as WHO, the Cochrane Centre, and EPPI-Centre. To minimise risk of bias we restricted our meta-analysis to cohort studies, and we reported the quality of the included studies. By contacting the authors and obtaining reports not published in PubMed, we minimised the risk of missing relevant studies. Our systematic review has a large sample size and it is continuously increasing. Our living meta-analyses framework will enable us to rapidly update the findings as new data emerge. We undertook extensive work to ensure that duplicate data are not included. Our various comparative analyses allowed us to comprehensively assess the association between pregnancy and covid-19 related outcomes, covid-19 and pregnancy outcomes, risk factors for SARS-CoV-2 infection, and complications. Our review helps to understand the variations in estimates through sensitivity analyses by sampling strategies, population characteristics, and risk factors, and it provides confidence in the rates of reported outcomes. The update has allowed us to seamlessly incorporate new evidence from 115 studies and more than half a million women, published since our original review in June 2020.

Our systematic review also has limitations. The primary studies used varied sampling frames to identify women with covid-19, comprised women with suspected and confirmed covid-19, and primarily reported on pregnant women who required visits to hospital, including for childbirth, thereby affecting the generalisability of the estimates. Although our sensitivity analyses aimed to tackle some of these problems, the numbers and sample sizes of the individual studies were too small to identify differences between the subgroups. The timing of assessment of the clinical manifestations of disease was generally not available. The definitions of symptoms, tests, and outcomes were heterogeneous. Furthermore, poor reporting of the criteria for caesarean section, admissions to the neonatal unit, and the causes of preterm birth, made it difficult to disentangle iatrogenic effect from the true impact of the disease. There continues to be a paucity of comparative data to assess the risk of pregnancy complications in women with and without covid-19. Studies comparing maternal and perinatal outcomes in pregnant women with covid-19 against historical cohorts of pregnant women, could be biased owing to differences in the environment in which deliveries occur. During the pandemic, healthcare systems have faced increased pressure and strain on services, with resulting effects on service delivery and quality of care.[96 97] Lockdown measures, social distancing, and changes to livelihood have led to increased depression and anxiety, and reduction in physical activity and access or attendance

Table 1 | Outcomes in pregnant and recently pregnant women with coronavirus disease 2019 (covid-19)

Outcomes	No of studies	Women (No with event/No in group (%))		Odds ratio (95% CI)	I^2 (%)
		Pregnant women with covid-19	Comparison group		
Comparison group: non-pregnant women of reproductive age with covid-19					
All cause mortality	8	103/34 047 (0.3)	3388/567 075 (0.6)	0.96 (0.79 to 1.18)	0
ICU admission	7	616/34 035 (1.8)	9568/567 073 (1.7)	2.13 (1.54 to 2.95)	71.2
Invasive ventilation	6	270/34 001 (0.8)	3280/567 043 (0.6)	2.59 (2.28 to 2.94)	0
ECMO	2	17/30 446 (0.1)	120/431 490 (0.0)	2.02 (1.22 to 3.34)	0
Oxygen through nasal cannula	2	8/48 (16.7)	49/106 (46.2)	0.21 (0.04 to 1.13)	65.7
ARDS	1	0/17 (0)	0/26 (0)	1.51 (0.03 to 79.93)	NE
Major organ failure	1	0/17 (0)	0/26 (0)	1.51 (0.03 to 79.93)	NE
Comparison group: pregnant women without covid-19					
Maternal outcomes:					
All cause mortality	8*	8/1195 (0.7)	8/3625 (0.2)	2.85 (1.08 to 7.52)	0
ICU admission	7*	64/1508 (4.2)	4/3482 (0.1)	18.58 (7.53 to 45.82)	0
Preterm birth <37 weeks	18	147/1184 (12.4)	572/7365 (7.8)	1.47 (1.14 to 1.91)	18.6
Caesarean section	21*†	669/1854 (36.1)	4221/11842 (35.6)	1.12 (0.91 to 1.38)	57.6
Perinatal outcomes:					
Stillbirth	9*	9/1039 (0.9)	26/4755 (0.5)	2.84 (1.25 to 6.45)	0
Neonatal death	8*	4/970 (0.4)	5/3316 (0.2)	2.77 (0.92 to 8.37)	0
Admission to neonatal unit	10*	329/1285 (25.6)	519/4588 (11.3)	4.89 (1.87 to 12.81)	96.2
Abnormal Apgar score at 5 minutes	6	13/662 (2.0)	46/2823 (1.6)	1.38 (0.71 to 2.70)	0
Fetal distress	2	11/77 (14.3)	13/263 (4.9)	2.37 (0.77 to 7.31)	0

ICU=intensive care unit; ECMO=extracorporeal membrane oxygenation; ARDS=acute respiratory distress syndrome; NE=not estimable.
The denominator is number of pregnancies for all outcomes.
*Includes UK Obstetric Surveillance System[44] study with historical comparative cohort (694 women).
†Includes Gulersen et al 2020[60] with historical comparative cohort (50 women).

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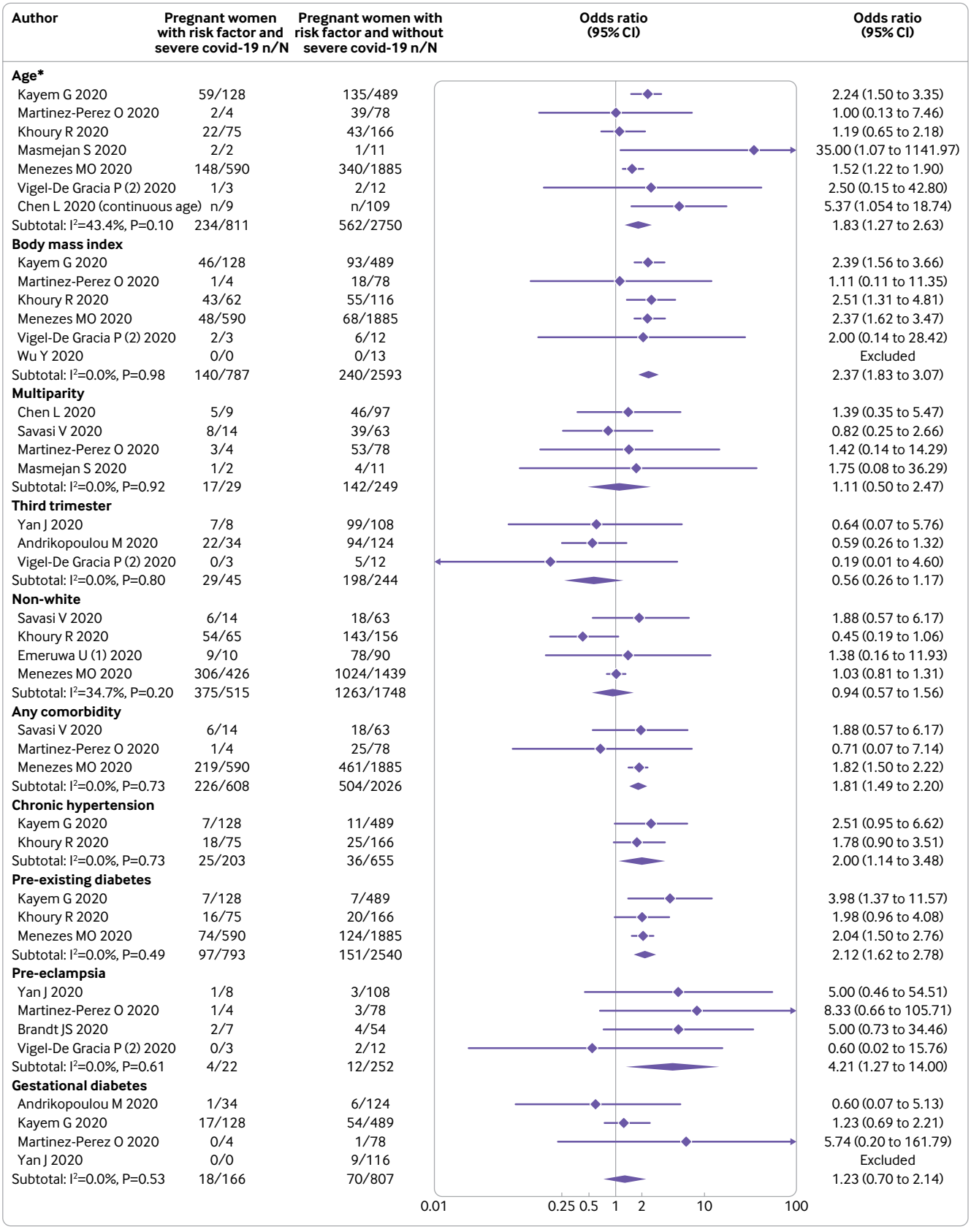

Fig 6 | Risk factors associated with severe coronavirus disease 2019 (covid-19) in pregnant and recently pregnant women. Symptom based screening: Savasi V, Kayem G; NHCC (National Health Commission China). Criteria based screening: Chen, Wu, Yan. All other studies used universal screening. Cut-off for age is 35 years or more, and for body mass index is 30 or more. *Includes one study with continuous measurement of risk factor

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to healthcare facilities, which could increase the risk of maternal and perinatal complications.[98]

Not many studies reported outcomes by trimester for symptom onset, making it difficult to assess the rates of miscarriage and postpartum complications. For some outcomes, the findings were influenced by a single large study.[42] Many studies had to be excluded as we could not rule out potential overlap in the study populations.

Areas of uncertainty in some of our review findings will still need to be resolved in the next updates of the living systematic review. In seeking an efficient balance between resource consumption and the value the review provides to end users, we will make

Table 2 | Maternal characteristics associated with severe coronavirus disease 2019 (covid-19) and all cause death in pregnant and recently pregnant women with a diagnosis of covid-19

Maternal risk factors and outcomes	No of studies	Total No of women	Pregnant women (No with risk factor/No in group (%))		Odds ratio (95% CI)	I^2 (%)
			With outcome	Without outcome		
Age ≥35 years:						
Severe disease	7	3561	811*	2750*	1.83 (1.27 to 2.63)	43
ICU admission	7	31710	348*	31362*	2.11 (1.69 to 2.63)	0
Invasive ventilation	3	718	18*	700*	1.72 (0.60 to 4.97)	17
Maternal death	3	31710	176*	31525*	0.91 (0.22 to 3.72)	93
Multiparity:						
Severe disease	4	278	17/159 (10.7)	12/119 (10.1)	1.11 (0.50 to 2.46)	0
ICU admission	3	815	34/501(6.8)	17/314 (5.4)	1.34 (0.72 to 2.50)	0
Invasive ventilation	1	350	1/216 (0.5)	0/134 (0)	1.87 (0.08 to 46.30)	NE
Body mass index ≥30:						
Severe disease	5	3367	787*	2580*	2.37 (1.83 to 3.07)	0
ICU admission	4	31456	339*	31117*	2.71 (1.10 to 6.63)	63
Invasive ventilation	2	485	12*	4473*	6.61 (1.98 to 22.02)	0
Maternal death	3	31085	113*	30972*	2.27 (1.20 to 4.31)	0
Non-white ethnicity:						
Severe disease	4	2263	375/1638 (22.9)	140/625 (22.4)	0.94 (0.57 to 1.57)	35
ICU admission	4	31543	306/23996 (1.3)	158/7547 (2.1)	1.66 (1.20 to 2.29)	26
Invasive ventilation	1	669	20/134 (14.9)	39/535 (7.3)	2.23 (1.25 to 3.97)	NE
Maternal death	3	31469	110/24 124 (0.5)	36/7345 (0.5)	1.61 (1.05 to 2.47)	0
Any comorbidity:						
Severe disease	3	2634	226/730 (31.0)	382/1904 (20.1)	1.81 (1.49 to 2.20)	0
ICU admission	5	31512	106/6639 (1.6)	226/24 873.9)	1.70 (1.34 to 2.15)	0
Invasive ventilation	3	715	7/71 (9.9)	11/644(1.7)	5.26 (1.76 to 15.68)	0
Maternal death	2	30639	19/6493 (0.3)	33/24 146 (0.1)	2.53 (0.78 to 8.17)	50
Chronic hypertension:						
Severe disease	2	858	25/61 (41.0)	178/797 (22.3)	2.00 (1.14 to 3.48)	0
ICU admission	5	31433	15/262 (5.7)	319/31 171 (1.0)	4.72 (2.37 to 9.41)	13
Invasive ventilation	2	484	5/24 (20.8)	7/460 (1.5)	63.82 (9.69 to 420.45)	0
Maternal death	3	31011	7/249 (2.8)	81/30762 (0.3)	4.25 (1.82 to 9.95)	0
Pre-existing diabetes:						
Severe disease	3	3333	97/248 (39.1)	696/3085 (22.6)	2.12 (1.62 to 2.78)	0
ICU admission	6	31473	36/638 (5.6)	306/30835 (1.0)	4.67 (1.94 to 11.22)	38
Invasive ventilation	2	482	2/12 (16.7)	9/470 (1.9)	18.61 (0.26 to 1324.16)	78
Maternal death	2	30723	11/620 (1.8)	41/30 103 (0.1)	14.88 (4.19 to 52.81)	53
Asthma:						
Severe disease	4	3332	39/148 (26.4)	717/3184 (22.5)	1.43 (0.85 to 2.38)	28
ICU admission	1	100	2/9 (22.2)	8/91 (8.8)	2.96 (0.53 to 16.74)	NE
Maternal death	3	889	5/39 (12.8)	63/850 (7.4)	1.68 (0.66 to 4.24)	0
Smoking:						
Severe disease	3	776	5/23 (21.7)	141/753 (18.7)	1.67 (0.64 to 4.40)	0
ICU admission	2	142	1/4 (25.0)	17/138 (12.3)	2.92 (0.35 to 24.23)	0
Maternal death	1	308	0/10 (0)	7/298 (2.3)	1.85 (0.10 to 34.60)	NE
Gestation ≥28 weeks:						
Severe disease	3	289	29/227 (12.8)	16/62 (25.8)	0.56 (0.27 to 1.17)	0
Maternal death	1	721	46/495 (9.3)	23/226 (10.2)	0.90 (0.53 to 1.53)	NE
Gestational diabetes:						
Severe disease	4	973	18/88 (20.5)	148/885 (16.7)	1.23 (0.70 to 2.14)	0
ICU admission	2	777	11/81 (13.6)	31/696 (4.5)	3.27 (1.55 to 6.89)	0
Invasive ventilation	1	350	0/32 (0)	0/318 (0)	—	NE
Pre-eclampsia:						
Severe disease	4	274	4/16 (25.0)	18/258 (7.0)	4.21 (1.27 to 14.00)	0
ICU admission	1	42	6/6 (100.0)	2/36 (5.6)	179.40 (7.69 to 4186.05)	NE

ICU=intensive care unit; NE=not estimable.
*Includes one or more studies with continuous measurement of risk factor.

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decisions about the pacing of the updates of our living systematic review using a formal framework for decision making. We will use a mixed approach based on the Ottawa method to identify quantitative or qualitative signals for the need of an update,[99] and a more complex statistical prediction tool to estimate the probability that new studies identified would change the review conclusions.[100]

Comparison with existing evidence

Between the publication of the original living systematic review and this update, estimates for the prevalence of covid-19, and rates of clinical manifestations and outcomes of pregnant and recently pregnant women with covid-19 have remained similar, with improved precision in the findings. The rates for postpartum haemorrhage and admission to the neonatal unit appear to be slightly increased from the first version, while the rate of maternal pneumonia appears to be lower. High heterogeneity remains in the estimates for rates of clinical manifestations and outcomes.

We found that the same risk factors for severe covid-19 identified in the original version of the living systematic review remained associated with severe covid-19 with increased precision. Additional risk factors for severe disease, such as non-white ethnicity identified in this update, were also identified from large cohort studies such as the UK Obstetric Surveillance System and the US CDC surveillance report.[42 101] Our findings are consistent with the reports of disproportionately high rates of severe covid-19 in non-pregnant ethnic minority populations,[102] and in other areas of maternity care.[103 104] The observed disparity could be attributed to associated comorbidities, socioeconomic characteristics, and factors related to access to and quality of care in the preconception, pregnancy, and postpartum periods.[105] The multifaceted contributors to ethnic disparities need to be investigated to reduce mortality and morbidity related to both covid-19 and pregnancy.

Our review update also identified an increased risk for maternal death, need for maternal admission to the intensive care unit, and stillbirth in pregnant women with covid-19 compared to pregnant women without the disease. However, our confidence in these estimates is not high, owing to the small numbers of events in both groups. Further data are still needed to robustly assess these outcomes, along with the emerging data on increased risk of severe outcomes such as the need for ECMO.[42]

Alongside the spread of the pandemic, a shift has occurred in the types of studies published, with initial studies involving pregnant women from epidemic regions in China, followed by reports of large regional and national datasets from the US, UK, Netherlands, Spain, and, more recently, Latin American countries. The study design has also changed from initial small case series and case reports to large observational data, with recent studies also providing comparative data.

The prevalence of covid-19 varied widely between studies, particularly when sampling was done based on symptoms or history of contact, highlighting the variations in criteria for testing. The current update includes 50 new studies from 11 additional countries on the prevalence of covid-19 in pregnancy. Despite the addition of five times more studies between the original version of our living systematic review and this update, from diverse populations globally, the prevalence of covid-19 in pregnant and recently pregnant women remains unchanged. Unlike the general population who are mostly tested for SARS-CoV-2 on the basis of symptoms or contact history, universal screening of all pregnant women attending the hospital for any reason could contribute to the consistency in the findings. However, the true prevalence of covid-19 in pregnancy is likely to be lower than the current estimate if all pregnant women, including those not attending the hospital are included.

In the recent cohort study of all individuals admitted with covid-19 in the UK, the cluster of respiratory symptoms of cough, fever, and breathlessness were observed in more than two thirds of individuals,[106] similar to reported rates in the US and China.[107-109] But in our review, fewer pregnant and recently pregnant women with covid-19 manifested these symptoms than the non-pregnant population, indicating possible high rates of asymptomatic presentation in this population. This is likely because of the strategy of universal screening for covid-19 in pregnancy and the low thresholds for testing in pregnant women than in non-pregnant women. Despite the potential higher possibility of universal screening to detect pregnant women with mild disease, we observed an increase in admissions to the intensive care unit and need for invasive ventilation compared with non-pregnant women of reproductive age with covid-19. The findings were mainly influenced by the recently updated large Centers for Disease Control and Prevention report from the US,[42] and a report from the Mexican General Directorate of Epidemiology registry.[41]

By accessing the unpublished data from our collaborators, we were able to include both women with and without symptoms from the US CDC surveillance data, in addition to the women with symptoms only who were included in the published report.[42] Pregnancy status was not ascertained in a large proportion of women of reproductive age in the CDC report, which could affect the estimates. Furthermore, the outcomes for which the data were missing from the report were considered to be absent, potentially leading to bias. The report from the Mexican General Directorate of Epidemiology registry, available only as a preprint, included only women with symptoms who might be at high risk of complications. We recommend that studies comparing covid-19 related outcomes in pregnant versus non-pregnant women report the relevant estimates for both women with and without symptoms to avoid overestimation of the risk of complications due to selective reporting. The pooled estimates for severe covid-19 and admission to an intensive care

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unit were, however, still relatively high in the non-comparative data, indicative of a potential high risk in pregnancy. This is supported by the recent analysis in a Swedish study suggesting a high risk of admission to an intensive care unit and invasive ventilation in pregnant women compared to non-pregnant women.[110]

Similar to the general population, high body mass index and pre-existing comorbidity seemed to be risk factors for severity of covid-19 in pregnancy, including admission to an intensive care unit and invasive ventilation.[106] Complications related to covid-19 did not seem to be increased in women presenting in the third trimester versus earlier in pregnancy or in multiparous versus primiparous women—but existing sample sizes are not large. Both chronic hypertension and pre-existing diabetes were associated with maternal death in pregnant women with covid-19, which are known risk factors in the general population. But it is not known if covid-19 was the direct cause of death for these women, and the numbers of studies are small. We observed an increase in rates of preterm birth in pregnant women with covid-19 compared with pregnant women without the disease. These preterm births could have been medically indicated, as the overall rates of spontaneous preterm births in pregnant women with covid-19 was broadly similar to those observed in the pre-pandemic period. Although about 50% of pregnant women underwent caesarean section in the non-comparative studies, we did not find a statistically significant difference in comparative studies of pregnant women with and without covid-19. The precision of the estimates is expected to improve with the publication of more data in the future. The overall rates of stillbirths and neonatal deaths do not seem to be higher than the background rates. The indications for admissions to the neonatal unit, observed in about a third of neonates delivered to mothers with covid-19, have not been reported. Local policies on observation and quarantine of infants with exposure to SARS-CoV-2 might have influenced these rates.

Relevance for clinical practice and research

Based on existing data, healthcare professionals should be aware that pregnant and recently pregnant women with covid-19 might manifest fewer symptoms than the general population, with the overall pattern similar to that of the general population. Pregnant women should be informed of the increase in severity of covid-19 including admission to intensive care units, need for ECMO and invasive ventilation compared with non-pregnant women, and encouraged to undertake safety measures to reduce the risk of infection. Pregnant women with pre-existing comorbidities will need to be considered as a high risk group for covid-19, along with those who are obese and of older maternal age. Healthcare professionals need to be aware of the increased risk of severe covid-19 in pregnant and recently pregnant women of non-white ethnic origin, to plan close monitoring and have a low threshold for escalation of care. Clinicians will need to balance the need for regular multidisciplinary antenatal care to manage women with pre-existing comorbidities against unnecessary exposure to the virus, through virtual clinic appointments when possible. Pregnant women with covid-19 before term gestation might need to be managed in a unit with facilities to care for preterm neonates.

