Safety and efficacy of the Covid-19 Pfizer-BioNTech vaccination in pregnancy: A systematic review and meta-analysis

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ABSTRACT

BACKGROUND: Pregnant women continue to be excluded from clinical trials, leading to vaccine hesitancy in this vulnerable population. Pfizer-BioNTech vaccination is the primary and widely available Coronavirus disease 2019 (Covid-19) vaccine in New Zealand (NZ). No systematic reviews and meta-analyses of the safety and efficacy outcomes of the maternal, foetal or neonate have been published.

OBJECTIVE: To assess the safety and efficacy of the Covid-19 Pfizer-BioNTech, also referred to as BNT162b2, Comirnaty, or Tozinameran, vaccination during pregnancy.

DESIGN: Systematic review and meta-analysis**.**

METHOD: Electronic databases were searched (Embase, Medline, Web of Science, PubMed, Scopus) to the 4th of February 2023 for the safety and efficacy of the Pfizer-BioNTech vaccination during pregnancy. Studies included had to have a control or placebo group of unvaccinated pregnant women for comparison. Maternal safety outcomes were antepartum bleeding, postpartum haemorrhage, placental abruption, meconium-stained amniotic fluid, gestational diabetes, pregnancy-related hypertension, and death. Foetal and neonatal safety outcomes were miscarriages, stillborn, infant death, preterm delivery with subgroups of <32 weeks, <35 weeks, <37 weeks of gestation, heart malformation, congenital anomalies, neonatal intensive care unit (NICU) admission, neonatal seizures, neonatal respiratory complications, neonatal meconium aspiration syndrome, abnormal foetal heart rate, one and five minute Apgar scores ≤7, small for gestational age (SGA), and birth weight. Efficacy outcomes were documented Covid-19 infection, hospitalisation, severe or critical illness, intensive care unit (ICU) admission and death. Study titles and abstracts were screened, and the full text was obtained if it met the inclusion criteria. All included studies were assessed using the Cochrane Risk of Bias in non-randomized studies of exposure (ROBINS-E). The data was analysed using Revman odds ratios (OR) and 95% confidence intervals (95%CI) for binary outcomes and weighted mean difference and 95%CI for continuous outcomes. Statistical heterogeneity was assessed using the Cochrane Q test and Higgins I^2 test.

RESULTS: Ten cohort studies met the inclusion criteria, with 44,883 pregnant women (mean age, 30.7 years) who received one or two doses of Pfizer-BioNTech compared to the control group of 34,988 unvaccinated pregnant women (mean age 30.0 years). Four studies were judged as having a low risk of bias, four having some concerns, and two as high risk.

There were no statistically significant differences for all outcomes except placental abruption (OR 0.45, 95% CI 0.27 to 0.75), meconium-stained amniotic fluid (OR 0.75 95% CI 0.64 to 0.88), preterm delivery <32 weeks of gestation (OR 0.57, 95% CI 0.39 to 0.83), neonatal respiratory complications (OR 0.65, 95% CI 0.43 to 0.99), neonatal meconium aspiration syndrome (OR 0.52, 95% CI 0.31 to 0.90) and abnormal foetal heart rate (OR 0.64, 95% CI 0.46 to 0.90), documented Covid-19 infections (OR 0.56, 95% CI 0.48 to 0.65) and pregnant women hospitalised with Covid-19 (OR 0.50, 95% CI 0.31 to 0.82) in favour of pregnant women vaccinated with Pfizer-BioNTech.

CONCLUSION: There were no adverse risks associated with the Pfizer-BioNTech vaccination during any trimester of pregnancy, and a small number of maternal, foetal and neonatal outcomes had reduced risk of occurrence. The Pfizer-BioNTech vaccination is safe and effective when used during pregnancy.

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Special thank you to my family, Mum and Dad, extended family, and friends for all their everlasting encouragement, support, and help with my daughter while I was studying. Last but not least, my beautiful daughter Rosealina, kept me motivated with her smiles, giggles, and cuddles. I am looking forward to quality time with my daughter and enjoying the motherhood journey.

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2 INTRODUCTION

On the 31st of December 2019 in China, one of the World Health Organization's (WHO) offices noticed a media statement from the Wuhan Municipal Health Commission website about numerous cases of 'viral pneumonia' and 'pneumonia of unknown cause' in Wuhan.[1] On the 1st of January 2020, WHO contacted Chinese authorities asking for information on the reported cluster of 'atypical pneumonia' in Wuhan.[1] The virus, soon to be well known as Covid-19, took the world by storm, causing thousands of deaths and morbidity worldwide. On the 21st of January 2020, the first confirmed case of Covid-19 was detected in the United States of America (USA). On the 24th of January, the first confirmed cases were detected in Europe, France.[1] End of January 2020, this new virus had spread outside of China to 18 countries with 98 cases.[2] On the 11th of March 2020, the WHO Director-General stated that the Covid-19 outbreak was declared a pandemic, with 114 countries detecting Covid-19 cases, with more than 118 000 confirmed cases and 4291 deaths