Further data are still needed to assess robustly if pregnancy related maternal and neonatal complications are increased in women with covid-19 compared to pregnant women without the disease. Similarly, the association between pregnancy specific risk factors such as pre-eclampsia and gestational diabetes on covid-19 related outcomes needs further evaluation. Pre-eclampsia was reported to be associated with severe covid-19 in small studies, but this requires further assessment as the clinical and laboratory presentation of severe pre-eclampsia could mimic worsening covid-19.[111] Robust collection of maternal data by trimester of exposure, including the periconception period, is required to determine the effects of covid-19 on early pregnancy outcomes, fetal growth, and risk of miscarriage or stillbirth. We need detailed reporting of outcomes by ethnicity to quantify the risk of severe covid-19 in women from different ethnicities. Qualitative studies on behaviour and attitude to the pandemic can disentangle the relative importance of factors behind the ethnic disparities observed in the severity of covid-19.

Systematic reviews are considered to be the highest quality evidence informing guidelines, and poor quality reviews will have a direct impact on clinical care. Despite the urgent need for evidence on the impact of covid-19 in pregnant women, systematic reviews and meta-analyses still need to adhere to the reporting guidelines on search criteria, quality assessment, and analysis. This is particularly important as large numbers of non-peer reviewed scientific papers and reports are currently available in the public domain in multiple versions. Primary studies need to explicitly state if duplicate data have been included to avoid double counting of participants in evidence synthesis. Individual participant data meta-analysis of the emerging cohorts is critical to assess both differential presentation and outcomes by underlying risk factors, and to determine the differential effects of interventions to reduce the rates of complications. With the establishment of several national and global prospective cohorts, we expect the sample size of our meta-analysis to increase further in the coming months. Our living systematic review and meta-analysis with its regular search and analyses updates is ideally placed to assess the impact of new findings on the rapidly growing evidence base.

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The corresponding author (ST) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been disclosed.

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Supplementary information: Appendices 1-9

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Annex 2: COVID-19 vaccination decision guide for women who are pregnant, breastfeeding or planning pregnancy

Version 6
15 September 2021

Australian Government

Australian Government

COVID-19 VACCINATION

COVID-19 vaccination decision guide for women who are pregnant, breastfeeding or planning pregnancy

Version 6

15 September 2021

What has changed?

- *The newly registered Spikevax COVID-19 vaccine (Moderna) has been included in this advice.*
- *If Pfizer or Moderna are not available, AstraZeneca can be considered if the benefits to the individual outweigh the potential risks*

The Department of Health will publish updated versions of this guide as more information and new vaccines become available.

Please note:

- *Spikevax COVID-19 vaccine (Moderna) will be referred throughout this guide as Moderna*
- *Comirnaty COVID-19 vaccine (Pfizer) will referred throughout this guide as Pfizer*
- *Vaxzevria COVID-19 vaccine/COVID-19 Vaccine AstraZeneca (AstraZeneca) will referred throughout this guide as AstraZeneca*

This decision guide contains information about Pfizer and Moderna, the COVID-19 vaccines recommended if you are pregnant, breastfeeding or planning pregnancy. This guide will be updated as new information becomes available.

Key points

- If you are pregnant you are a priority for COVID-19 vaccination and should be routinely offered Pfizer or Moderna at any stage of pregnancy.
- If you are trying to become pregnant, you do not need to delay vaccination or avoid becoming pregnant after vaccination.
- Real-world evidence has shown that Pfizer and Moderna are safe if you are pregnant and breastfeeding.
- AstraZeneca can be considered if you are pregnant, breastfeeding or planning pregnancy, if you cannot access Pfizer or Moderna, and if the benefits of vaccination outweigh the risks for you.
- If you are pregnant, you have a higher risk of severe illness from COVID-19.
- Your baby may also have a higher risk of being born prematurely.
- COVID-19 vaccination may provide indirect protection to babies by transferring antibodies through the placenta (during pregnancy) or through breastmilk (during breastfeeding).

What are the current recommendations for COVID-19 vaccination in pregnancy?

If you are pregnant you are in a priority group for COVID-19 vaccination. You should be routinely offered Pfizer or Moderna at any stage of pregnancy. Research has shown that those who are pregnant have a higher risk of severe illness from COVID-19 and their babies have a higher risk of being born prematurely. Vaccination is the best way to reduce these risks.

If you are pregnant, you are recommended to complete the routine schedule of Pfizer or Moderna to ensure adequate protection.

- For Pfizer, this is two doses, 3-6 weeks apart.
- For Moderna, this is two doses, 4-6 weeks apart.

The recommended interval between COVID-19 vaccine and any other vaccine given during pregnancy is seven days. In special circumstances this interval can be shortened (including same day administration), such as after a tetanus prone wound or during an outbreak of influenza or COVID-19.

Vaccine preference recommendations

Pfizer and Moderna are the preferred COVID-19 vaccines for people under 60 years in Australia, and if you are pregnant, breastfeeding or planning pregnancy. This is for two reasons:

- Research has shown that Pfizer and Moderna are safe in pregnancy and during breastfeeding. This research has not yet been carried out for AstraZeneca.
- AstraZeneca is associated with a rare risk of a clotting condition called thrombosis with thrombocytopenia syndrome (TTS), which appears to be more common in people under 60 years of age.

If Pfizer or Moderna are not available, AstraZeneca can be considered if the benefits of vaccination outweigh the risks for an individual. For example, in outbreak settings. There are no theoretical safety concerns associated with AstraZeneca specific to pregnancy, breastfeeding or planning pregnancy.

Pfizer and Moderna are registered for use in people aged 12 and older. AstraZeneca is registered for use in people aged 18 and older. All three vaccines work by delivering the genetic code for an important part of the COVID-19 virus called the spike protein. After vaccination your body reads the genetic code and makes copies of the spike protein. This trains your immune system to recognise and fight against the COVID-19 virus.

Recommendations if you are pregnant and have already received a dose of AstraZeneca

If you are pregnant and have already received a first dose of AstraZeneca, you can receive Pfizer, Moderna or AstraZeneca for your second dose, although Pfizer or Moderna are preferred.

While generally it is recommended that the same vaccine brand is used for both doses, Pfizer or Moderna is preferred in pregnancy because there is more information regarding safety of Pfizer and Moderna in pregnancy compared with AstraZeneca.

You and your provider may wish to consider the following factors:

- There is a growing body of evidence supporting the safety of mRNA COVID-19 vaccines (Pfizer or Moderna) in pregnancy
- There are still very limited data on the safety of viral vector vaccines (such as AstraZeneca) in pregnancy
- There is comparatively less data on the safety and efficacy of mixed vaccine schedules than completing the series with the same vaccine.

Why have the recommendations for COVID vaccination during pregnancy changed?

Pregnant women were not included in the first clinical trials for COVID-19 vaccines, so at the time of initial guidance there was limited evidence confirming the safety of COVID-19 vaccines during pregnancy. The initial advice from immunisation expert groups was therefore cautious, and COVID-19 vaccines were not routinely recommended in pregnancy.

Over time, 'real-world' evidence from other countries has accumulated and reports show that the mRNA COVID-19 vaccines Pfizer and Moderna are safe to use in pregnancy. Emerging research also demonstrates there is a similar immune response to mRNA vaccines in pregnancy compared to those who are not pregnant. Therefore, it is likely there is similar protection from the vaccines against COVID-19 during pregnancy. Results from the vaccine program in Israel have suggested that Pfizer is effective in preventing COVID-19 in pregnancy.[1] Furthermore, research shows that the antibodies produced by vaccination cross the placenta and may provide some protection to newborn babies.

What are the risks of COVID-19 in pregnancy?

Those who contract COVID-19 whilst pregnant have a higher risk of certain complications compared to those who are not pregnant with COVID-19 of the same age, including:

- An increased risk (about 5 times higher) of needing admission to hospital.[2]
- An increased risk (about 2-3 times higher) of needing admission to an intensive care unit.[3,4]
- An increased risk (about 3 times higher) of needing invasive ventilation (breathing life support).[3,4]

COVID-19 during pregnancy also increases the risk of complications for the newborn, including:

- A slightly increased risk (about 1.5 times higher) of being born prematurely (before 37 weeks of pregnancy).[3]

- An increased risk (about 3 times higher) of needing admission to a hospital newborn care unit.[3]

Some who are pregnant are more likely to have severe illness from COVID-19 compared to those who are pregnant *without* these conditions. The conditions are:

- Being older than 35 years
- Being overweight or obese (body mass index above 30 kg/m^2)
- Having pre-existing (pre-pregnancy) high blood pressure
- Having pre-existing (pre-pregnancy) diabetes (type 1 or type 2)

Are mRNA COVID-19 vaccines (Pfizer and Moderna) safe in pregnancy?

Yes, mRNA vaccines have been shown to be safe in pregnancy based on accumulated real-world evidence from other countries. A US study of over 35,000 women who were pregnant and had an mRNA COVID-19 vaccine showed that the side effects following vaccination were very similar in those who were pregnant when compared to those who were not.[5] Those who were pregnant appeared slightly more likely to report pain at the injection site, but were less likely to report generalised symptoms such as fever or tiredness. Fever of 38°C or above was reported in fewer than 1% of those who were pregnant who had Pfizer or Moderna after the first dose, fewer than 5% after the second dose of Pfizer, and 11.8% after the second dose of Moderna. The findings from this large study are supported by other smaller studies.[6–8]

This study also reported the outcomes for 827 completed pregnancies. They did not identify any safety concerns for those who received an mRNA COVID-19 vaccine in pregnancy. Complications such as premature delivery, stillbirth, small for gestational age infants and congenital anomalies occurred at a similar rate to what is seen in the general population.[5]

A number of smaller studies have shown that receiving an mRNA vaccine during pregnancy does not increase the risk of pregnancy complications for those who are pregnant or their babies.[6,7,9,10]

Animal studies of Pfizer and Moderna have not shown any negative effects on fertility or pregnancy.[11,12]

Overall the data on COVID-19 vaccines in pregnancy are still limited, but growing. A clinical trial of Pfizer is underway in the US, and further real-world evidence is being gathered.[13]

There are still very limited data on the safety of viral vector vaccines (such as AstraZeneca) in pregnancy.

What are the possible harms from vaccination with Pfizer or Moderna during pregnancy?

1. You may experience side effects after vaccination. Common side effects reported after Pfizer and Moderna in the clinical trials in people aged 18-55 (Pfizer) or 18-65 (Moderna) include:
    - pain at the injection site (in about 84% after Pfizer and 90% after Moderna). Those who are pregnant appear more likely to report injection site pain compared to those who are not.[5]
    - tiredness (in about 62% and 68%)
    - headache (in about 52% and 63%)
    - muscle pain (in about 37% and 62%)
    - chills (in about 35% and 49%)
    - joint pain (in about 22% and 46%)
    - fever (in about 16% and 17%)
    - diarrhoea (in about 10% and 21%)

Fever is considered undesirable in early pregnancy, but most people who have COVID-19 vaccination will not have a fever. As Paracetamol is safe in pregnancy, you can take it to reduce the following symptoms if you experience them:

- fever
- pain at the injection site
- headache
- muscle pain
- joint pain
- chills

2. COVID-19 vaccination may cause rare side effects in those who are pregnant or their babies that we do not yet know about:
    - Real-world evidence is available from a study of over 35,000 women who were pregnant and who had an mRNA COVID-19 vaccine.[5] This study did not find any side effects specific to those who were pregnant or their babies. However, it is still possible that there are very rare side effects that have not been detected in this study.

Are there any benefits for my baby from having a COVID-19 vaccine during pregnancy?

COVID-19 in pregnancy may present a higher risk of stillbirth or premature (early) delivery.[3] Babies are also more likely to show distress during delivery, or to need treatment in a newborn intensive care unit. COVID-19 vaccination during pregnancy may reduce the risk of premature delivery of the baby, if it prevents infection in the mother.

Several studies have shown that the antibodies induced by COVID-19 vaccine can cross the placenta, particularly in those vaccinated early in pregnancy, and who received both doses prior to delivery.[6,7,10,14,15]These antibodies may provide your baby with some protection against COVID-19 for the first few months of life. However, there have not yet been any studies to confirm such protection.

When is the best time to have a COVID-19 vaccine if I am pregnant?

Currently we do not know if there is an optimal time to have a COVID-19 vaccine during pregnancy, either for the benefit of the mother or to protect her baby. Therefore, you are recommended to have a COVID-19 vaccine as soon as you are offered one. COVID-19 vaccines can be given at any stage of pregnancy.

Can I just have one dose during pregnancy, and delay the second dose?

Having only one dose will provide partial protection against COVID-19, and we do not yet know how long this protection will last. Having the second dose is important to gain optimal protection against COVID-19. Two doses of a COVID-19 vaccine provides good protection against COVID-19, including against the Delta strain. A single dose is not as effective at preventing infection but does reduce the risk of severe illness. Now that there is good data on the safety of mRNA vaccines in pregnancy, it is recommended to have two doses of Pfizer 3-6 weeks apart or Moderna 4-6 weeks apart.

If you choose to delay the second dose, you will not need to repeat the first dose.

Can Pfizer or Moderna be given at the same time as influenza or whooping cough vaccines?

It is not routinely recommended to co-administer COVID-19 vaccine with other vaccines. The minimum recommended interval between COVID-19 vaccine and any other vaccine is seven days. However, this interval can be shortened (including same day administration) in special circumstances, such as a tetanus prone wound or outbreak of influenza or COVID-19.

What are the recommendations if you are breastfeeding?

Pfizer and Moderna are the preferred vaccines for people under 60 years of age, which includes those who are breastfeeding. You do not need to stop breastfeeding before or after vaccination.

If you are breastfeeding can you have AstraZeneca?

If Pfizer or Moderna is not available, you can consider having AstraZeneca after talking to your healthcare provider about the benefits and potential rare risks. AstraZeneca has not been formally studied in those who are breastfeeding, however there are no theoretical safety concerns for its use while breastfeeding. It is not a live vaccine and cannot cause COVID-19 in your infant.

Are Pfizer and Moderna safe if you are breastfeeding?

Yes, these vaccines are considered safe for those breastfeeding and their babies. While there is limited research on the safety of COVID-19 vaccines in those who are breastfeeding, there are no theoretical safety concerns. Several small studies have shown that those breastfeeding have similar side effects after having an mRNA COVID-19 vaccine compared to the general population.[6,7,16]

The mRNA in Pfizer and Moderna is rapidly broken down in the body and we do not think that it passes into breastmilk. This has been confirmed by one small study.[17] Even if it did, it would be quickly destroyed in the baby's gut and is therefore extremely unlikely to have any effect on your baby.

Are there any benefits for my baby from having COVID-19 vaccine while breastfeeding?

Several small studies have shown that the antibodies induced by COVID-19 vaccines pass into breastmilk.[6,7,16,18] This may provide your baby with some protection against COVID-19, however there have not yet been any studies to confirm such protection.

What are the recommendations if you are planning pregnancy?

If you are planning pregnancy you are recommended to receive Pfizer or Moderna. You do not need to avoid becoming pregnant before or after vaccination. Getting vaccinated before conceiving means you are likely to have protection against COVID-19 throughout your pregnancy. Vaccination does not affect fertility. You are not required to have a pregnancy test before getting vaccinated. If Pfizer or Moderna is not available, you can consider having AstraZeneca if the benefits outweigh the potential risks for you.

For more information

For more information about COVID-19 and COVID-19 vaccines, refer to:

- Joint statement between RANZCOG and ATAGI about COVID-19 vaccination for pregnant women
- Information on COVID-19 Pfizer (Pfizer) vaccine
- Information on COVID-19 Moderna (Moderna) vaccine
- Preparing for COVID-19 vaccination
- After your Pfizer (Pfizer) vaccine
- After your COVID-19 Moderna (Moderna vaccine)

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Annex 3: Impact of SARS-CoV-2 variant on the severity of maternal infection and perinatal outcomes: Data from the UK Obstetric Surveillance System national cohort.

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Impact of SARS-CoV-2 variant on the severity of maternal infection and perinatal outcomes: Data from the UK Obstetric Surveillance System national cohort.

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ABSTRACT

Background

In the UK, the Alpha variant of SARS-CoV-2 became dominant in late 2020, rapidly succeeded by the Delta variant in May 2021. The aim of this study was to compare the impact of these variants on severity of maternal infection and perinatal outcomes within the time-periods in which they predominated.

Methods

This national, prospective cohort study collated data on hospitalised pregnant women with symptoms of confirmed SARS-CoV-2 infection and compared the severity of infection and perinatal outcomes across the Wildtype (01/03/20-30/11/20), Alpha (01/12/20-15/05/21) and Delta dominant periods (16/05/21-11/07/21), using multivariable logistic regression.

Findings

Of 3371 pregnant women, the proportion that experienced moderate to severe infection significantly increased between Wildtype and Alpha periods (24.4% vs. 35.8%; aOR1.75 95%CI 1.48-2.06), and between Alpha and Delta periods (35.8% vs. 45.0%; aOR1.53, 95%CI 1.07-2.17). Compared to the Wildtype period, symptomatic women admitted in the Alpha period were more likely to require respiratory support (27.2% vs. 20.3%, aOR1.39, 95%CI 1.13-1.78), have pneumonia (27.5% vs. 19.1%, aOR1.65, 95%CI 1.38-1.98) and be admitted to intensive care (11.3% vs. 7.7%, aOR1.61, 95%CI 1.24-2.10). Women admitted during the Delta period had further increased risk of pneumonia (36.8% vs. 27.5%, aOR1.64 95%CI 1.14-2.35). No fully vaccinated pregnant women were admitted between 01/02/2021 when vaccination data collection commenced and 11/07/2021. The proportion of women receiving pharmacological therapies for SARS-CoV-2 management was low, even in those critically ill.

Interpretation

SARS-CoV-2 infection during Alpha and Delta dominant periods was associated with more severe infection and worse pregnancy outcomes compared to the Wildtype infection, which

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itself increased risk compared to women without SARS-CoV-2 infection.[1] Clinicians need to be aware and implement COVID-specific therapies in keeping with national guidance. Urgent action to tackle vaccine misinformation and policy change to prioritise uptake in pregnancy is essential.

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INTRODUCTION

In 2020 the World Health Organisation's (WHO) living systematic review concluded that SARS-CoV-2 infection during pregnancy was associated with an increased risk of admission to intensive care (ICU) for the mother, increased risk of preterm birth and admission for neonatal care for the infant.[2] Included studies predominantly contained data from the USA and China and were conducted in the first six months of the pandemic, prior to the spread of new variants.

In the UK, a new variant of SARS-CoV-2 (B.1.1.7, Alpha Variant of Concern (VOC)) was initially reported in South East England in September 2020 and then circulated at very low levels in the population until mid-November 2020 when it then dominated.[3] This was then succeeded by the Delta VOC (B.1.617.2) which quickly became the dominant variant in late May 2021.[4] There is growing evidence that in the non-pregnant population, the Alpha VOC may be associated with increased risk of hospitalisation and mortality compared with other lineages.[5] Most recently, data from a Scottish national cohort demonstrated that infection with the Delta VOC approximately doubled the risk of hospital admission in the general population, compared to infection with the Alpha VOC.[6] However, there are very limited published studies exploring the impact of different SARS-CoV-2 variants on pregnancy and perinatal outcomes.

A single centre study from the UK reported a significant increase in peripartum referrals for extracorporeal membrane oxygenation (ECMO) during the second wave of the pandemic, when the Alpha VOC became dominant (n=19 vs n=4)[7]. This was in keeping with findings of a national registry of patients admitted to ICU, which reported an increase in the number of pregnant or recently pregnant women in the second wave compared to the first.[8] However, these reports were limited by the absence of a comparator, meaning it was not possible to determine whether this was a result of changing variants as opposed to an increasing total numbers of infected women.

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To the best of our knowledge, only two further publications have explored the potential impact of different SARS-CoV-2 variants in pregnancy. A retrospective cohort from a single centre in India concluded that pregnant women admitted during the Delta VOC dominant second wave (n=387) had higher rates of admission to ICU or high dependency unit (11.6 vs 2.4%) and case fatality (5.7 vs. 0.7%) than those in the first wave (n=1143).[9] This is in keeping with a review of 803 maternal deaths with SARS-CoV-2 in Brazil, where a significantly higher case fatality rate was reported in 2021 (Gamma VOC) compared to 2020 (15.6% vs. 7.4%).[10] These preliminary studies suggest an urgent need for robust national data on the impact of new variants on maternal and perinatal outcomes in order to inform policy.

The primary aim of this study was therefore to compare the impact of SARS-CoV-2 infection on severity of maternal infection and perinatal outcomes across three time periods in which the Wildtype, Alpha and Delta VOCs were dominant.

METHODS

Data sources

A national, prospective observational cohort study was conducted using the UK Obstetric Surveillance System (UKOSS).[11] UKOSS is a research platform that was established in 2005. All 194 hospitals in the UK with a consultant-led maternity unit collect population-based information about specific severe pregnancy complications. Nominated reporting clinicians, facilitated by research midwives and nurses from the UK's National Institute of Health Research Clinical Research Network, notified all pregnant women admitted to their hospital with confirmed SARS-CoV-2 infection. In addition to receipt of real-time reports, zero reports were confirmed. Reporters who had notified a case but not returned data received email reminders. Hospital admission was defined as an overnight hospital stay, or longer, for any cause, or admission of any duration to give birth. Women were taken as confirmed SARS-CoV-2 if they were hospitalised during pregnancy or within two days after giving birth and had

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a positive test during or within seven days of admission. Women not meeting this case definition, and those without any symptoms of SARS-CoV-2 infection, were excluded (Supplementary Figure 1). Information on women who died, or who had stillbirths or neonatal deaths, was cross-checked with data from the organisation responsible for maternal and perinatal death surveillance in the UK (MBRRACE-UK).[12]

Measures

The primary outcome was a composite indicating moderate to severe SARS-CoV-2 infection: oxygen saturation <95% on admission, need for oxygen therapy, evidence of pneumonia on imaging, admission to ICU or maternal death, based on the WHO criteria of COVID-19 disease severity[13]. Each of those components was also analysed separately, as were pregnancy and perinatal outcomes including mode and gestation of birth, stillbirth, live birth, admission to neonatal intensive care and neonatal death.

As individual-level SARS-CoV-2 variant data were not recorded in medical records, the outcomes were compared across three proxy groups according to the time-period in which three different SARS-CoV-2 variants were the dominant circulating strain in the UK. The original 'Wildtype' period included women admitted to hospital from 1st March to 30th November 2020, the Alpha period, from 1st December 2020 to 15th May 2021, and the Delta period, from 16th May 2021 to 11th July 2021. Cut-offs for the Delta period were chosen using data on variant sequencing from Public Health England to identify the week that this variant first contributed more than 50% of cases nationally.[4]

Study registration

The study was registered with ISRCTN, number 40092247 and the protocol is available at https://www.npeu.ox.ac.uk/ukoss/current-surveillance/covid-19-in-pregnancy.

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Role of the funding source

The funder played no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; nor the decision to submit the paper for publication.

Ethics and consent

This study was approved by the HRA NRES Committee East Midlands – Nottingham 1 (Ref. Number: 12/EM/0365).

Statistical methods and analysis

Statistical analyses were performed using STATA version 15 (Statacorp, TX, USA). Numbers and proportions are presented with 95% confidence intervals (CI). Where data were missing, proportions are presented out of cases known. Odds ratios (ORs) with 95% CI were estimated using unconditional logistic regression.

The hypothesised relationships between SARS-CoV-2 variant and severity of infection were identified using directed acyclic graphs, created with DAGitty.net.[14,15] (Supplementary Figure 2). These were informed by associations identified in the literature and underlying theory. The minimum adjustment set to control for confounding bias was sociodemographics (age, ethnicity, body mass index (BMI) and employment), and vaccine status. However, there were insufficient data to include vaccine status as a covariate (as data were only collected from 01/02/2021) and therefore, based on the DAG, it was necessary to also include pre-existing medical conditions (asthma, cardiac disease, diabetes or hypertension) in order to block a further potential biasing pathway (Supplementary Figure 2).[1] These were included in the model as a combined covariate if any of the conditions were identified. In the absence of data sparsity or multicollinearity (highest Spearman correlation coefficient of 0.19), all pre-specified covariates as identified by the DAG were included. Following testing for departure from linearity using likelihood ratio testing, age and BMI were included as ordered categorical

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variables. Potential effect modifiers were identified *a priori* as the covariates identified in the DAG, in addition to parity and trimester of pregnancy at time of infection. Plausible interactions were tested by the addition of interaction terms and subsequent likelihood ratio testing on removal, with a p-value <0.01 considered as evidence of significant interaction. No interaction terms were included in the model. In this national observational study, the study sample size was governed by the disease incidence, thus no formal power calculation was carried out.

RESULTS

In total, 3371 women were admitted to hospital across the UK with symptoms of confirmed SARS-CoV-2 infection between 1st March 2020 and 11th July 2021. Most cases were during the second wave when the Alpha VOC was dominant (Figure 1). Of those where the primary reason for admission was known (74.8%, n=2521), just under half (45.0%, n=1137) were admitted for COVID-19, 30.0% (n=755) for labour and birth and 25.0% (n=629) for other obstetric reasons. The proportion admitted primarily for COVID-19 increased across the variants from 41.4% (n=204), to 45.9% (n=384) and 54.2% (n=90) in the Wildtype, Alpha and Delta periods, respectively.

The characteristics of each group are described in Table 1. The proportion of women admitted during the Delta period aged 35 years or over was 22.9% (n=39) compared to 29.5% (n=422) and 28.8% (n=508) in Wildtype and Alpha periods respectively. Two thirds reported that they or their partner were in paid employment in the Delta period (62.6% (n=107)) compared to nearly 80% in the Alpha and Wildtype periods (79.6% (n=1142) and 75.8% (n=1338) respectively). Across all three periods, the majority of women were overweight or obese. The proportion of women admitted in the Alpha and Delta periods with one or more pre-existing medical conditions was 14.0%, (n=247) and 13.5% (n=23), compared to 11.8% (n=169) of those admitted in the Wildtype period. The most common time for admission was at term across all three time periods.

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Out of 742 women where vaccine status was collected (n=571 during the Alpha period and n=171 during the Delta period), a total of four women admitted with symptomatic SARS-CoV-2 infection had received their first dose of SARS-CoV-2 vaccination prior to their positive test (from 5 to 16 weeks prior). One was admitted during the Alpha period (0.2% of women) and three during the Delta period (1.8% of women). One woman was recorded as vaccinated but was missing a date and therefore it was not possible to confirm that this preceded infection. There were no women admitted with symptoms of SARS-CoV-2 in this study period that had received both doses of vaccine.

Overall, 25% of women admitted with symptomatic COVID-19 during the Wildtype period had at least one marker of moderate to severe infection. This significantly increased to 35.8% during the Alpha period (aOR 1.75, 95% CI 1.48-2.06) and was greater still during the Delta period when nearly half of women had moderate to severe infection (45.0%, aOR 1.53, 95% CI 1.07-2.17, for Alpha vs Delta periods)(Table 2). There was a total of 15 maternal deaths in women with COVID-19, 10 during the Wildtype and five during the Alpha period (Table 2). After adjustment, women admitted during the Alpha period were significantly more likely to require admission to ICU than those admitted during the Wildtype period (11.3% vs. 7.7%, aOR 1.61, 95% CI 1.24-2.10). There was also a statistically non-significantly increased risk of ICU admission in women being admitted during the Delta compared to Alpha periods (15.2% vs. 11.3%, aOR 1.60, 95% CI 0.99-2.59).

Women admitted during the Alpha period were more likely to have SARS-CoV-2 pneumonia confirmed on imaging (27.5% vs 19.1%; aOR 1.65, 95% CI 1.38-1.98) and require respiratory support (27.2% vs. 20.3%; aOR 1.39 95% CI 1.13-1.71) than those admitted in the Wildtype period (Table 2). Furthermore, women admitted during the Delta period were at greater risk again of pneumonia compared to the Alpha period, with more than a third having SARS-CoV-2 pneumonia (36.8% vs. 27.5%; aOR 1.64, 95% CI 1.14-2.35) and a third of women requiring respiratory support (33.3% vs. 27.2%; aOR 1.43, 95% CI 0.97-2.11). Whilst not statistically

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significant, there also appeared to be reduced use of invasive ventilation and increased use of high flow oxygen and continuous positive airway pressure (CPAP) over time.

The proportion that received any pharmacological treatment for COVID-19 (one or more of an antiviral, Tocilizumab, maternal steroids and monoclonal antibodies) was small, but did increase over time: 6.9% in Wildtype vs. 14.3% in Alpha period (aOR 2.37; 95% CI 1.83-3.07) and 16.3% in Delta period (aOR 1.35, 95% CI 0.87-2.12). A greater proportion of women admitted to ICU received any pharmacological therapy for COVID-19 than those not admitted to ICU (39.9%, n=134 vs. 8.1% n=246), although this proportion was still small: 12.5% (n=42) received antivirals, 8.0% (n=27) received Tocilizumab, 27.1% (n=91) received maternal steroids, and 0.6% (n=2) received monoclonal antibodies.

Of those with complete outcome information (96.9% Wildtype, 89.1% Alpha and 42.7% Delta), the median gestation at birth was the same across periods (Table 3). In the Alpha period, 1.4% (n=22) gave birth at between 22 and <28 weeks' compared to 0.7% (n=10) in the Wildtype period (aOR 2.15, 95% CI 0.97-4.76). The proportion that gave birth at 28 to <32 weeks' was similar between these periods (3.7% (n=57) vs. 3.3% (n=45), aOR 1.20, 95% CI 0.79-1.83). Given that 10.1% of women in the Alpha period had incomplete delivery information compared to 3.1% in the Wildtype period, a sensitivity analysis assuming the remainder delivered at term was undertaken and demonstrated similar results (22 to <28 weeks aOR 1.99, 95% CI 0.94-4.23; 28 to <32 weeks aOR1.15, 95% CI 0.77-1.71). Since, as anticipated due to timing of this analysis, fewer pregnancies were completed in the Delta period, formal comparison of the proportion of preterm births was not performed.

The majority of babies were live born with no change in the proportion of stillbirths across the time periods. There were six neonatal deaths, five in the Wildtype period and one in the Alpha period, none of which were directly related to neonatal SARS-CoV-2 infection. Overall, nearly one in five babies were admitted for neonatal care, with significantly increased risk in those

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born to mothers admitted in the Alpha compared to Wildtype period (22.0% vs. 18.7%, aOR1.23, 95% CI 1.01-1.48).

DISCUSSION

This national prospective cohort study has identified that, after adjusting for sociodemographics and pre-existing medical conditions, the proportion of symptomatic pregnant women admitted who experienced moderate to severe COVID-19 has significantly increased from 24% to 36% and then 45% in the Wildtype, Alpha, and Delta periods respectively. Women admitted in the Alpha period were more likely to require respiratory support, have pneumonia, and be admitted to ICU, compared to women admitted in the Wildtype period. Women admitted during the Delta period had a further increase in risk compared to those admitted in the Alpha period, with a greater proportion having pneumonia and non-significant increases in respiratory support and ICU admission. Whilst the majority of babies were live born, babies born to mothers in the Alpha period were more likely to require admission for neonatal care compared to during the Wildtype period.

To our knowledge, this is the first national prospective cohort to compare pregnancy and perinatal outcomes by time-period according to different dominant SARS-CoV-2 variants. A key strength of these data is the existing mechanism for national case identification of all women admitted to hospital. In the UK universal SARS-CoV-2 testing for all obstetric admissions was implemented from May 2020. It is therefore a further strength that this study was restricted to those with symptomatic infection in order to minimise bias associated with universal screening. Women presenting to hospital are inherently more likely to have an adverse outcome and therefore increased adverse outcomes may be incorrectly attributed to SARS-CoV-2 rather than misclassification bias, which impacts most non-population based studies.[16] Whilst it is a limitation that women with mild infection diagnosed and treated in the

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community will not be included in this study, it is highly likely that all women with severe infection would have been captured.

A further limitation of our study is that variant sequencing data were not available for individual women, therefore proxy time periods were utilised instead. However, the Delta VOC is now known to have contributed more than 90% of all sequenced cases since 7th June 2021 so major contamination is unlikely.[17] Other time-dependent changes will exist which we cannot account for, for example varying thresholds for admission to hospital or ICU depending on clinician familiarity with managing COVID-19. In the general population, national guidance was updated in January 2021 to inform community management of those with oxygen saturations >92%.[18] However, it is unclear that this admission threshold was used extensively in pregnancy and given that the RCOG has never released national admission guidance for pregnant patients, this is unlikely to account for differences observed. Differing thresholds based on bed capacity may have been a contributory factor during the peak of the Alpha VOC when hospital pressures may have restricted admission to the most severe cases. However, this is not supported by our finding of an increased proportion of admissions primarily for COVID-19 in this time compared to the Wildtype period. In addition, current hospital pressures from COVID-19 (Delta VOC dominant) are not reported to be as high as during the second wave,[19] therefore this could explain the greater proportion of women admitted for COVID-19 in this period, but it does not explain the increase in severe outcomes observed in this study.

We have reported a potential change in the proportion of pregnant women in paid employment between periods. This may be a result of increased unemployment during this period, or an increased proportion of women from more deprived socioeconomic backgrounds. It is a limitation of this study that further information on socioeconomic circumstances could not be collected due to ethics committee requirements. This is important when considering whether disease severity can be attributed to the variant because the variant also impacts on disease transmission. For example, Alpha VOC has been shown to have a higher secondary attack

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rate and therefore factors that increase transmission, such as multi-occupancy housing and public-facing occupations, are important.[5] Since socioeconomic deprivation is also a known independent risk factor for adverse pregnancy outcome, this could be a source of residual confounding in this study.

COVID-19-specific pharmacological therapies, which are now standard care, were used infrequently, even for women that were critically unwell. Based in the interim report from the RECOVERY trial, The Royal College of Obstetricians and Gynaecologists (RCOG) recommended in June 2020 that corticosteroid therapy should be considered for all women who were clinically deteriorating.[20] Whilst usage of steroids has improved, it remains low at 14.6% during the Delta period, and whilst it was double in those critically unwell (30.8% during the Delta period) this still represents a small proportion of pregnant women being treated appropriately. The recent confidential enquiry (MBRRACE-UK)[20] into care of all pregnant and postnatal women who died with SARS-CoV-2 found that only one in ten had received treatment in accordance with the evidence-based guidance. This study highlights that pregnant woman are at increasing risk of severe disease from SARS-CoV-2.[21] Health care professionals need to be alert to the risk of deterioration and initiate management for all women in line with national guidance. Pregnant women need to be reassured about the availability and safety of effective treatments and advised to avoid delay in seeking care.

Vaccination for all pregnant women regardless of risk group in the UK was recommended by the Joint Committee on Vaccination and Immunisation (JCVI) on 16th April 2021.[22] Prior to this, vaccination has been available to pregnant women with underlying health conditions or increased risk of exposure since 31st December 2020.[23] National data from Scotland suggests that vaccine update in pregnancy is very low, with 2% of the 3603 women that delivered in May 2021 having any vaccine dose.[24] Public Health England have also recently reported that to date, 51,724 pregnant women in England have received their first dose, and of these 20,648 are fully immunised, where approximately 643,000 women give birth each year.[22] Whilst it is

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greatly reassuring that in our study there were no fully vaccinated pregnant women admitted with symptomatic SARS-CoV-2, it is a limitation that there were insufficient data to examine the impact of vaccination status on severity of infection. A survey undertaken by the RCOG in May 2021 reported that of 844 pregnant women offered vaccination, 58% had declined, predominantly due to fear over safety for the mother and baby.[25] There has been widespread misinformation regarding the safety of the vaccination in young women[26], likely fuelled by changing advice on the safety of vaccines in pregnant women when they first became available. The findings of this study strongly highlight the urgent need for an international approach to tackle this misinformation and improve uptake of the vaccine during pregnancy, potentially through change of policy to prioritise appointments for pregnant women and bring forward second doses. This is of even greater importance as Delta VOC continues to rapidly rise in both high and low-resourced settings.[27]

In conclusion, this national study has demonstrated that pregnant women admitted during the periods in which the Alpha VOC and Delta VOC are dominant, are at increased risk of moderate to severe COVID-19, resulting in admission to ICU. This is against the background of an already increased risk compared to the pregnant population without SARS-CoV-2.[1] Effective treatments are now available, but are used in only a minority of cases, even amongst those that are critically unwell. Healthcare professionals need to be aware of the increased risk of deterioration observed with Delta VOC and increase utilisation in keeping with national guidance. The absence of admission in pregnant women that have been fully vaccinated against SARS-CoV-2 supports the effectiveness of immunisation, yet vaccine uptake is reported to be low compared to the general population. Urgent action to tackle misinformation and policy change to prioritise actions to promote uptake are required, given the increasing rates of Delta VOC nationally and internationally.[28]

Data Sharing

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Data cannot be shared publicly because of confidentiality issues and potential identifiability of sensitive data as identified within the Research Ethics Committee application/approval. Requests to access the data can be made by contacting the National Perinatal Epidemiology Unit data access committee via general@npeu.ox.ac.uk.

Author Contributions

All authors contributed to conceptualisation, the writing and editing of this study, had final approval of the version to be published and agree to be accountable for all aspects of the work. KB, EM, NS, CG, PO, MQ, PB, JK and MK contributed to funding acquisition, supervision, and methodology. NV, RR, KB and MK contributed to data curation and formal analysis, and all had access to verify the underlying data.

Declarations of Interest

MK, MQ, PB, PO'B, JJK received grants from the NIHR in relation to the submitted work. KB, NV, NS, CG have no conflicts of interest to declare. EM is Trustee of RCOG, British Menopause Society and Newly Chair of the Board of Trustees Group B Strep Support.

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Table 1: Characteristics of pregnant women with confirmed symptomatic SARS-CoV-2 infection admitted to hospital in the UK during the periods in which the Wildtype, Alpha and Delta variants were dominant

Characteristic	Wildtype	Alpha	Delta
Age (years):	**N=1435 (%)**	**N=1765 (%)**	**N=171 (%)**
<20	20 (1.4)	18 (1.0)	4 (2.4)
20-34	991 (69.2)	1236 (70.2)	127 (74.7)
≥35	422 (29.5)	508 (28.8)	39 (22.9)
Missing	2	3	1
Body Mass Index (BMI) (kg/m^2):			
Underweight (<18.5)	21 (1.5)	22 (1.3)	0 (0)
Normal (18.5 to <25)	456 (33.1)	564 (33.6)	59 (37.1)
Overweight (25 to <30)	444 (32.2)	486 (28.9)	48 (30.2)
Obese (>30)	458 (33.2)	609 (36.2)	52 (32.7)
Missing	56	84	12
Either woman or partner in paid work	1142 (79.6)	1338 (75.8)	107 (62.6)
Ethnic Group			
White	707 (50.4)	1012 (58.8)	83 (51.2)
Asian	418 (29.8)	411 (23.9)	51 (31.5)
Black	177 (12.6)	179 (10.4)	16 (9.9)
Chinese/Other	71 (5.1)	71 (4.1)	9 (5.6)
Mixed	31 (2.2)	37 (2.7)	3 (1.9)
Missing	31	45	9
Current smoking	98 (7.2)	147 (8.6)	14 (8.8)
Missing	67	46	12
Pre-existing medical conditions			
Asthma	91 (6.3)	178 (10.1)	15 (8.8)
Hypertension	40 (2.8)	35 (2.0)	5 (2.9)
Cardiac disease	20 (1.4)	25 (1.4)	2 (1.2)
Diabetes	39 (2.7)	30 (1.7)	2 (1.2)
Gestational Diabetes	147 (10.2)	184 (10.4)	19 (11.1)
Multiparous	857 (60.2)	1147 (65.5)	105 (64.8)
Missing	11	15	9
Multiple pregnancy	36 (2.5)	35 (2.0)	1 (0.6)
Gestation at admission (weeks)			
<22	142 (10.0)	157 (9.0)	18 (10.7)
22-27	159 (11.2)	207 (11.9)	31 (18.3)
28-31	190 (13.3)	213 (12.2)	24 (14.2)
32-36	340 (23.9)	452 (25.9)	42 (24.9)
37 or more	594 (41.7)	717 (41.1)	54 (32.0)
Missing	10	19	2

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Table 2: Respiratory and medical support of pregnant women symptomatic of SARS-CoV-2 during the periods in which the Wildtype, Alpha and Delta variants were dominant

	Wildtype N=1435 (%)	Alpha N=1765 (%)	Delta N=171 (%)	OR Alpha vs. Wildtype (95% CI)	aOR Alpha vs. Wildtype (95% CI)	OR Delta vs. Alpha (95% CI)	aOR Delta vs. Alpha (95% CI)
Composite indicator of moderate to severe infection	350 (24.4)	631 (35.8)	77 (45.0)	1.72 (1.48-2.01)	1.75 (1.48-2.06)	1.47 (1.07-2.02)	1.53 (1.07-2.17)
Oxygen saturation measured on admission (Yes)	539 (37.6)	1255 (71.1)	132 (77.2)	NC	NC	NC	NC
Median Oxygen saturation (IQR)	98 (96-99)	97 (96-98)	97 (96-99)	NC	NC	NC	NC
Oxygen saturation <95%	54 (3.8)	185 (10.5)	17 (9.9)	NC	NC	NC	NC
Evidence of pneumonia on imaging	274 (19.1)	486 (27.5)	63 (36.8)	1.61(1.36-1.90)	1.65 (1.38-1.98)	1.54 (1.12-2.13)	1.64 (1.14-2.35)
Respiratory support required	183 (20.3)	466 (27.2)	52 (33.3)	1.47 (1.21-1.78)	1.39 (1.13-1.71)	1.34 (0.95-1.90)	1.43 (0.97-2.11)
Non-invasive oxygen (nasal canulae, mask or non-rebreathe mask at <15l/min)	107 (61.1)	292 (64.8)	29 (69.1)	REF	REF	REF	REF
High flow oxygen (>15l/min) or CPAP	28 (16.0)	71 (15.7)	11 (26.2)	0.93 (0.57-1.52)	1.04 (0.61-1.77)	1.56 (0.74-3.27)	2.01 (0.91-4.44)
Invasive Ventilation or ECMO	40 (22.9)	88 (19.5)	2 (4.5)	0.81 (0.52-1.24)	0.99 (0.61-1.59)	0.23 (0.05-0.98)	0.30 (0.07-1.30)
Level not known	8	15	10	-	-	-	-
Critical Care received	111 (7.7)	199 (11.3)	26 (15.2)	1.52 (1.19-1.94)	1.61 (1.24-2.10)	1.41 (0.91 - 2.20)	1.60 (0.99-2.59)
Maternal Death	10 (0.7)	5 (0.3)	0 (0)	NC	NC	NC	NC
Pharmacological Management Total*	99 (6.9)	253 (14.3)	28 (16.3)	2.26 (1.77-2.88)	2.37 (1.83-3.07)	1.17 (0.76-1.79)	1.35 (0.87-2.12)
Antivirals Total	43 (3.0)	33 (1.9)	3 (1.8)	NC	NC	NC	NC
Tocilizumab	0 (0)	22 (1.3)	7 (4.1)	NC	NC	NC	NC
Steroids for maternal indication	68 (4.7)	219 (12.4)	25 (14.6)	NC	NC	NC	NC
Regeneron Monoclonal Antibodies	0 (0)	6 (0.3)	0 (0)	NC	NC	NC	NC
Recruited to RECOVERY	21 (1.5)	87 (4.9)	0 (0)	NC	NC	NC	NC
Steroids for fetal lung maturation	252 (17.6)	336 (19.0)	26 (15.2)	NC	NC	NC	NC

* Any of the listed medications given for medical management of SARS-CoV-2: Antivirals, Tocilizumab, maternal steroids, monoclonal antibodies. NC=not compared. IQR = interquartile range. CPAP = continuous positive airway pressure. ECMO = extracorporeal membrane oxygenation.

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Table 3: Pregnancy outcomes for women symptomatic of SARS-CoV-2 during the periods in which the Wildtype, Alpha and Delta variants were dominant

Pregnancy outcomes	**Wildtype**	**Alpha**	**Delta**	**OR Alpha vs. Wildtype (95% CI)**	**aOR Alpha vs. Wildtype (95% CI)**	**OR Delta vs. Alpha (95% CI)**	**aOR Delta vs. Alpha (95% CI)**
	N=1435 (%)	**N=1765 (%)**	**N=171 (%)**				
Ongoing pregnancy	44 (3.1)	193 (10.9)	98 (57.3)	NC	NC	NC	NC
Pregnancy Loss	33 (2.4)	29 (1.8)	1 (1.4)	NC	NC	NC	NC
Birth	1358 (94.5)	1543 (87.4)	72 (42.1)	NC	NC	NC	NC
Gestation at birth (weeks)*							
22-27	10 .7)	22 (1.4)	0 (0)	1.99 (0.94-4.23)	2.15 (0.97-4.76)	NC	NC
28-31	45 (3.3)	57 (3.7)	6 (8.3)	1.15 (0.77-1.71)	1.20 (0.79-1.83)	NC	NC
32-36	193 (14.2)	242 (15.7)	12 (16.7)	1.14 (0.93-1.40)	1.15 (0.93-1.43)	NC	NC
37 or more	1092 (80.4)	1206 (78.2)	53 (73.6)	REF	REF	REF	REF
Median (IQR)	39 37-40)	39 (37-40)	39 (37-40)	0.97 (0.95-1.00)	0.97 (0.94-1.00)	0.99 (0.91-1.07)	0.97 (0.90-1.05)
Missing	18	16	1	-	-	-	-
Delivery expedited due to COVID-19	87 (11.7)	204 (13.9)	17 (25.4)	1.22 (0.93-1.59)	1.15 (0.87-1.53)	NC	NC
Missing	617	78	5	-	-	-	-
Mode of birth							
Pre-labour Caesarean	431 (32.0)	561 (36.7)	30 (42.3)	NC	NC	NC	NC
Caesarean after labour onset	201 (14.9)	211 (13.8)	6 (8.5)	NC	NC	NC	NC
Operative vaginal	150 (11.2)	139 (9.1)	8 (11.3)	NC	NC	NC	NC
Unassisted vaginal	563 (41.9)	616 (40.3)	27 (38.0)	NC	NC	NC	NC
Missing	13	16	1	-	-	-	-

* Excluding pregnancy loss. NC=not compared. IQR = interquartile range.

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Table 4: Perinatal outcomes for women symptomatic of SARS-CoV-2 during the periods in which the Wildtype, Alpha and Delta variants were dominant

Perinatal outcomes	Wildtype	Alpha	Delta	OR Alpha vs. Wildtype (95% CI)	aOR Alpha vs. Wildtype (95% CI)	OR Delta vs. Alpha (95% CI)	aOR Delta vs. Alpha (95% CI)
	N=1393 (%) *	N=1571 (%)	N=72 (%)				
Stillbirth	15 (1.1)	17 (1.1)	1 (1.4)	1.00 (0.50-2.02)	0.93 (0.44-2.00)	NC	NC
Livebirth	1376 (98.9)	1554 (98.9)	71 (98.6)	NC	NC	NC	NC
Admission to Neonatal Unit	257 (18.7)	342 (22.0)	16 (22.5)	1.22 (1.02-1.47)	1.23(1.01-1.48)	NC	NC
Neonatal Death	5 (0.4)	1 (<0.1)	0 (0)	NC	NC	NC	NC

* Two women with singleton pregnancies known to have given birth but lost to follow up and were excluded from the denominator of this column. NC=not compared.

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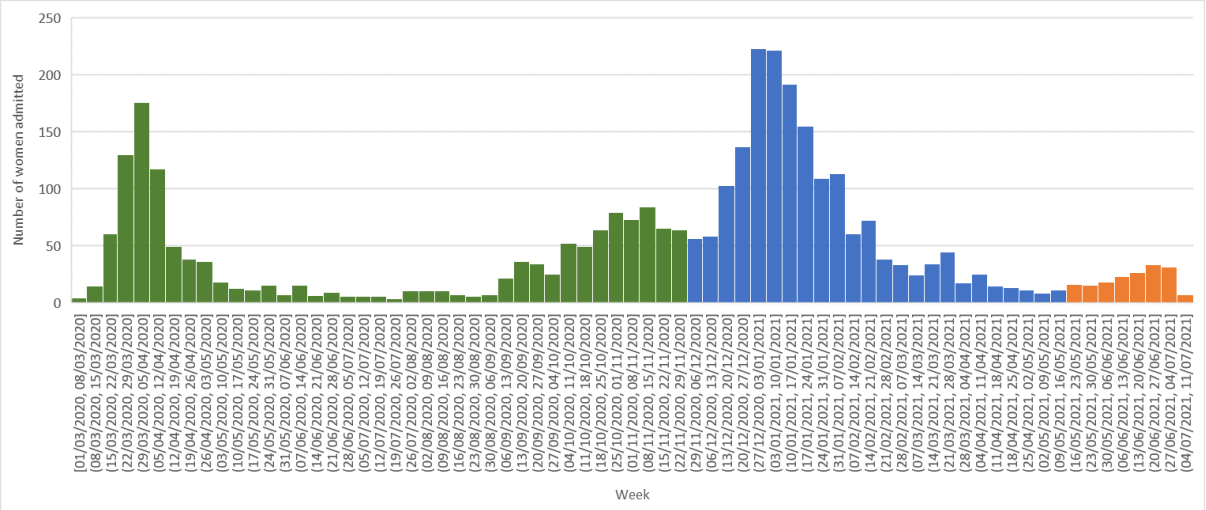
Figure 1: Admissions of pregnant women with symptomatic confirmed SARS-CoV-2 to UK hospitals during Wildtype (01/03/20-30/11/2 2020, Green), Alpha (01/12/20 – 15/05/21, Blue) and Delta periods (16/05/21-11/07/21, Orange)



Annex 4: Knight et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study

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Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study

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ABSTRACT

OBJECTIVES

To describe a national cohort of pregnant women admitted to hospital with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the UK, identify factors associated with infection, and describe outcomes, including transmission of infection, for mothers and infants.

DESIGN

Prospective national population based cohort study using the UK Obstetric Surveillance System (UKOSS).

SETTING

All 194 obstetric units in the UK.

PARTICIPANTS

427 pregnant women admitted to hospital with confirmed SARS-CoV-2 infection between 1 March 2020 and 14 April 2020.

MAIN OUTCOME MEASURES

Incidence of maternal hospital admission and infant infection. Rates of maternal death, level 3 critical care unit admission, fetal loss, caesarean birth, preterm birth, stillbirth, early neonatal death, and neonatal unit admission.

RESULTS

The estimated incidence of admission to hospital with confirmed SARS-CoV-2 infection in pregnancy was 4.9 (95% confidence interval 4.5 to 5.4) per 1000 maternities. 233 (56%) pregnant women admitted to hospital with SARS-CoV-2 infection in pregnancy were from black or other ethnic minority groups, 281 (69%) were overweight or obese, 175 (41%) were aged 35 or over, and 145 (34%) had pre-existing comorbidities. 266 (62%) women gave birth or had a pregnancy loss; 196 (73%) gave birth at term. Forty one (10%) women admitted to hospital needed respiratory support, and five (1%) women died. Twelve (5%) of 265 infants tested positive for SARS-CoV-2 RNA, six of them within the first 12 hours after birth.

CONCLUSIONS

Most pregnant women admitted to hospital with SARS-CoV-2 infection were in the late second or third trimester, supporting guidance for continued social distancing measures in later pregnancy. Most had good outcomes, and transmission of SARS-CoV-2 to infants was uncommon. The high proportion of women from black or minority ethnic groups admitted with infection needs urgent investigation and explanation.

STUDY REGISTRATION

ISRCTN 40092247.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Published evidence on transmission, incidence, and effect of SARS-CoV-2 infection in mothers and their babies remains limited mainly to reports of single cases or small case series

Evidence from other similar viral illnesses suggest that pregnant women are at greater risk of severe maternal and neonatal morbidity and mortality

Cases of transmission of SARS-CoV-2 infection to the neonate have been reported, but how frequent this is on a population basis is unclear

WHAT THIS STUDY ADDS

More than half of pregnant women admitted to hospital with SARS-CoV-2 infection in pregnancy were from black or other ethnic minority groups

Most women did not have severe illness, and most were admitted in the third trimester of pregnancy

Transmission of infection to infants of infected mothers may occur but is uncommon

Introduction

The World Health Organization declared a global pandemic of coronavirus disease 2019 (covid-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in March 2020.[1] As the number of confirmed cases increases, evidence on the transmission, incidence, and effect of SARS-CoV-2 infection in mothers and their babies remains limited. Pregnant women are not thought to be more susceptible to the infection than the general population.[2 3] However, changes to the immune system mean that pregnant women may be more vulnerable to severe infection.[4] Evidence from other similar viral illnesses, such as influenza A/H1N1,[5-8] severe acute respiratory syndrome,[9] and Middle East respiratory syndrome,[10 11] suggest that pregnant women are at greater risk of severe maternal and neonatal morbidity and mortality. Some evidence suggests that the risk of critical illness may be greatest in the later stages of pregnancy.[5 10 11]

To the best of our knowledge, as of 12 May 2020 more than 90 scientific reports of SARS-CoV-2 infection in pregnancy had been published in English,[2 10 12 13] none of which was population based. Most reported cases occurred in the third trimester, and around half of women gave birth during the acute infection episode. Most women were delivered by caesarean section, predominantly for maternal indication, although at least three studies reported cases of fetal distress.[13-17] Most women developed mild or moderate symptoms including cough, fever, and breathlessness, and only a small number developed severe disease.[15 16 18-21]

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Risk factors are suggested to mirror those in the general population, with a high proportion of women with severe covid-19 having a raised body mass index or comorbidities such as pulmonary conditions (25%) or pre-existing cardiac disease (17%).[15 17]

Evidence suggests that severe covid-19 in pregnancy is associated with iatrogenic preterm delivery (75%), predominantly for maternal indication and in the third trimester.[17] Most neonates born to mothers with confirmed SARS-CoV-2 infection were asymptomatic and discharged home well. A small number of neonates had symptoms, with a minority needing admission to neonatal specialist care[14 15]; only in a few instances have neonates had positive tests for SARS-CoV-2 following delivery.[22-25] Three neonates had elevated serum IgM antibodies identified shortly after birth in umbilical blood, but SARS-CoV-2 was not identified in any of these infants in the neonatal period despite testing.[23 25] These three infants had no symptoms, so the significance of vertical transmission remains unknown.

The aim of this study was to describe, on a population basis, characteristics and outcomes of pregnant women admitted to hospital with SARS-CoV-2 in the UK, in order to inform ongoing guidance and management. This study was designed in 2012 and hibernated pending a pandemic; it was activated by the UK Department of Health and Social Care as an urgent public health study in response to the SARS-CoV-2 pandemic.

Methods

We did a national prospective observational cohort study using the UK Obstetric Surveillance System (UKOSS).[26] UKOSS is a research platform that collects national population based information about specific severe complications of pregnancy from all 194 hospitals in the UK with a consultant led maternity unit. We asked nominated reporting clinicians to notify us of all pregnant women with confirmed SARS-CoV-2 infection admitted to their hospital, using a live reporting link specific to each individual reporter. For the purposes of this study, we defined confirmed maternal infection as detection of viral RNA on polymerase chain reaction testing of blood or a nasopharyngeal swab, respiratory compromise in the presence of characteristic radiographic changes of covid-19, or both. At the time covered by the study, women were tested only if they had symptoms of SARS-CoV-2 infection. We defined neonatal infection as detection of viral RNA on polymerase chain reaction testing of blood or a nasopharyngeal swab or aspirate. The process of data collection was enabled by research midwives and nurses from the UK's National Institute of Health Research Clinical Research Network following its adoption as an urgent public health priority study.[27] In addition, we sent nominated clinicians a reporting email at the end of the month to ensure that all cases had been reported and to confirm zero reports (active negative surveillance). After notification, we asked clinicians to complete an electronic data collection form containing details of each woman's characteristics, management, and outcomes. Reporters who had not returned data were contacted by email at weeks one, two, and three after notification. This analysis reports characteristics and outcomes of women who were notified as admitted to hospital between 1 March and 14 April 2020 and for whom complete data had been received by 29 April 2020.

We defined body mass index on the basis of the first recorded weight in pregnancy and gestational age according to the final estimated date of delivery based on ultrasound assessment. Ethnic group was based on women's self-report, as recorded in medical records. We cross checked data on maternal and perinatal deaths with data from the MBRRACE-UK collaboration, the organisation responsible for maternal and perinatal death surveillance in the UK.[28]

Sample size and statistical analysis

In this national observational study, the study sample size was governed by the disease incidence, so we did no formal power calculation. We calculated the incidence of admission to hospital with confirmed SARS-CoV-2 infection in pregnancy and among population subgroups by using denominator estimates based on the most recently available (2018) national maternity data for the constituent countries of the UK and National Maternity and Perinatal Audit data from 2016-17 for body mass index groups. We present numbers, proportions, and risk ratios with 95% confidence intervals. Continuous data are summarised as medians with interquartile ranges. We did a sensitivity analysis excluding women from London, the West Midlands, and the North West of England to explore the proportion of women from black and minority ethnic groups admitted with SARS-CoV-2 in pregnancy outside of the major urban centres. We used Stata version 15 for statistical tabulation and analyses.

Study registration

The study is registered with ISRCTN, number 40092247, and is still open to case notification. The study protocol is available at https://www.npeu.ox.ac.uk/ukoss/current-surveillance/covid-19-in-pregnancy.

Patient and public involvement

Patients and the public were involved in the design of the study, and, as part of the UKOSS Steering Committee, in the conduct of the study and interpretation of the result.

Results

We received responses from all 194 hospitals with obstetric units in the UK. From 1 March to 14 April 2020, 630 women admitted to hospital with confirmed SARS-CoV-2 infection in pregnancy were notified in the UK, among an estimated 86 293 maternities. Data were returned for 579 (92%) women; 15 were duplicate cases, 35 were reported in error, 87 had the diagnosis made as outpatients and were not admitted overnight, nine had no positive polymerase chain reaction test

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and no evidence of pneumonitis on imaging, and six had no evidence of infection during pregnancy, leaving 427 pregnant women admitted to hospital with confirmed SARS-CoV-2 across the UK. This represents an estimated incidence of hospital admission of 4.9 (95% confidence interval 4.5 to 5.4) pregnant women per 1000 maternities.

Women had symptoms at a median of 34 (interquartile range 29-38) completed weeks' gestation, with most women admitted to hospital having symptoms in the third trimester of pregnancy or peripartum (342/424; 81%). The most common symptoms reported by women were fever, cough, and breathlessness (fig 1). Table 1 shows the characteristics of the women. In the sensitivity analysis excluding women from London, the West Midlands, and the north west of England, 75 (46%) of 162 women admitted were from black and minority ethnic groups. The incidence of admission with confirmed SARS-CoV-2 infection in pregnancy seemed to vary according to women's ethnic group, age, and body mass index (table 2).

Two hundred and sixty six (62%) women admitted to hospital gave birth or had a pregnancy loss; the remaining 161 (38%) women had ongoing pregnancies at the time of this analysis. Forty one (10%) women needed level 3 critical care; four of these women received extracorporeal membrane oxygenation (table 3). Of the women who received critical care, 33 (80%) had been delivered, 27 (66%) of them owing to worsening respiratory condition; eight (20%) were still pregnant. All eight (100%) of the women who were still pregnant after their critical care admission had been discharged. Nineteen (58%) of the 33 postnatal women had been discharged at the time of this analysis; three women admitted to critical care had died, and 11 (33%) were still inpatients, of whom seven (64%) remained in critical care. Overall, five women who were admitted with confirmed SARS-CoV-2 died, a case fatality of 1.2% (95% confidence interval 0.4% to 2.7%) and a SARS-CoV-2 associated maternal mortality rate of 5.8 (1.9 to 13.5) per 100 000 maternities. Three women died as a direct result of complications of covid-19 and two from other causes. In total, 25 (6%) women, 7 (28%) antenatal and 18 (72%) postnatal, were still inpatients at the time of this analysis.

Nine (2%) women were treated with an antiviral agent. Eight of them were given oseltamivir, one of whom also received lopinavir/ritonavir. One woman was given remdesivir. All women managed with antivirals were discharged home. Sixty four (15%) women were given corticosteroids for fetal lung maturation, of whom 47 (73%) had given birth. Thirteen (20%) of these 64 women remained as inpatients, 12 (92%) of whom had given birth.

Four women (0.9% of those admitted; 4.6 (1.3 to 11.2) per 100 000 maternities) had a miscarriage, at a range of 10 to 19 weeks' gestation. Of the 262 women who had given birth, 196 (75%) gave birth at term (table 4). Sixty six women gave birth preterm; 53 (80%) had iatrogenic preterm births, 32 (48%) due to maternal covid-19, nine (14%) due to fetal compromise, and 12 (18%) due to other obstetric conditions. Fifty nine per cent of women (n=156) had a caesarean delivery, but most of the caesarean births occurred for indications

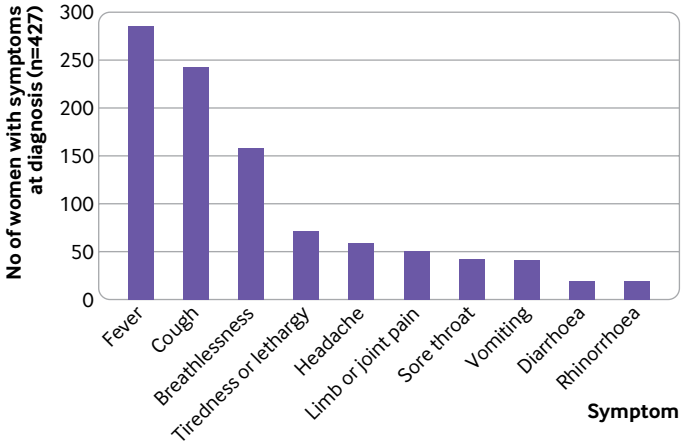

Fig 1 | Maternal symptoms at diagnosis of covid-19

Table 1 | Characteristics of pregnant women with confirmed SARS-CoV-2 infection for whom data were available, UK, 1 March to 14 April 2020

Characteristic	No (%)* of women (n=427)
Age, years:	
<20	4 (1)
20-34	248 (58)
≥35	175 (41)
Body mass index:	
Normal	126 (31)
Overweight	141 (35)
Obese	140 (34)
Missing data	20
Woman and/or partner in paid work	343 (80)
Black or other minority ethnic group (all)	233 (56)
Asian	103 (25)
Black	90 (22)
Chinese/other	30 (7)
Mixed	10 (2)
Missing data	10
Current smoking	20 (5)
Missing data	8
Pre-existing medical problems	145 (34)
Asthma	31 (7)
Hypertension	12 (3)
Cardiac disease	6 (1)
Diabetes	13 (3)
Multiparous	263 (62)
Missing data	4
Multiple pregnancy	8 (2)
Gestational diabetes	50 (12)
Gestation at symptom onset, weeks:	
<22	22 (5)
22-27	60 (14)
28-31	64 (15)
32-36	106 (25)
≥37	142 (33)
Peripartum	30 (7)
Missing data	3

*Percentages of those with complete data.

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Table 2 | Estimated incidence of admission with SARS-CoV-2 infection in pregnancy among different population subgroups

Characteristic	Estimated No of maternities	No of pregnant women admitted with SARS-CoV-2	Incidence per 1000 maternities	Rate ratio (95% CI)
Age*, years:				
<20	2532	4	1.6	0.4 (0.1 to 1.1)
20-34	63 768	248	3.9	1 (reference)
≥35	19 992	175	8.8	2.3 (1.8 to 2.7)
Body mass index†:				
Normal (<25)	36 377	126	3.5	1 (reference)
Overweight (25 to <30)	20 836	141	6.8	2.0 (1.5 to 2.5)
Obese (≥30)	16 154	140	8.7	2.5 (2.0 to 3.2)
Ethnic group (England only)‡:				
White	49 282	173	3.5	1 (reference)
Asian	7400	103	13.9	4.0 (3.1 to 5.1)
Black	3135	89	28.4	8.1 (6.2 to 10.5)
Chinese/other	2960	28	9.5	2.7 (1.7 to 4.0)
Mixed	1304	9	6.9	2.0 (0.9 to 3.8)

*Estimated number of maternities based on number of maternities in UK occurring during March and 14/30 of April 2018. Four women with unknown age excluded from denominator.
†Estimated number of maternities based on number of maternities in GB during March and 14/30 of April in year April 2016 to 31 March 2017. Women with unknown body mass index excluded from both numerator (20) and denominator (12 291).
‡Estimated number of maternities based on number of maternities in England occurring during March and 14/30 of April 2018. Women with unknown ethnicity excluded from both numerator (10) and denominator (7996).

other than maternal compromise due to SARS-CoV-2 infection. Forty two women (27% of those who had a caesarean birth) had a caesarean birth for reasons of maternal compromise, 37 (24%) due to concerns about fetal compromise, 30 (19%) due to failure to progress in labour or failed induction of labour, 25 (16%) for other obstetric reasons, 16 (10%) because of previous caesarean birth, and 6 (4%) at maternal request. Twenty nine (19%) women had general anaesthesia for their caesarean birth; 18 (62%) of these women were intubated because of maternal respiratory compromise, and 11 (38%) were intubated to allow for urgent delivery.

Five babies died; three were stillborn and two died in the neonatal period. Three deaths were unrelated to SARS-CoV-2 infection and were due to obstetric conditions unrelated to SARS-CoV-2 infection and/or pre-existing fetal conditions; for two stillbirths, whether SARS-CoV-2 contributed to the death was unclear. Sixty seven (25%) of 265 liveborn infants were admitted to a neonatal unit, 50 (75%) of whom were preterm, including 23 (34%) who were less than 32 weeks' gestation (table 5). One infant was diagnosed as having neonatal encephalopathy (grade 1) after a spontaneous vaginal birth at term. Twelve (5%) infants of women admitted to hospital with infection tested positive for SARS-CoV-2 RNA, six of them within the first 12 hours after birth. Two of the six infants with early onset SARS-CoV-2 infection were from unassisted vaginal births; four were born by caesarean, three of which were pre-labour. No viral analyses were performed on umbilical cord blood, placenta, or vaginal secretions. The six infants who developed later infection were born by pre-labour caesarean (n=4) and vaginal birth (n=2). Only one of the infants with an early positive test for SARS-CoV-2 RNA was admitted to a neonatal unit, compared with five infants with a later positive test.

Table 3 | Hospital outcomes and diagnoses among women with confirmed SARS-CoV-2 infection in pregnancy

Maternal outcomes	No (%) of women (n=427)
Needed critical care	41 (10)
Needed extracorporeal membrane oxygenation	4 (1)
SARS-CoV-2 pneumonia on imaging	104 (24)
Final outcome:	
Died	5 (1)
Discharged well	397 (93)
Still in hospital	25 (6)

Discussion

The clinical data from this national surveillance study show that one in 10 pregnant women admitted to hospital in the UK with SARS-CoV-2 infection needed respiratory support in a critical care setting, and one in 100 died. More than half of pregnant women admitted to hospital with SARS-CoV-2 infection in pregnancy were from black or other ethnic minority groups, 70% were overweight or obese, 40% were aged 35 or over, and a third had pre-existing comorbidities. More than half of all women admitted with SARS-CoV-2 infection had given birth at the time of the analysis; 12% were delivered preterm solely because of maternal respiratory compromise. Almost 60% of women gave birth by caesarean section; most caesarean births were for indications other than maternal compromise due to SARS-CoV-2 infection. One in 20 of the babies of mothers admitted to hospital subsequently had a positive test for SARS-CoV-2; half had infection diagnosed on samples taken at less than 12 hours after birth.

Strengths and limitations of study

A major strength of this study is the design using the population based UKOSS research platform and thus the identification of a comprehensive, national cohort of infected pregnant women with high case ascertainment across all obstetric units in the UK. However, this

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Table 4 | Pregnancy and infant outcomes among pregnant women with confirmed SARS-CoV-2 infection

Pregnancy outcomes	No (%) of women (n=427)
Ongoing pregnancy	161 (38)
Pregnancy completed	266 (62)
Pregnancy loss	4 (1)
Stillbirth	3 (1)
Live birth (including six women who gave birth to twins)	259 (97)
Neonatal death	2 (1)
Gestation at end of pregnancy, weeks:	
<22	4 (2)
22-27	6 (2)
28-31	17 (6)
32-36	43 (16)
≥37	196 (74)
Median (interquartile range)	38 (36-40)
Mode of birth*:	
Caesarean, maternal indication due to SARS-CoV-2	42 (16)
Caesarean, other indication	114 (44)
Operative vaginal	28 (11)
Unassisted vaginal	78 (30)

*Excluding four women with pregnancy losses.

rapid report has been produced at a time when active transmission of SARS-CoV-2 is still occurring, with around 100 pregnant women admitted to hospital in the UK with infection each week, and the limitations of these data must therefore be recognised. We do not yet have complete pregnancy outcomes for women who were admitted but subsequently discharged well, and several women were still inpatients at the time of writing. The data collected for this rapid national cohort study were restricted to essential items, so we do not have daily indicators of women's clinical condition or results of blood and other tests. We sought to collect national, population based information on severe SARS-CoV-2 infection, defined as hospital admission, to capture the incidence and outcomes of severe disease in pregnancy. This study does not therefore provide any information about overall infection rates or the possibility of asymptomatic infection. Nevertheless, this study shows the strength of systems such as UKOSS, which can be rapidly activated to do comprehensive population based studies such as this in a public health emergency. UKOSS studies were activated for influenza A/H1N1 and Zika virus in pregnancy[29 30]; countries in the International Network of Obstetric Survey Systems (INOSS)[31] are also doing similar national studies to allow for the unification of population based data across multiple countries and avoiding the biases of data collected through centre based registries. The National Institute for Health Research's Clinical Research Network,[32] with midwifery and obstetric leads coordinating networks of research staff, was another strength of this study, helping to ensure rapid and accurate collection of these valuable data even in the context of the pressurised health system in a pandemic. UKOSS is the only national research platform in the UK for conducting such studies, and it should be noted that all other reports of women admitted to hospital with SARS-CoV-2 in pregnancy in the UK will be subsets of UKOSS data.

Table 5 | Infant outcomes among liveborn babies of women with confirmed SARS-CoV-2 infection in pregnancy

Infant outcomes	No (%) of liveborn infants of women with SARS-CoV-2 (n=265)*
Neonatal unit admission	67 (25)
Positive SARS-CoV-2 test (liveborn infants only):	
No	253 (95)
Positive test <12 hours of age	6 (2)
Positive test ≥12 hours of age	6 (2)

*Includes six sets of twins.

Comparison with other studies

The addition of these national, population based data to existing reports provides clarity on the outcomes of infection in pregnant women. Previous published information has been largely based on case series from individual hospitals or cases identified across small series of hospitals but with a lack of clarity about the proportion of cases ascertained, with problems of overlap and duplicate reporting; population based data are essential to provide unbiased information on incidence and outcomes. During the period when these data were collected, around 90 000 women gave birth in the UK; 427 were notified as having been admitted with SARS-CoV-2 in pregnancy—fewer than one woman admitted for every 200 women giving birth. Approximately one woman per 2400 giving birth needed critical care admission. The overall maternal mortality rate with confirmed SARS-CoV-2 infection was around one in 18 000 women giving birth. The rates of critical care unit admission and mortality among pregnant women admitted to hospital with SARS-CoV-2 infection are comparable to the rates among the general population of women of reproductive age admitted to UK hospitals with infection, of whom 20-35% receive critical care and 1-4% die.[33]

The high proportion of women from black and other minority ethnic groups admitted to hospital with SARS-CoV-2 in pregnancy is of concern and should be investigated further. Our sensitivity analysis suggests that this cannot simply be explained by a higher incidence in the main metropolitan areas with higher proportions of women from ethnic minority groups, as the high proportion remained when we excluded women from London, the West Midlands, and the north west of England. Ethnic disparities in incidence and outcomes have been noted among non-pregnant populations with SARS-CoV-2 infection, notably in the US,[34] and various possible reasons have been suggested for these observed disparities, including social behaviours, health behaviours, comorbidities, and potentially genetic influences.[35] It should be noted that over-representation of ethnic minority and other groups among the cohort of pregnant women admitted with SARS-CoV-2 infection may reflect a higher risk of infection, a higher risk of severe disease given infection among vulnerable subgroups, or both. Health system factors have been suggested to underlie the disparity in the US; the fact that these disparities exist in a country with a universal free to access healthcare

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system indicate that the health system cannot be the sole explanation.

In common with previous reports, most women admitted to hospital with SARS-CoV-2 infection in pregnancy were in the late second or third trimester, which replicates the pattern seen for other respiratory viruses with women in later pregnancy being more severely affected. This supports the current guidance for strict social distancing measures among pregnant women, particularly in their third trimester.[2] It should be noted, however, that higher hospital admission rates in the third trimester were also reported in the context of influenza,[36] and thought to be for precautionary reasons, rather than necessarily because of maternal compromise. Although case notification has been augmented through a link with the UK Early Pregnancy Surveillance System (UKEPSS),[37] the route of identification of the women included in this series, through UK obstetric units, could also have led to under-ascertainment of women admitted in the early stages of pregnancy.

Outcomes for infants are largely reassuring when considering potential effects of SARS-CoV-2 infection acquired before or during birth; the small number of early polymerase chain reaction positive infants of mothers with infection did not have evidence of severe illness. This observation of only mild disease has also been reflected in early case reports of infant infection in the perinatal period.[22-25] Nevertheless, 2% of infants did have evidence of viral RNA in a sample taken within 12 hours of birth, which suggests that mother-to-infant viral transmission may be occurring. We have no evidence as to whether IgM was raised in these infants or whether viral transmission occurred in utero, during delivery via an infected birth canal, or postpartum via respiratory droplets, skin-to-skin contact, or breast feeding, but three infants had a positive test for SARS-CoV-2 following pre-labour caesarean section. We do not have information on whether these infants were isolated from the mother immediately after delivery, nor whether skin-to-skin contact was permitted. Using a recently suggested classification system,[38] we therefore do not have sufficient evidence to suggest that these were congenitally acquired infections; they should be classified as possible neonatally acquired infections. During the study period, UK guidance for postnatal management of infants born to mothers with confirmed or suspected SARS-CoV-2 infection was to keep mother and infant together and to encourage breast feeding with consideration of using a fluid resistant surgical face mask for the mother. These findings emphasise the importance of infection control measures around the time of birth and support the advice given by WHO around precautions to take while breast feeding.

We did this study in a high resource setting with universal healthcare free at the point of access, and findings would therefore be generalisable to similar settings. The fact that most women experience mild infection would suggest that outcomes are likely to be good in settings with less well developed health systems. However, given the proportion of women admitted who needed critical care, the outcomes of severe infection will probably be poorer in the absence of such facilities.

Conclusions

In the context of the covid-19 pandemic, ongoing collection of data on the outcomes of infection during pregnancy will remain important. Unanswered questions remain about the extent and effect of asymptomatic or mild infection. Serological studies, as well as those using retrospective data to identify women with either confirmed or presumed mild infection in pregnancy, will be essential to fully assess potential effects such as congenital anomalies, miscarriage, or intrauterine fetal growth restriction. Nevertheless, these data suggest that most women do not have severe illness and that transmission of infection to infants of infected mothers can occur but is uncommon.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: MK, MQ, PB, POB, and JJK received grants from the NIHR in relation to the submitted work; EM is trustee and president of the Royal College of Obstetricians and Gynaecologists, trustee of the British Menopause Society, and chair of the Multiprofessional Advisory Committee, Baby Lifeline; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the HRA NRES Committee East Midlands – Nottingham 1 (reference 12/EM/0365).

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Data sharing: Data from this study will be shared according to the National Perinatal Epidemiology Unit Data Sharing Policy available at https://www.npeu.ox.ac.uk/downloads/files/npeu/policies/Data%20Sharing%20Policy.pdf

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Dissemination to participants is not possible as this study collected anonymous data only. Dissemination to women, families, and healthcare practitioners will be undertaken via social media and the programme website (https://www.npeu.ox.ac.uk/ukoss/publications-ukoss) and through summary articles for professional and third sector organisations.

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Annex 5: Melbourne Children's Campus

Weekly COVID-19
Vaccine Updates
Number 29, 14 October 2021

Weekly COVID-19 Vaccine Updates

Number 29, 14 October 2021

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Introduction

This document summarises the vaccine efficacy and effectiveness, the vaccine specifications, the vaccine development pipeline and the timeline for World Health Organization (WHO) review of the various COVID-19 vaccines in late phase development. This document is updated weekly.

- Vaccine efficacy refers to the performance of a vaccine in a controlled clinical trial (study) situation
- Vaccine effectiveness refers to the performance of a vaccine in a population under real-world conditions

Key messages

- COVID-19 vaccine efficacy results from different trials cannot be directly compared against each other. They must be interpreted in the context of study designs (including case definitions, clinical endpoints, access to testing), target populations, and COVID-19 epidemiologic conditions (including circulation of variants of concern)
- All COVID-19 vaccines in late phase development report high vaccine efficacy against severe COVID-19 and favourable safety profiles
- Pfizer/BioNTech and AstraZeneca both have high vaccine effectiveness against the Delta variant and both vaccines are similarly effective against transmission in the UK. Sinovac has shown high vaccine effectiveness in Chile where the Gamma and Alpha variants are circulating. Sinopharm has shown high vaccine effectiveness in Bahrain and several vaccines have shown effectiveness against mortality in infected adults in Bahrain: Unvaccinated: 1.32% mortality (857 deaths); Sinopharm: 0.46% (112 deaths); Pfizer/BioNTech: 0.15% (3 deaths); Sputnik: 0.09 (3 deaths); AstraZeneca: 0.03% (1 death).[1] The Johnson & Johnson and Moderna vaccines have both shown good vaccine effectiveness against infection in the US. One or 2 doses of the Moderna vaccine is effective against the Alpha variant in Canada, and a single dose is effective against infection and very effective against severe disease with the Delta variant.
- The US FDA, UK MHRA, EU EMA, NZ Medsafe, Health Canada and the Australian TGA have authorised the Pfizer/BioNTech vaccine for emergency use in adolescents aged 12-15 years.[2–6] The EMA, MHRA and TGA have also authorised the Moderna vaccine in this age group.[7–9]
- WHO SAGE recommends that 1) immunocompromised persons should be offered an additional dose of all WHO EUL COVID-19 vaccines as part of an extended primary series; and 2) following the Sinovac and Sinopharm inactivated vaccines, a third dose of the same vaccine or a different vaccine should be offered as part of an extended primary series.[10] Australia is recommending that immunocompromised persons receive a third dose.[11] Several countries, including the US and UK, are offering boosters to older age groups and at-risk groups.[12,13]
- Mixed vaccine schedules (i.e. delivering different types of vaccine for the first and second dose) are under investigation as these could facilitate better protection against variants of concern and enable vaccination programs to continue if a particular vaccine is unavailable
- Seven intranasal vaccines are in development (6 live-attenuated viruses or virus-vectored vaccines; 1 protein subunit.[14] These may be beneficial in preventing transmission (Page 15)
- A very rare clotting disorder with low platelets (Thrombosis with Thrombocytopaenia Syndrome – TTS) has been associated with the AstraZeneca and Johnson & Johnson vaccines.[15–17] The majority of cases fully recover with adequate treatment. The risk following the first dose of AstraZeneca vaccine has been estimated by the EMA as 1 in 100,000 and by the Australian Technical Advisory Group on Immunisation (ATAGI) as 1 in 50,000.[18,19] Risk of TTS is much lower following the *second* dose of AstraZeneca vaccine: estimate in the UK is 1 in 1.5 million second doses.[20]
- The risk of TTS following the first dose of Johnson & Johnson vaccine has been estimated as 1 in 319,000 in the USA[21]
- The risk of myocarditis/pericarditis is increased following the second dose of Pfizer/BioNTech and Moderna vaccines, particularly in younger males, occurring in >1 in 20,000 males under 25 years of age.[22] Highest rate in in males 16-17 years of age following Pfizer/BioNTech vaccine but no clear difference in risk between Moderna and Pfizer/BioNTech.[23] There is a small increase in risk of myocarditis in females <30 and males >50 years of age. Data from Ontario, Canada, and the UK suggest higher rates following Moderna than Pfizer/BioNTech vaccine. ATAGI in Australia continue to review the data.
- Appropriate communication on the benefit-risk profile of COVID-19 vaccines (Page 13) remains crucial to maintain confidence in immunisation programmes and to avoid vaccine hesitancy.

New updates

Key updates include *(also highlighted in yellow text in the document)*:

- Effectiveness of Moderna vaccine against Delta in USA (Page 6, 7, 10, 23, 24 and 25):
  - Infection:
    - Overall: 86.7% (84.3-88.7)
    - 14-60 days after vaccination: 94.1% (90.5-96.3)
    - 151-180 days after vaccination: 80.0% (70.2-86.6)
    - 18-64 years: 87.9% (85.5-89.9)
    - ≥65 years: 75.2% (59.6-84.8)
  - Hospitalisation:
    - 97.6% (92.8-99.2)
- Effectiveness against any infection in the UK (Pages 6, 7 and 23):
  - Pfizer/NBioNTech
    - Alpha: 78% (68-84)
    - Delta: 80% (77-83)
    - Delta 14 days post-second dose: 85% (79-90)
    - Delta 90 days post-second dose: 75% (70-80)
  - AstraZeneca
    - Alpha: 79% (56-90)
    - Delta: 67% (62-71)
    - Delta 14 days post-second dose: 68% (61-73)
    - Delta 90 days post-second dose: 61% (53-68)
- Decline in effectiveness of the Moderna vaccine beyond the fourth month after the second dose in Qatar; effectiveness against severe or critical disease was maintained to 6 months, with possible drop after 7 months (Pages 6, 10 and 23):
  - Any infection
    - First month after second dose: 77.5% (76.4-78.6)
    - ≥7 months: 22.3% (−1.7-40.7)
  - Symptomatic infection
    - First month after second dose: 81.5% (79.9-83.0)
    - ≥7 months: 27.8% (−1.4-48.7)
  - Asymptomatic infection
    - First month after second dose: 73.1% (70.3-75.5)
    - ≥7 months: −33.3% (−181.8-36.9)
  - Hospitalisation and Death:
    - First month after second dose: 96.0% (93.9-97.4)
    - ≥7 months: 55.6% (−44.3-86.3)
- Updated data on protection from Pfizer/BioNTech boosters in Israel between 30 July and 6 October:
  - Rate ratios in non-booster group vs at least 12 days post-booster:
    - Infection: ~10 (ranging 8.8-17.6 across five age groups)
    - Severe disease 40-59 years: 22.0 (10.3-47.0)
    - Severe disease ≥60 years: 18.7 (15.7-22.4)
    - Death ≥60 years: 14.7 (9.4-23.1)
- New WHO SAGE recommendations related to third vaccine doses:
  - Immunocompromised persons should be offered an additional dose of all WHO EUL COVID-19 vaccines as part of an extended primary series
  - Following the Sinovac and Sinopharm inactivated vaccines, a third dose of the same vaccine or a different vaccine should be offered to persons aged ≥60 years as part of an extended primary series
  - A priority is to use available vaccine to vaccinate high-risk populations and 70% of the world's population by mid-2022
- ATAGI in Australia has recommended a third primary dose of COVID-19 vaccine in individuals who are severely immunocompromised
- The FDA has recommended that those who received Moderna's COVID-19 vaccine should get a half-dose booster
- Third dose recommendations have been added to the COVID-19 Vaccine Specifications table (Page 4)
- Homologous and heterologous third dose boosters of Pfizer/BioNTech, Moderna and Johnson & Johnson vaccines in the US were well-tolerated and immunogenic in adults who completed primary vaccination at least 12 weeks earlier (Page 11)
  - Homologous boosters increased neutralising antibody titres 4.2 to 20-fold
  - Heterologous boosters increased neutralising antibody titres 6 to 76-fold

COVID-19 Vaccine Specifications

	ASTRAZENECA	GAMALEYA	JOHNSON & JOHNSON	MODERNA	NOVAVAX	PFIZER/ BIONTECH	SINOVAC	SINOPHARM	BHARAT BIOTECH	CLOVER
VACCINE TYPE	Viral vector (chimpanzee adenovirus ChAdOx1)	Viral vector (recombinant adenovirus types 5 and 26)	Viral vector (recombinant adenovirus type 26)	mRNA	Protein subunit	mRNA	Inactivated virus	Inactivated virus	Inactivated virus	Protein
Available Through COVAX	✓	-	✓	-	✓	✓	-	-	-	-
Doses Required	4-12 weeks apart	3 weeks apart		4 weeks apart*	3 weeks apart	3-4 weeks apart*	2-4 weeks apart*	3-4 weeks apart*	3 weeks apart	3 weeks apart
Third dose/ boosters	As part of primary series for those with immunocomp.	-	As part of primary series for those with immunocomp.	As part of primary series for those with immunocomp.	-	As part of primary series for those with immunocomp.	As part of primary series for ≥60 years	As part of primary series for ≥60 years	-	-
Shipping, Storage & Presentation	Normal cold chain requirements (2-8°C); 10-dose vials	-18.5°C (liquid form); 2-8°C (dry form)	Shipped at -20°C; 2-8°C for up to 3 months; 5-dose vials	-25°C to -15°C; 10-dose vials	2-8°C; 10-dose vials	-80°C to -60°C; 2-8°C for up to 1 month; 6-dose vials	2-8°C; Single-dose vials	2-8°C; Single-dose vials/ pre-filled syringes	2-8°C; 10-dose or 20-dose vials	2-8°C
Approval by a Stringent Regulatory Authority (SRA)	WHO EUL, EMA, TGA, MHRA	Under review by WHO SAGE	WHO EUL, EMA, FDA, MHRA	WHO EUL, EMA, FDA, TGA	Under review by WHO SAGE	WHO EUL, EMA, FDA, TGA, MHRA	WHO EUL	WHO EUL	-	-

*Based on WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommendations

WHO EUL: WHO Emergency Use Listing
EMA: European Medicines Agency
FDA: Food and Drug Administration (US)
TGA: Therapeutic Goods Administration (Australia)
MHRA: Medicines and Healthcare Products Regulatory Agency

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COVID-19 Vaccine Efficacy

VACCINE	VACCINE EFFICACY			
	SYMPTOMATIC INFECTION	MODERATE-SEVERE	SEVERE	HOSPITALISATION/DEATH
AstraZeneca	UK: 66.7% (57.4-74.0)[24] USA, Chile, Peru: 76%[25] (not peer-reviewed) Single dose in UK (22-90 days post-vaccination): 76.0% (59.3 to 85.9)[24] Efficacy with different interval between doses in UK: 12+ weeks: 82.4% (2.7-91.7) <6 weeks: 54.9% (32.7-69.7)[24]	-	Severe/critical and hospitalisation in USA, Chile, Peru: 100%[25] (not peer-reviewed) UK: 100% (15 cases in the placebo group)[24]	Hospitalisation in UK: 100% (9 cases in placebo group)[24]
Bharat Biotech	India: 77.8% (65.2-86.4)[26]	-	India: 93.4% (57.1-99.8)[26]	-
Clover	Philippines, Colombia, Brazil, South Africa and Belgium: Overall: 67.2% (54.3-76.8); Delta: 78.7% (57.3-90.4)[27]	Philippines, Colombia, Brazil, South Africa and Belgium: Overall: 83.7% (55.9-95.4); Delta: 81.7% (35.9-96.6)[27]		Hospitalisation in Philippines, Colombia, Brazil, South Africa and Belgium: 100% (42.7-100)[27]
Gamaleya	Russia: 91.6% (85.6–95.2)[28] SInlge dose (Sputnik Light) in Argentina: 78.6%[29]	Moderate-severe: 100% (20 cases in the placebo group)[28]	-	-
Johnson & Johnson	USA: 93.2% (91.0-94.8)[30]	Moderate to severe/critical: All sites: 66.1% (55.0-74.8) USA: 72.0% (58.2-81.7) Latin America: 61.0% (46.9-71.8) South Africa: 64.0% (41.2-78.7)[31,32] South Africa: 67-71%[33]	85.4% (54.2-96.9)[32] USA: 98.2% (92.8-99.6)[30]	100% (5 deaths in placebo group)[32] Death in South Africa: 96%[33]
Moderna	USA: 94.1% (89.3-96.8)[34] USA: >90%[35] Efficacy in USA: 12-17 years: Symptomatic: 92.7% (67.8-99.2) Infection: 69.8% (49.9-82.1) Asymptomatic infection: 59.5% (28.4-77.3)[36]	-	USA: 100% (30 cases in placebo group)[34] US: >95%[35]	USA: 100% (1 death in placebo group)[34]
Novavax	UK: 89.7% (80.2-94.6)[37] US and Mexico: 90.4% (82.9-94.6)[38]	US and Mexico: 100% (87.0-100)[38]	-	-
Pfizer/BioNTech	Argentina, Brazil, Germany, South Africa, Turkey and the USA: 94.6% (89.9–97.3)[39] Infection over 6 months: 91.3% (89.0-93.2)[40]	-	Argentina, Brazil, Germany, South Africa, Turkey and the USA: 88.9% (20.1–99.7)[39] Severe disease: 96.7% (80.3-99.9)[40]	-
Sinopharm	UAE, Bahrain, Egypt and Jordan: 78.1% (64.9-86.3)[41]	-	-	Hospitalisation in UAE, Bahrain, Egypt and Jordan: 78.7% (26.0-93.9)[41]
Sinovac	Brazil: 50.7% (35.9-62.0) Chile: 67% (65-69) Indonesia: 65% (20-85)[41] Turkey: 83·5% (65·4-92·1)[42]	Requiring medical assistance in Brazil: 83.7% (58.0-93.7) Moderate-severe: 100% (56.4-100.0)[43]	-	Hospitalisation: Brazil: 100% (56-100) Chile: 85% (83-97) Turkey: 100% (20-100)[41]

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Vaccine Effectiveness Summary at-a-glance

Detailed summary available in Appendix 1.

VACCINE	ANY INFECTION	SYMPTOMATIC INFECTION	HOSPITALISATION/ SEVERE DISEASE	DEATH
AstraZeneca	54-67%[44–47] Single dose 30-67%[44,46,48]	56-78%[47,49–51] Single dose: 50-68%[49,52,53]	88-100%[47,50,51,54–57] Single dose: 71-94%[52,56,58]	94-100%[50,51]
Bharat Biotech	Efficacy: 65.2%[26]			
Johnson & Johnson	50-79%[47,59,60]	54%[47]	71-91%[33,47,57,60,61]	-
Moderna	76-87%[47,62–65] Single dose: 72%[48]	82-95%[47,51,63,64,66] Single dose: 72%[66,67]	92-98%[47,51,57,61–65] Single dose: 96%[48]	98%[63]
Pfizer/BioNTech	63-95%[44,45,47,52,62,68–75] Single dose: 36-57%[44,46,48]	72-97%[47,49–52,66,68,72,76,77] Single dose: 49-61%[49,66,67]	85-98%[47,50–52,56,57,61,62,68,70,72,73,76,78–80] Single dose: 85-94%[56,58]	91-100%[50,51,68,72,73,78,79]
Sinopharm	-	90%[41]	-	-
Sinovac	60%[78]	59[50]	86-91%[50,78]	86-95%[50,78]

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Vaccine Efficacy/Effectiveness Against Delta VOC at-a-glance

Detailed summary and vaccine efficacy/effectiveness against other variants available in Appendix 2

VACCINE	LAB STUDIES	VACCINE EFFECTIVENESS UNLESS OTHERWISE STATED		
		ANY INFECTION	SYMPTOMATIC INFECTION	HOSPITALISATION AND DEATH
AstraZeneca	✓	60-67%[44–46] Single dose 30-67%[44,46,48]	67%[51]	88-94%[51,55,56] Single dose: 71-88%[48,56]
Bharat Biotech	✓	Efficacy: 65.2%[26]	-	-
Clover	-	-	Efficacy: 79% [27]	Efficacy (moderate-severe): Delta: 82%[27]
Gamaleya	✓	-	-	-
Johnson & Johnson	✓	78%[60]	-	71-85%[33,60]
Moderna	✓	76-87%[62,65] Single dose: 72%[48]	95%[51]	81-98%[51,62,65] Single dose: 96%[48]
Pfizer/BioNTech	✓	39-93%[44,45,62,69,70] Single dose: 36-57%[44,46,48]	90%[51]	75-100%[51,56,62,69,70] Single dose: 78-94%[48,56]

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Vaccine Efficacy/Effectiveness in High-Risk Groups at-a-glance

Detailed summary available in Appendix 3

VACCINE	VACCINE EFFICACY/EFFECTIVENESS			
	DIABETES	OBESITY	AT RISK FOR SEVERE COVID-19	ELDERLY*
AstraZeneca	-	-	Effectiveness of single dose against: Symptomatic infection: 60%[49] Efficacy against symptomatic infection: 76%[25] Effectiveness against symptomatic infection: 80%[49] Effectiveness against hospitalisation: 63%[54]	Effectiveness of single dose against: Symptomatic infection: 53-61%[49,52] Hospitalisation: 80%[81] Death: 83%[67] Efficacy against infection: 85%[25] Effectiveness against: Symptomatic infection: 59-76%[49,51,82] Hospitalisation: 37-73%[82,83] Death: 94%[67]
Bharat Biotech	-	-	Efficacy against infection: 66%[26]	Efficacy against symptomatic infection: 68%[26]
Gamaleya	-	-	-	Symptomatic infection: 92%[28]
Johnson & Johnson	Efficacy: 23%[31]	Efficacy: 66%[31]	Efficacy: 59%[31]	Efficacy 66%[31]
Moderna	-	-	Efficacy against symptomatic infection: 84-91%[34] Effectiveness against hospitalisation: 84% (80-87)[57]	Efficacy against symptomatic infection: 86%[34] Effectiveness against infection: 75-83%[63,65]
Novavax			Efficacy against infection: 91%[38]	
Pfizer/BioNTech	Effectiveness against infection: 82%[71] 89%[79]	Effectiveness against infection: 90%[79]	Effectiveness of single dose against symptomatic infection: 56%[49] Efficacy against symptomatic infection: 95%[39] Effectiveness against: Infection: 71-90%[73,79] Symptomatic infection: 89%[49] Hospitalisation: 72-81%[73]	Effectiveness of single dose against: Infection: 76%[52] Symptomatic infection: 40-56%[49,66] Hospitalisation: 71-81%[81,83] Death 77%[67] Efficacy against symptomatic infection: 95-100%[39,40] Effectiveness against: Infection: 70-89%[71,73,79,84] Smptomatic infection: 61-93%[49,51,66,82] Hospitalisation: 43-93%[82–84] Death: 98%[67]
Sinopharm	-	81%[41]	-	Effectiveness against symptomatic infection 91%[41]
Sinovac	-	75%[41]	49%[41]	-

*Estimates in those ≥60 years to ≥80 years

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Vaccine Efficacy/Effectiveness in Children

VACCINE	VACCINE EFFICACY/EFFECTIVENESS	COUNTRIES VACCINATING CHILDREN BY AGE GROUP
AstraZeneca	Trials suspended when evidence emerged of the higher risk of TTS in younger adults compared to older adults	-
Bharat Biotech	-	-
Gamaleya	-	-
Johnson & Johnson	-	-
Moderna	Efficacy in USA, 12-15 years: 96%[85]	Authorised in those aged ≥12 years by EMA and MHRA France, Italy: ≥12 years
Novavax	Study in 12-18 years has started recruitment and study in birth-11 years is planned	-
Pfizer/BioNTech	Efficacy in USA, 12-15 years: 100%[86] 5-11 years: Antibody response and safety profile for reactogenicity similar to 16-25 year-olds[87]	Authorised in those aged ≥12 years by EMA, FDA, TGA, Medsafe UK, Sweden: 16-17 years and high-risk groups ≥12 years US, Canada, France, Spain, Italy, Netherlands, Germany, Singapore, Australia: ≥12 years The UK Chief Medical Officers have advised the government to offer a single dose to all 12-15 year olds[88]
Sinopharm	Phase I/II studies in 3-17 year olds in China	China: ≥3 years
Sinovac	Phase I/II studies complete in 3-17 year olds in China[89]; efficacy studies underway	Indonesia: ≥12 years China: ≥3 years

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Vaccine Efficacy/Effectiveness Against Transmission

There are limitations related to the analysis and comparison of transmission data between studies and vaccines. Criteria for testing vary between studies and may include, for example, random testing, testing at defined intervals, or retrospective serology.

VACCINE	EFFICACY/EFFECTIVENESS AGAINST ASYMPTOMATIC INFECTION	OTHER OUTCOMES
AstraZeneca	EFFICACY (UK only): 22·2% (−9·9-45·0); Symptomatic and asymptomatic combined (UK, SOUTH AFRICA & BRAZIL): 54.1% (44.7-61.9)[24] ENGLAND: Hazard ratio for single dose in vaccinated vs. unvaccinated care facility residents: 0.32 (0.15-0.66)[90]; Odds ratio for household contacts of vaccinated vs non-vaccinated health workers testing positive: 0.52 (0.43-0.62)[91] UK: Regular testing of randomly selected households: 79% (65-88)[92]; Single dose against symptomatic and asymptomatic infection: 60% (49–68)[93] NETHERLANDS: Effectiveness against transmission (secondary attack rate among household contacts): 58% (−12-84)[80]	SCOTLAND: POOLED ANALYSIS OF PFIZER/BIONTECH AND ASTRAZENECA: Hazard ratio for household contacts of vaccinated vs non-vaccinated health workers testing positive: 0.70 (0.63-0.78)[94]
Bharat Biotech	EFFICACY IN INDIA: Asymptomatic: 63.6% (29.0-82.4); Symptomatic and asymptomatic combined: 68.8% (46.7-82.5)[26]	-
Johnson & Johnson	EFFICACY (multiple countries): Asymptomatic infection: 59.7% (32.8-76.6)[31] UK: Single dose against symptomatic and asymptomatic infection: 60% (49–68)[93] Netherlands: Effectiveness against transmission (secondary attack rate among household contacts): 77% (6-94)[80]	USA (Kentucky): OR for reinfection in unvaccinated vs vaccinated with Johnson & Johnson, Moderna or Pfizer/BioNTech): 2.34 (1.58–3.47)[95]
Moderna	USA: Asymptomatic infection: 72.7% (53.4-84.0)[63] USA: POOLED ANALYSIS OF PFIZER/BIONTECH AND MODERNA: 88.7% (68.4-97.1)[96]; 90% (68%-97)[97]; single dose: 80% (59-90)[97]; Relative risk of infection in asymptomatic pre-surgical patients >10 days after first dose compared to unvaccinated residents: 0.21 (0.12-0.37)[98]; Incident cases in unvaccinated nursing home residents decreased from 4.3% within 14 days of the first vaccination clinic to 0.3% after 42 days[99] MODELLING: Reduced potential for transmission: at least 61%[100] UK: Single dose against symptomatic and asymptomatic infection: 60% (49–68)[93] Netherlands: Effectiveness against transmission (secondary attack rate among household contacts): 88% (50-97)[80] USA: 63.0% (56.6-68.5)[30] Qatar: First month after second dose: 73.1% (70.3-75.5); declining to no evidence of any effect by 4 months post-vaccination[64]	USA (Kentucky): OR for reinfection in unvaccinated vs vaccinated with Johnson & Johnson, Moderna or Pfizer/BioNTech): 2.34 (1.58–3.47)[95]
Pfizer/BioNTech	ENGLAND: 86% (76-97) 7 days after 2 doses; 72% (58-86) 21 days after 1 dose[101] ISRAEL: 92% (88-95)[76]; 91.5% (90.7-92.2)[72]; 65% (45-79%)[102]; single dose: 75% (72-84)[103]; Effectiveness against transmission: 88.5% (82.3-94.8)[104]; Effectiveness against infection in the household: 78% (30-94)[105] USA: Asymptomatic screening: 90% (78-96)[77] USA: POOLED ANALYSIS OF PFIZER/BIONTECH AND MODERNA: 88.7% (68.4-97.1)[96]; 90% (68%-97)[97]; single dose: 80% (59-90)[97]; Relative risk of infection in asymptomatic pre-surgical patients >10 days after first dose compared to unvaccinated residents: 0.21 (0.12-0.37)[98]; Incident cases in unvaccinated nursing home residents decreased from 4.3% within 14 days of the first vaccination clinic to 0.3% after 42 days[99] UK: single dose: 4-fold decrease in risk amongst HCWs ≥12 days post-vaccination[106]; Regular testing of randomly selected households: 80% (73-85)[92]; Single dose against symptomatic and asymptomatic infection: 72% (63–79)[93]; 60% (49–68)[93] FINLAND: Effectiveness against transmission to unvaccinated household contacts: 2 weeks after first dose: 8.7% (-28.9-35.4); 10 weeks after first dose: 42.9% (22.3-58.1)[107] Netherlands: Effectiveness against transmission (secondary attack rate among household contacts): 70% (61-77)[80] Finland: Effectiveness against transmission to unvaccinated household contacts of vaccinated cases: 42.9% (22.3-58.1)[107]	ISRAEL: Lower viral load in vaccine failure cases 12-37 days after the first dose of vaccine compared to within the first 11 days, indicating potentially lower infectiousness[108]; Data from 223 communities: strong correlation between community vaccination rate and a later decline in infection among children under 16 years of age who were unvaccinated[109]; Substantially decreased viral load for infections occurring 12-37 days after the first dose of vaccine, indicating likely lower infectiousness[108] Detectable transmission in long-term care facilities in Spain reduced by 90% (76-93)[110] ENGLAND: Odds ratio for household contacts of vaccinated health workers vs non-vaccinated health workers testing positive: 0.54 (0.47-0.62)[91] SCOTLAND: POOLED ANALYSIS OF PFIZER/BIONTECH AND ASTRAZENECA: Hazard ratio for single dose in vaccinated vs. unvaccinated care facility residents: 0.35 (0.17-0.71)[90] USA (Kentucky): OR for reinfection in unvaccinated vs vaccinated with Johnson & Johnson, Moderna or Pfizer/BioNTech): 2.34 (1.58–3.47)[95]

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Mixed Dose Vaccine Safety and Immune Responses

Mixed vaccine schedules (i.e. delivering different types of vaccine for the first and second dose) could be particularly useful to facilitate better protection against variants of concern and enable vaccination programs to continue if a particular vaccine is unavailable.

SCHEDULE	SAFETY	IMMUNE RESPONSES OR EFFECTIVENESS	COUNTRIES USING SCHEDULE
AZ-PF	Spain: Similar side effects to those receiving 2 doses of the same vaccine; no safety concerns (not peer reviewed)[111] UK: Greater systemic side effects (mild-moderate symptoms) following the booster dose than with 2 doses of the same vaccine; no safety concerns[112] Germany: greater reactogenicity with first dose of AstraZeneca than with the Pfizer/BioNTech booster[113] Increased reactogenicity (54.4%; 49.4-59.5) vs AstraZeneca-AstraZeneca (33.5%; 28.0-39.2)[114] Total adverse event reporting in Korea: 0.28% (vs AZ-AZ: 0.22%; and PF-PF: 0.31%)	Spain: ≥8 week dose interval: Stronger immune response following Pfizer/BioNTech than after 2 doses of AstraZeneca vaccine (not peer reviewed)[111] Spain: 8-12 week dose interval: robust antibody response[115] UK: 4 week dose interval: stronger antibody and cellular response than after 2 doses of AstraZeneca vaccine[116] Germany: 9-12 week dose interval: Significantly stronger immune response following Pfizer/BioNTech booster than AstraZeneca, and slightly stronger than after 2 doses of Pfizer/BioNTech (not peer reviewed)[117] Germany: 4-fold greater immune response than 2 doses of AstraZeneca[118] South Korea: 6-fold greater neutralising antibody response than 2 doses of AstraZeneca Germany: Higher neutralising antibody response against wild-type, Alpha, Beta, Gamma and Delta variants than AZ-AZ[119]	Canada, Denmark, Finland, France, Germany, Sweden, Norway, Spain and South Korea[120]
PF-AZ	UK: Greater systemic side effects (mild-moderate symptoms) following the booster dose than with 2 doses of the same vaccine; no safety concerns[112] Greater reactogenicity with first of homologous and heterologous prime-boost immunisation with BNT162b2 and ChAdOx1-nCoV19: a prospective cohort study increased reactogenicity (55.2%; 46.1-64.1) vs Pfizer/BioNTech-Pfizer/BioNTech (33.3%; 23.4-44.5)[114]	UK: 4 week dose interval: weaker antibody response than after 2 doses of Pfizer/BioNTech vaccine (but stronger than after 2 doses of AstraZeneca vaccine)[116]	-
PF, J&J or MO followed by PF, J&J or MO	Reactogenicity for all combinations similar to primary series[121]	Homologous boosters increased neutralising antibody titres 4.2 to 20-fold; Heterologous boosters increased neutralising antibody titres 6 to 76-fold[121]	-
AZ, MO and PF	-	Canada: Trial underway mixing and matching all three vaccines with study arms assessing 4 week and 16 week dose intervals[122] Denmark: Vaccine effectiveness against infection: AZ-PF or AZ-MO: 88% (83-92)[123]	AstraZeneca followed by either Moderna or Pfizer/BioNTech: Denmark, Finland, France, Germany, Sweden, Norway and Spain[120]
Sinovac-AZ	-	-	Thailand

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Adverse Events Following Immunisation with WHO EUL Vaccines

Adverse events following immunisation (AEFIs) are any reactions occurring after immunisation. They can be either expected or unexpected. The vaccine may not actually cause the AEFI; it may occur coincidentally as millions of people are being vaccinated so some people may get sick after vaccination but this does not necessarily mean that it is due to the vaccine. Special investigations determine whether they are due to the vaccine. Adverse events of special interest (AESIs) are of scientific and medical concern that are found through active surveillance, that have the potential to be causally associated with a vaccine and that need to be carefully monitored and confirmed by further special studies.

For all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following administration.

	ASTRAZENECA	MODERNA	PFIZER/BIONTECH	JOHNSON & JOHNSON	SINOPHARM	SINOVAC	CLOVER
Adverse events following immunisation (AEFIs)*	Very common (more than 1 in 10 people): headache, nausea, muscle pain, joint pain, injection site tenderness/ pain/ warmth/ itch, fatigue, malaise, fever, chills Common (between 1 in 10 and 1 in 100 people): injection site swelling/ redness[124]	Injection site pain (92%)/ swelling (15%)/ redness (10%), fatigue (70%), headache (65%), muscle pain (62%), joint pain (46%), fever (16%), chills (45%), nausea/vomiting (23%), axillary swelling/tenderness (20%)[125]	Very common: headache, muscle pain, joint pain, injection site pain/ swelling, fatigue, fever, chills; Common: nausea, injection site redness[124] Uncommon (between 1 in 100 and 1 in 1000 people): lymphadenopathy, insomnia, pain in extremity of vaccinated arm, malaise, injection site itch; Rare: (between 1 in 1000 and 1 in 10,000): acute peripheral facial paralysis[6]	Injection site pain/ redness/ swelling, headache, fatigue, muscle pain, nausea, fever[126]	Injection site pain (16%)/ itch (1%)/ swelling (2%)/ redness (1%), fever (4%), fatigue (3%), nausea (1%), headache (1%), diarrhoea (1%), muscle pain (<1%), itch (non-injection site) (1%)[127]	Fatigue (8.3%), fever (3.3%), diarrhoea (0.8%), nausea (1.7%), headache (2.5%), muscle pain (1.7%), injection site pain (10.0%)/ redness (0%)/ swelling (0%)[128]	Very common: Injection site pain, fatigue, headache Common: Injection site erythema, myalgia, arthralgia, loss of appetite, nausea, chills Uncommon: Injection site swelling, fever[27]
Adverse events of special interest (AESIs)	Thrombosis with thrombocytopaenia syndrome (TTS) (see page 13 for estimated risk); EMA PRAC: Guillain-Barre syndrome (GBS)[129] Australia: Guillain-Barre syndrome: 52 cases (10.4 per million doses)[130]	USA: Myocarditis/pericarditis: 40.6 males and 4.2 females aged 12-29 years per million second doses of mRNA vaccine; and 2.4 males and 1.0 females aged 30+;[131] >1 in 20,000 males under 25 years of age[22] Immune thrombocytopaenia (ITP)**[132]	USA: Myocarditis/pericarditis: 40.6 males and 4.2 females aged 12-29 years per million second doses of mRNA vaccine; and 2.4 males and 1.0 females aged 30+;[131] >1 in 20,000 males under 25 years of age[22] Israel: 1 to 5 cases of myocarditis per 100,000 persons[133,134] ITP**[132]	TTS (see page 14 for estimated risk) USA: Guillain-Barre Syndrome: 100 preliminary reports of GBS following 12.5 million doses of vaccine administered (mostly males >50 years)[135]	-	-	-

*Details for AstraZeneca, Moderna, Pfizer/BioNTech and Johnson & Johnson from product information sheets in SRA countries, based on data from clinical trials; Sinopharm and Sinovac details from published clinical trials
**The ITP cases are mostly without the thrombotic events characteristic of TTS

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Serious Adverse Events

Caution is required when comparing safety profiles as definitions and reporting systems vary in trials and in particular phase IV studies.

VACCINE	VACCINE SAFETY
AstraZeneca	108 SAEs in 12,282 (0.9%) vaccine recipients and 127 in 11,962 (1.1%) placebo recipients; 7 deaths all considered unrelated to vaccination (2 vaccine, 5 placebo)[24] US Phase III study: No serious safety concerns involving 32,449 participants[25] (not peer-reviewed) EMA investigation: possible link between the AstraZeneca vaccine and Thrombosis with Thrombocytopaenia Syndrome (TTS) Blood clots affected the brain (central venous sinus thrombosis, CVST) and abdomen (splanchnic vein thrombosis) There have been reports of 169 cases of CVST and 53 cases of splanchnic vein thrombosis in ~34 million vaccinated people in Europe The EMA confirmed the overall benefits of the vaccine in preventing COVID-19 outweigh the risks of side effects[16] UK: Risk factors for death in patients with TTS following the AstraZeneca vaccine: baseline platelet count; and intracranial haemorrhage[136] TTS reported to occur in ~1 in 50,000 vaccinated adults in Australia[19] Several countries introduced age recommendations for the vaccine: >60 years in Germany and Australia; >55 years in France and Canada; >40 years in the UK[137–139] EMA has started a review of reports of capillary leak syndrome following 5 cases of this very rare disorder post vaccination[140] WHO GACVS reports Guillain Barre Syndrome (GBS) rates following adenovirus vector vaccines: EU/EEA: 4.4; AUS: 9.7; KOR: 0.4; PHL: <1[141]
Gamaleya	45 SAEs in 16,427 (0.3%) vaccine recipients and 23 in 5,435 (0.4%) placebo recipients; 4 deaths all considered unrelated to vaccination (3 vaccine, 1 placebo)[28]
Johnson & Johnson	83 SAEs in 21,895 (0.4%) vaccine recipients and 96 in 21,888 placebo recipients (0.4%); 19 deaths all considered unrelated to vaccination (3 vaccine, 16 placebo)[31] EMA investigation of 8 reports of TTS. Most cases occurred in women <60 years of age but specific risk factors have not been confirmed[17] The CDC and FDA have now recommenced the vaccination program in the USA following a thorough safety review[142] 15 cases of TTS have been reported in 7.98 million people vaccinated in USA[15] Guillain-Barre Syndrome: 100 preliminary reports of GBS following 12.5 million doses of vaccine administered in USA (mostly males >50 years)[135] WHO GACVS reports Guillain Barre Syndrome (GBS) rates following adenovirus vector vaccines: USA: 7.8; KOR: 0.9; EU/EEA: AZ: 2.1[141]
Moderna	153 SAEs in 15,166 (1.0%) placebo recipients and 147 in 15,185 (1.0%) vaccine recipients; 5 deaths considered unrelated to vaccine (2 vaccine, 3 placebo)[34] Anaphylaxis reported in the US at a rate of 2.5 per million doses[143] No obvious safety signals among pregnant women who received mRNA COVID-19 vaccines in USA[144] USA: Myopericarditis highest in males 18-34 years: 37.7 cases per million doses[23] USA: Myo/pericarditis reported in 40.6 males and 4.2 females aged 12-29 years per million second doses of mRNA vaccine; and 2.4 males and 1.0 females aged 30+[131] Ontario, Canada; Myo/pericarditis cases per million second doses in those aged 18-24 years: Males 198.6; Females 59.6[145] Overall rates in the UK per million second doses: Myocarditis: 28.3; Pericarditis: 17.2[146]
Novavax	SAEs at low levels and similar between vaccine and placebo groups[147]
Pfizer/BioNTech	SAEs and deaths were low and comparable between vaccine and placebo groups (total 37,586 participants)[39] Anaphylaxis reported in the US at a rate of 4.7 per million doses[143] No obvious safety signals among pregnant women who received mRNA COVID-19 vaccines in USA[144] USA: Myopericarditis highest in males 16-17 years: 71.5 cases per million doses[23] USA: Myopericarditis reported in 40.6 males and 4.2 females aged 12-29 years per million second doses of mRNA vaccine; and 2.4 males and 1.0 females aged 30+[131] Brazil: SAEs: 5.4/100,000 doses Ontario, Canada; Myo/pericarditis cases per million second doses in those aged 18-24 years: Males 35.5; females 39.9[145] Overall rates in the UK per million second doses: Myocarditis7.4; Pericarditis 5.6[146] Israel: Myo/pericarditis: 106.9 (69.3-144.6) cases per million in those aged 16-29[148]; 137.3 (81.1-194.6) cases per million people aged 16-19[149]
Sinovac	Brazil: SAEs: 79.7/100,000 doses

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Who Can be Vaccinated Based on WHO SAGE Recommendations?

So far, WHO SAGE have made recommendations for use of AstraZeneca, Moderna, Pfizer/BioNTech, Johnson & Johnson and Sinopharm vaccines: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials

	ASTRAZENECA	MODERNA	PFIZER/BIONTECH	JOHNSON & JOHNSON	SINOPHARM	SINOVAC
Minumum Age	18 years	18 years	12 years	18 years	18 years	18 years
Maximum Age (SAGE WHO)	None	None	None	None	None	None
Pregnancy	Yes if high priority group & approved by health provider	Yes if high priority group & approved by health provider	Yes if high priority group & approved by health provider	Yes if high priority group & approved by health provider	Yes if high priority group & approved by health provider	Yes if high priority group & approved by health provider
Breastfeeding	Yes	Yes	Yes	Yes	Yes	Yes
Timing after previous SARS-CoV-2 infection	May delay 6 months; Within 90 days if VOCs associated with reduced effectiveness are circulating (e.g. Beta)	May delay 6 months; Within 90 days if VOCs associated with reduced effectiveness are circulating (e.g. Beta)	May delay 6 months; Within 90 days if VOCs associated with reduced effectiveness are circulating (e.g. Beta)	May delay 6 months; <6 months may be advisable if VOCs with reduced neutralisation activity are circulating	May delay 6 months; <6 months may be advisable if VOCs associated with reduced effectiveness are circulating	May delay 6 months; <6 months may be advisable if VOCs associated with reduced effectiveness are circulating
Immunocompromised Including HIV	✓	✓	✓	✓	✓	✓
People Previously Infected by SARS-CoV-2 (PCR Confirmed)	Yes, although that person may choose to delay vaccination by 6 months	Yes, although that person may choose to delay vaccination by 6 months	Yes, although that person may choose to delay vaccination by 6 months	Yes, although that person may choose to delay vaccination by 6 months	Yes, although that person may choose to delay vaccination by 6 months	Yes, although that person may choose to delay vaccination by 6 months
History of Anaphylaxis (Severe Allergy)	Yes (unless the allergy is to the vaccine or its components)	Yes (unless the allergy is to the vaccine or its components)	Yes (unless the allergy is to the vaccine or its components)	Yes (unless the allergy is to the vaccine or its components)	Yes (unless the allergy is to the vaccine or its components)	Yes (unless the allergy is to the vaccine or its components)

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Vaccine Development Pipeline

WHO has recommended that vaccines adopted by countries have WHO SAGE EUL and/or Stringent Regulatory Approval. Last updated 4 October 2021.

VACCINE TYPE	NUMBER OF VACCINE CANDIDATES AT EACH PHASE OF DEVELOPMENT				
	PRE-CLINICAL	PHASE I/II	PHASE III	PHASE IV	IN USE*
RNA	27	10	3	2	2 (Pfizer/BioNTech, Moderna)
DNA	18	7	3	0	1 (Zydus Cadila Healthcare Limited)
Vector (non-replicating)	27	7	2	3	4 (CanSino, Gamaleya, Johnson & Johnson, AstraZeneca)
Vector (replicating)	18	6	1	0	0
Inactivated	7	7	8	2	8 (Sinopharm/BIBP; Sinopharm/WIBP; Sinovac; Bharat; Chumakov; Research Instutute for Biological Safety Problems; Shenzhen Kangtai Biological Products; Shifa Pharmed)
Live-attenuated	2	1	0	0	0
Protein subunit	73	22	12	1	6 (Vector institute; Anhui Zhifei Longcom Biopharmaceutical Chinese Academy of sciences; Center for Genetic Engineering and Biotechnology; Instituto Finlay de Vacunas, Cuba [peptides 1 and 2]; Medigen Vaccine Biologics, Taiwan)
Virus-like particle	20	4	1	0	0
Other/unknown	32	5	0	0	0

*Not all vaccines in use have SRA (as recognised by WHO) approval (see Vaccine specifications table and WHO SAGE Emergency Use Listing and prequalification timeline for approval status of vaccines).

Source: London School of Hygiene and Tropical Medicine
COVID-19 vaccine tracker.

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WHO SAGE Emergency Use Listing and Prequalification Timeline

MANUFACTURER	NAME OF VACCINE	PLATFORM	STATUS OF ASSESSMENT	ANTICIPATED DECISION DATE
Pfizer/BioNTech	BNT162b2/COMIRNATY Tozinameran (INN)	mRNA	Final decision made	Authorised 31/12/20
AstraZeneca	AZD1222	Adenoviral vector	Final decision made	SK Bio: Authorised 15/02/21 EU nodes: Authorised 16/04/21 CSL, Australia: Authorised 09/07/21 Daiichi Sankyo, Japan: Authorised 09/07/21
Serum Institute of India	Covishield (ChAdOx1_nCoV19)	Adenoviral vector	Final decision made	Authorised 15/02/21
Sinopharm/Beijing Institute of Biological Products (BIBP)	SARS-CoV-2 Vaccine (Vero Cell), Inactivated (InCoV)	Inactivated	In progress	Authorised: 07/05/2021
Sinovac	SARS-CoV-2 Vaccine (Vero Cell), Inactivated	Inactivated	In progress	Authorised 01/06/2021
Moderna	mRNA-1273	mRNA	In progress (to use abridged procedure relying on EMA)	Authorised 30/04/2021
Johnson & Johnson	Ad26.COV2.S	Adenoviral vector	Final decision made	Authorised 12/03/21
The Gamaleya National Center	Sputnik V	Adenoviral vector	On hold, awaiting completion of rolling submission	Will be determined when all data are submitted
CanSinoBIO	Ad5-nCoV	Adenoviral vector	Rolling data assessment started 9 August 2021	TBC
Novavax	NVX-CoV2373	Protein subunit	Pre-submission meeting held; rolling data starting in August 2021	TBC
CureVac	Zorecimeran	mRNA	Expression of interest accepted; Pre-submission meeting planned for Q4 2021	-
Bharat Biotech	Covaxin; BBV152	Inactivated	Rolling data assessment started 6 July 2021	October 2021
Clover Biopharmaceuticals	SCB-2019 (CpG 1018/Alum)	Protein subunit	Rolling data starting 20 September	TBC

Source: WHO Guidance Document: Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process. Available at: https://www.who.int/teams/regulation-prequalification/eul/covid-19

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Other resources on COVID-19 vaccines:

WHO COVID-19 vaccines website: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines
EMA COVID-19 vaccines website: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines

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Appendix 1: COVID-19 Vaccine Effectiveness

VACCINE	SEVERE / HOSPITALISATION / DEATH	INFECTION AND OTHER OUTCOMES
AstraZeneca	Single dose in Scotland: 94% (73-99)[58] Risk of death in vaccine failures compared to unvaccinated cases in England reduced by: 55% (41-66)[150] (not peer reviewed) Single dose against hospitalisation in Spain: 92% (46-99)[52] Pooled analysis of AstraZeneca, Pfizer/BioNTech and Moderna vaccines in Italy: Hospitalisation: 89% (85-91); Death: 93% (89-96)[151] Chile: Hospitalisation: 100%; ICU admission: 100%; Death: 100%[50] Scotland: Hospitalisation: 94% (90-99)[54] Netherlands: Hospitalisation: 94% (92-95)[57] Spain: Hospitalisation: 95% (79-99)[47]	Pooled analysis of Pfizer/BioNTech and AstraZeneca vaccines in elderly care home residents in UK: Reduction in risk of infection 4 weeks after-single dose: 56% Reduction in risk of infection 5 weeks after single dose: 62%[152] Pooled analysis of Pfizer/BioNTech and AstraZeneca vaccines: reduced odds of infection post-second dose: 70% (62-77)[153] Single dose in Spain: Any infection: 44% (31-54); Symptomatic infection: 50% (37-61)[52] Pooled analysis of AstraZeneca, Pfizer/BioNTech and Moderna vaccines in Italy: Infection: 78% (76-79)[151] Single dose against symptomatic infection in multiple European countries: 68% (39-83)[53] Symptomatic infection in 16-64 years in UK: single dose: 50.2% (40.8-58.2); 2 doses: 78.0% (69.7-84.0)[49] Symptomatic infection in Chile: 68.7% (39.8-83.7)[50] Spain: Any infection: 54% (48-60); Symptomatic infection: 56% (48-63)[47]
Johnson & Johnson	USA: Hospitalisation: 81% (79-84)[60] USA: 71% (56-81)[61] Netherlands: Hospitalisation: 91% (88-94)[57] Spain: Hospitalisation: 74% (43-88)[47]	USA: Any infection: 76.7% (30.3-95.3)[59] USA: Infection: 79% (77-80)[60] Efficacy following booster 2 months after first dose: Moderate-Severe infection in USA: 94% (58-100); worldwide: 75% (55-87)[154] Spain: Any infection: 50% (42-57); Symptomatic infection: 54% (45-62)[47]
Moderna	Pooled analysis of AstraZeneca, Pfizer/BioNTech and Moderna in Italy: Hospitalisation: 89% (85-91); Death: 93% (89-96)[151] Pooled analysis of Pfizer/BioNTech and Moderna against hospitalisation: 2-12 weeks after second dose: 86% (82%-90%) 13-24 weeks after second dose: 84% (77%-90%)[155] USA: Hospitalisation: 95.8% (90.7-98.1); Death: 97.9% (66.9-99.9)[63] Pooled Pfizer/BioNTech and Moderna against hospitalisation in Scotland: 92% (85-99)[54] USA: 93% (91-95)[61] Spain: Hospitalisation: 98% (82-100)[47] Qatar: Decline in effectiveness accelerated beyond the fourth month after the second dose; First month after second dose: 96.0% (93.9-97.4); ≥7 months: 55.6% (−44.3-86.3)[64] USA: Hospitalisation: 97.6% (92.8-99.2)[65]	Pooled analysis of Moderna and Pfizer/BioNTech vaccines in USA: Infections in nonvaccinated: 234 of 8969; 2.61% (2.29-2.96) Fully vaccinated: 4/8121; 0.05% (0.01-0.13)[156] Pooled analysis of Moderna and Pfizer/BioNTech vaccines against infection in USA: Fully vaccinated: 90% (68–97) Two weeks after first dose: 80% (59–90)[157] Pooled analysis of AstraZeneca, Pfizer/BioNTech and Moderna vaccines in Italy: Infection: 78% (76-79)[151] Single dose against symptomatic disease in the UK: Age 15-39 years: 72% (46-86)[67] Minnesota, USA: January to July 2021 (Delta variant <0.7% in May): Infection: 86% (81-91); Hospitalisation: 92% (81-97) July (Delta variant >70%): Infection: 76% (58-87); Hospitalisation: 81% (33-96)[62] Infection in USA (98% vaccines used Pfizer/BioNTech and Moderna): Pre-Delta variant predominant: 91% (81–96); Delta variant predominant: 66% (26–84)[158] Infection in Canada: 1 dose: 72% (63-80); 2 doses: 94% (86-97)[66] USA: Any infection: 87.4% (84.8-89.6); Symptomatic infection: 88.3% (86.1-90.2)[63] Spain: Any infection: 82% (78-86); Symptomatic infection: 85% (80-89)[47] Qatar: First month after second dose: 77.5% (76.4-78.6); ≥7 months: 22.3% (−1.7-40.7)[64] USA: Any infection: 86.7% (84.3-88.7)[65]
Pfizer/BioNTech	Severe in Israel: 92% (75-100)[76] Severe/critical in Israel: 97.5% (97.1-97.8)[72] Single dose against hospitalisation in Scotland: 85% (76-91)[58] Risk of death in vaccine failures compared to unvaccinated cases in England reduced by: Single dose: 44% (32-53) Fully vaccinated: 69% (31-86)[150] (not peer reviewed) Israel: Hospitalisation: 97.2% (96.8-97.5); Death: 96.7% (96.0-97.3)[72] Hospitalisation in Spain: 94% (60-99)[52] Priority groups in Denmark: Hospitalisation: 93% (89-96); Death: 94% (90-96)[73] Pooled analysis of AstraZeneca, Pfizer/BioNTech and Moderna vaccines in Italy: Hospitalisation: 89% (85-91); Death: 93% (89-96)[151] USA care facility: Hospitalisation: 94.4 (73.9-98.8); Death 94.4 (44.6–99.4)[68] Uruguay: Hospitalisation: 97.8% (96.0-98.8); Death: 96.2 (95.4-96.8)[78] Israel: Hospitalisation: 93·4% (91·9-94·7); Death: 91·1% (86·5-94·1)[79] Chile: Hospitalisation: 97.2% (96.6-97.6); ICU admission: 98.3% (97.6-98.8); Death: 100%[50] Pooled analysis of Pfizer/BioNTech and Moderna against hospitalisation: 2-12 weeks after second dose: 86% (82%-90%) 13-24 weeks after second dose: 84% (77%-90%)[155] Pooled analysis of Moderna and Pfizer/BioNTech against hospitalisation or death: 98% (83-100)[66] Pooled Pfizer/BioNTech and Moderna against hospitalisation in Scotland: 92% (85-99)[54] USA: 88% (85-91)[61] Netherlands: Hospitalisation: 96% (95-96)[57] USA: Hospitalisation: 93% (84–96)[70] Spain: Hospitalisation: 93% (88-96)[47]	Pooled analysis of Moderna and Pfizer/BioNTech vaccines in USA: Infections in nonvaccinated: 234 of 8969; 2.61% (2.29-2.96) Fully vaccinated: 4/8121; 0.05% (0.01-0.13)[156] Pooled analysis of Moderna and Pfizer/BioNTech vaccines in USA: Fully vaccinated: 90% (68–97); Two weeks after first dose: 80% (59–90)[157] Symptomatic infection in Israel: 94% (87-98)[76] Any infection in Israel: 90% (79-95)[71] Israel: Any infection: 95.3% (94.9-95.7); Symptomatic infection: 97.0% (96.7-97.2)[72] Pooled analysis of Pfizer/BioNTech and AstraZeneca vaccines in elderly care home residents in UK: 4 weeks after first dose: 56%; 5 weeks after first dose: 62%[152] Documented infection in Israel: incidence decreased from 9.4 infections per 1,000 HCWs in the week following first dose to <1.0 infection per 1,000 HCWs per week from 1 week after the second dose[159] Pooled analysis of Pfizer/BioNTech and AstraZeneca vaccines: reduced odds of infection post-second dose: 70% (62-77)[153] Spain: Any infection: 65% (56-73); Symptomatic infection: 82% (73-88)[52] Infection in priority groups in Denmark: 82% (79-84)[73] USA: Symptomatic infection: 84% (75-90)[77] Denmark: Infection in care facility residents: >14 days after first dose:17% (4-28); >7 days after second dose: 64% (14-84)[74] USA: Single dose against infection in 2 care facilities: 63% (33-79)[75] A care facility in USA: Infection 66% (41-81); Symptomatic illness 87% (66-95)[68] Pooled analysis of AstraZeneca, Pfizer/BioNTech and Moderna vaccines in Italy: Infection: 78% (76-79)[151] Uruguay: Infection: 78.1% (77.0-79.1)[78] Israel: Infection: 93·0% (92·6-93·4)[79] Single dose against symptomatic disease in the UK: Age 15-39 years: 61% (56-66)[67] Symptomatic infection in multiple European countries: single dose: 61% (39-75); 2 doses: 87% (74-93)[53] Symptomatic infection in 16-64 years in UK: single dose: 48.6% (27.9-63.3); 2 doses: 93.3% (85.8-96.8)[49] Symptomatic infection in Chile: 87.7% (87.3-88.1)[50] Minnesota, USA: January to July 2021 (Delta variant <0.7% in May): Infection: 76% (69-81); Hospitalisation: 85% (73-93) July (Delta variant >70%): Infection: 42% (13-62); Hospitalisation: Hospitalisation: 75% (24-94)[62] Infection in USA (98% vaccines used Pfizer/BioNTech and Moderna): Pre-Delta variant predominant: 91% (81–96); Delta variant predominant: 66% (26–84)[158] Infection in Canada: 1 dose: 59% (55-62); 2 doses: 91% (88-93)[66] Any infection with Delta in USA: 93% (85–97)[70] Spain: Any infection: 69% (66-72); Symptomatic infection: 72% (69-75)[47]
Sinovac	Uruguay: Hospitalisation: 90.9% (88.6-92.7); Death: 94.7% (93.4-95.7)[78] Chile: Hospitalisation: 86.0% (85.6-86.5); ICU admission: 89.7% (89.1-90.2); Death: 86.4% (85.6-87.2)[50]	Uruguay: Infection: 59.9% (59.1-60.7)[78] Symptomatic infection in Chile: 58.5% (58.0-59.0)[50]
Sinopharm	-	Symptomatic infection in Bahrain: 90% (88-91)[41]

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Appendix 2: Vaccine Efficacy/Effectiveness Against Variants

Refer to Appendix 1 for vaccine effectiveness results for the Pfizer/BioNTech vaccine in Scotland, England and Israel, where all locations had predominant B.1.1.7 circulation.
There are four Variants of Concern listed by WHO.[160] The WHO recommends labelling SARS-CoV-2 variants with letters of the Greek alphabet, as in the table below.[161]

VACCINE	VACCINE EFFICACY/EFFECTIVENESS (EFFECTIVENESS AGAINST INFECTION UNLESS SPECIFIED)			
	B.1.1.7 (ALPHA) VARIANT	B.1.351 (BETA) VARIANT	P.1 (GAMMA) VARIANT	B.1.617.2 (DELTA) VARIANT
AstraZeneca	UK: 70·4% (43·6-84·5) (vs. 81·5% (67·9-89·4) against wild variant)[162] England: ≥21 days after one dose: 48.7% (45.2-51.9); ≥14 days after two doses: 74.5% (68.4-79.4)[44] Scotland: 73% (66-78)[45] Canada: Single dose: 64% (60-68)[48] UK: Single dose: 63% (55-69); 2 doses: 79% (56-90)[46] Severe disease in Canada: Single dose: 85% (81-88)[48]	South Africa: 10.4% (−76.8 to 54.8)[163] Study against severe disease underway[31]	-	England: ≥21 days after one dose: 30.0% (24.3-35.3); ≥14 days after second dose: 67.0% (61.3-71.8)[44] Scotland: 60% (53-66)[45] Canada: Single dose: 67% (44-80)[48] UK: Single dose: 46% (35-55); 2 doses: 67% (62-71)[46] Symptomatic infection in England: 66.7% (66.3-67.0)[51] Hospitalisation in England: 1 dose: 71% (51-83); 2 doses: 92% (75-97)[55]; 93.9% (91.3-95.7)[51] Death in England: 94.1% (91.8-95.8)[51] Severe disease in Canada: Single dose: 88% (60-96)[48] Hospitalisation and death in Scotland: 88% (85-90)[55]
Johnson & Johnson	-	Moderate to severe/critical: 64.0% (41.2-78.7) Severe/critical: 81.7% (46.2-95.4)[31] Efficacy against hospitalisation in South Africa: 67%[33]	Moderate to severe/critical: 68.1% (48.8-80.7); Severe/critical: 87.6% (7.8-99.7)[31]	Efficacy against hospitalisation in South Africa: 71%[33] USA: Infection: 78% (73-82); Hospitalisation: 85% (73-91)[60]
Moderna	Canada: Single dose: 83% (80-86); 2 doses: 92% (86-96)[48] Severe disease in Canada: Single dose: 79% (74-83); 2 doses: 94% (89-97)[48]	-	-	Canada: Single dose: 72% (57-82)[48] Minnesota, USA: 76% (58-87)[62] England: 95.2% (94.4-95.9)[51] Severe disease in Canada: Single dose: 96% (72-99)[48] Severe disease in Minnesota: 81% (33-96)[62] Hospitalisation in England: 97.5% (82.3-99.7)[51] Pooled Pfizer/BioNTech and Moderna against hospitalisation and death in Scotland: 91% (88-93)[55] USA: Infection: 86.7% (84.3-88.7); Hospitalisation: 97.6% (92.8-99.2)[65]
Novavax	UK: 86.3% (71.3-93.5) (vs. 96.4% (73.8-99.5) against wild variant)[37]	South Africa: 51.0% (−0.6 to 76.2)[164]	-	
Pfizer/BioNTech	Case-control study in Israel: After one dose, vaccinees were disproportionally infected with B.1.1.7 (OR: 26:10) [165] Qatar: 89.5% (85.9-92.3)[166] England: ≥21 days after one dose: 47.5% (41.6 to 52.8) ≥14 days after second dose: 93.7% (91.6-95.3)[44] Scotland: 92% (90-93)[45] Canada: Single dose: 66% (64-68); 2 doses: 89% (86-91)[48] UK: Single dose: 59% (52-65); 2 doses: 78% (68-84)[46] Severe disease in Qatar: 100% (81.7-100)[166] Severe disease in Canada: Single dose: 80% (78-82); 2 doses: 95% (92-97)[48]	Israel case-control study: Vaccinees infected at least 1 week after the second dose were disproportionally infected with B.1.351 (odds ratio: 8:1)[165] Qatar: 75.0% (70.5-78.9)[166] South Africa: 100% (53.5-100)[167] Severe disease in Qatar: 100% (73.7-100)[166]	-	England: ≥21 days after one dose: 35.6% (22.7-46.4); ≥14 days after second dose: 88.0% (85.3-90.1)[44] Scotland: 79% (75-82)[45] Canada: Single dose: 56% (45-64); 2 doses: 87% (64-95)[48] Effectiveness in Israel: Infection: 64%; Symptomatic illness: 64%[168] Israel 6m after roll out: 39.0% (9.0-59.0)[69] Minnesota, USA: 42% (13-62)[62] UK: Single dose: 57% (50-63); 2 doses: 80% (77-83)[46] England: 89.8% (89.6-90.0)[51] Hospitalisation in England: 1 dose: 94% (46-99); 2 doses: 96% (86-99)[56]; 99.7% (97.6-100.0)[51] Death in England: 98.2% (95.9-99.2)[51] Severe disease in Canada: Single dose: 78% (65-86)[48] Hospitalisation in Israel: 93%[168] Severe disease in Israel: 91.4% (82.5-95.7)[69] Severe disease in Minnesota: 75% (24-94)[62] Pooled Pfizer/BioNTech and Moderna against hospitalisation and death in Scotland: 91% (88-93)[55]
Sinovac	Chile: 67% (65-69)*[41]	-	Brazil: 1 or 2 doses: 37.9% (−46.4-73.6)[169] Chile: 67% (65-69)*[41] Brazil: ≥70 years: 41.6% (26.9-53.3); 70-74 years: 61.8% (34.8-77.7); 75-79 years: 48.9% (23.3-66.0); ≥80 years: 28.0% (0.6-47.9)[170]	China (combined Sinovac and Sinopharm): Single dose: 13.8% (-60.2-54.8);; 2 doses: 59.0% (16.0-81.6) Severe disease: 100%[171]
Sinopharm				China (combined Sinovac and Sinopharm): Single dose: 13.8% (-60.2-54.8); 2 doses: 59.0% (16.0-81.6) Severe disease: 100%[171]
Bharat Biotech	-	-	-	Efficacy against infection in India: 65.2% (33.1-83.0)[26]
Clover	-	-	-	Efficacy in Philippines, Colombia, Brazil, South Africa and Belgium: Symptomatic infection: 78.7% (57.3-90.4); Mod-Severe: 81.7% (35.9-96.6)[27]

* While it is known P.1. and B.1.1.7 were circulating at the time of the study, the extent is unknown based on available surveillance

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Appendix 3: Vaccine Efficacy/Effectiveness in High-Risk Groups 2

VACCINE	VACCINE EFFICACY UNLESS OTHERWISE STATED			
	DIABETES	OBESITY	AT RISK FOR SEVERE COVID-19	ELDERLY
AstraZeneca	-	-	76% against symptomatic infection in a sample where 60% had comorbidities, including diabetes, severe obesity or cardiac disease[25] (not peer-reviewed) Effectiveness against symptomatic infection in the UK in those with comorbidities and ≥65 years: Single dose: 60.0% (46.5-70.1); 2 doses: 79.7% (61.6-89.3)[49] Hospitalisation in Scotland: 63% (46-75)[54]	In ≥65 years: 85%[25] (not peer-reviewed) Effectiveness against hospitalisation at 28-34 days after a single dose (pooled analysis of AstraZeneca and Pfizer vacines): 18-64 years: 85% (68-93); 65-79 years: 79% (17-95); ≥80 years: 81% (65-90)[58] Effectiveness of single dose against hospitalisation in England: ≥80 years: 73% (60-81)[83] Effectiveness in England: Symptomatic infection ≥70 years: 73% (27-90); Hospitalisation ≥80 years: 37% (3-59)[82] Hospitalisation following single dose in the UK: ≥80 years: 80.4% (36.4-94.5)[81] Single dose in Spain: ≥60 years: 53% (19-72) vs. 18-59 years: 50% (34-62)[52] Effectiveness against death in the UK: ≥65 years: Single dose: 83% (78-86); Two doses: 94% (80-98)[67] Effectiveness against symptomatic infection in the UK, ≥65 years: single dose: 60.9% (49.0-70.0); 2 doses: 76.4% (58.8-86.5)[49]
Gamaleya	-	-	-	Symptomatic infection >60 years: 91.8% (67.1–98.3)[28]
Johnson & Johnson	Moderate to severe/critical: 23.0% (-90.1-69.8)[31]	Moderate to severe/critical: 65.9% (47.8-78.3)[31]	Moderate to severe/critical: With any comorbidity: 58.6% (40.6-71.6)[31] No comorbidity: 68.8% (59.0-76.6)[31]	Moderate-severe/critical disease ≥28 post vaccination: 18-59 years: 66.1% (53.3-75.8) 60+ years: 66.2% (36.7-83.0)[31]
Moderna	-	-	Symptomatic infection, comorbidities, including diabetes and obesity: In low risk: 95.1% (89.6-97.7) In high risk: 90.9% (74.7-96.7)[34] Pooled Pfizer/BioNTech and Moderna against hospitalisation in Scotland: 72% (51-84)[54] Netherlands: Hospitalisation in a population at high risk for severe COVID-19: 84% (80-87)[57]	Symptomatic infection: 18-64 years: 95.6% (90.6-97.9) ≥65 years: 86.4% (61.4-95.2)[34] Pooled Moderna and Pfizer vaccines against hospitalisation ≥65 years: 94% (49-99)[172] Infection in Canada: 1 dose ≥70 years: 54% (31-69); 2 doses ≥70 years: 95% (83-98)[66] Pooled Moderna and Pfizer vaccines in Portugal: Hospitalisation 65-79 years: 94% (88-97); ≥80 years: 82% (72-89); Death 65-79 years: 96% (92-98); Death ≥80 years: 81% (74-87)[173] USA: Hospitalisation: ≥65 years: 75.2% (59.6-84.8) vs 18-64 years: 87.9% (85.5-89.9)[65]
Pfizer/BioNTech	Effectiveness in Israel: Diabetes or cardoiovascular disease: 82% (62-92)[71] Effectiveness against infection in Israel: (88·9% (87·3-90·2)[79]	Effectiveness against infection in Israel: (89·7% (88·6-90·7)[79]	Symptomatic infection: With any comorbidity or obesity: 95.3% With no comorbidity: 94.7%[39] Denmark: Infection: 71% (58-80); Hospitalisation: 81% (49-93)[73] Effectiveness against infection in Israel: Hypertension: (89·7% (88.6-91.7)[79] Effectiveness against symptomatic infection in the UK in those with comorbidities and ≥65 years: Single dose: 56.4% (46.2-64.6) 2 doses: 88.5% (81.5-92.9)[49] Pooled Pfizer/BioNTech and Moderna against hospitalisation in Scotland: 72% (51-84)[54]	Efficacy against infection ≥75 years: 96.2% (76.9-99.9)[40] Mymptomatic infection: >55 years: 93.7% (80.6-98.8); >65 years: 94.7% (66.7-99.9); >75 years: 100% (-13.1-100)[39] Effectiveness against hospitalisation 28-34 days after a single dose (pooled analysis of AstraZeneca and Pfizer vacines): 18-64 years: 85% (68-93); 65-79 years: 79% (17-95); ≥80 years: 81% (65-90)[58] England 80-83 years: Documented infection: 70.1% (55.1-80.1) Hospital attendance: 78.9% (60.0-89.9); Hospital admission: 75.6% (52.8-87.6)[84] Reduction in incidence of infection in vaccinated people aged >60 years and unvaccinated people aged 20-39 years, respectively: Documented infection: 45% versus 28%; Hospitalisation: 68% versus 22%[174] Pooled Moderna and Pfizer vaccines against hospitalisation ≥65 years: 94% (49-99)[172] Effectiveness in England: Symptomatic infection ≥70 years: 61% (51-69); Hospitalisation ≥80 years: 43% (33-52); Death ≥80 years (vaccine failure vs non-vaccinated): 51% (37-62)[82] Effectiveness against hospitalisation in England ≥80 years: Single dose: 81% (76-85) Fully vaccinated: 93% (89-95)[83] (not peer reviewed) Effectiveness in Israel: 65-74 years: 82% (63-92); ≥75 years: 82% (61-91)[71] Hospitalisation following single dose in the UK: ≥80 years: 71.4% (43.1-86.2)[81] Single dose in Spain: ≥60 years: 76% (55-87) vs. 18-59 years: 85% (74-91)[52] Effectiveness against infection in Denmark: ≥80 years: 77% (50-89)[73] Effectiveness against infection in Israel: ≥70 years: 89·1% (83-93)[79] Effectiveness against death in the UK: ≥65 years: Single dose: 77% (72-81); Two doses: 98% (94-99)[67] Effectiveness against symptomatic infection in the UK, ≥65 years: single dose: 56.6% (47.6-64.1); 2 doses: 86.7% (80.1-91.1)[49] Infection in Canada: 1 dose ≥70 years: 40% (29-50); 2 doses ≥70 years: 93% (82-98)[66] Pooled Moderna and Pfizer vaccines in Portugal: Hospitalisation 65-79 years: 94% (88-97); ≥80 years: 82% (72-89); Death 65-79 years: 96% (92-98); Death ≥80 years: 81% (74-87)[173]
Novavax			Any infection with comorbidity, age ≥65 years or frequent COVID-19 exposure in USA and Mexico: 91.0% (83.6-95.0)[38]	
Sinovac	-	74.9% (53.7-86.4)[41]	Any comorbidity: 48.9% (26.6-64.5)[41]	-
Sinopharm	-	80.7% (56.7-91.4)[41]	-	Effectiveness against symptomatic infection in Bahrain: ≥60 years: 91% (87-94)[41]
Bharat Biotech	-	-	Any infection with comorbidity: 66.2% (33.8-84.0)[26]	Symptomatic infection in India: ≥60 years: 67.8% (8.0-90.0) vs 18-59 years: 79.4% (66.0-88.2)[26]

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Appendix 4: Risk of Rare Unusual Blood Clotting with Low Blood Platelets (Thrombosis with Thrombocytopaenia Syndrome – TTS)

Estimated number of TTS that potentially might occur in Pacific Island Countries if all adults received the AstraZeneca or Johnson & Johnson vaccines, based on most recent official estimate of the adult population in each country and the incidence of these events in Europe and Australia.

COUNTRY	TOTAL POPULATION	ESTIMATED POPULATION AGED 18 YEARS AND OVER*	POTENTIAL NUMBER OF TTS CASES IF ALL ADULTS IN EACH COUNTRY RECEIVED ASTRAZENECA VACCINE**	POTENTIAL NUMBER OF TTS CASES IF ALL ADULTS IN EACH COUNTRY RECEIVED JOHNSON & JOHNSON VACCINE***
American Samoa	55,519	33,311	<1	<1
Cook Islands	15,300	9,180	<1	<1
Federated States of Micronesia	102,300	61,380	0.6-1.2	<1
Fiji	867,000	520,200	5.2-10.4	1.6
French Polynesia	275,918	165,551	1.7-3.3	<1
Guam	159,358	95,615	1.0-1.9	<1
Kiribati	113,400	68,040	0.7-1.4	<1
Marshall Islands	54,900	32,940	<1	<1
Nauru	10,900	6,540	<1	<1
New Caledonia	271,407	162,844	1.6-3.3	<1
Niue	1,611	967	<1	<1
Northern Mariana Islands	53,883	32,330	<1	<1
Palau	18,000	10,800	<1	<1
Papua New Guinea	7,744,700	4,646,820	46.5-92.9	14.6
Samoa	195,979	117,587	1.2-2.4	<1
Solomon Islands	642,000	385,200	3.9-7.7	1.2
Tokelau	1,160	696	<1	<1
Tonga	99,419	59,651	0.6-1.2	<1
Tuvalu	10,507	6,304	<1	<1
Vanuatu	272,173	163,304	1.6-3.3	<1
Wallis and Futuna	11,558	6,935	<1	<1
All Pacific Island Countries	10,976,992	6,586,195	65.9-131.7	20.8

* Based on estimate of 60% of population aged ≥18 years[175]
** Based on estimates of TTS occurring in ~1 in 100,000 vaccinated adults by the European Medicines Agency and ~1 in 50,000 in Australia[18,19]
*** Based on estimates of TTS occurring in ~1 in 319,000 vaccinated adults in USA (may be an underestimate as only cerebral venous sinus thrombosis are reported)[21]

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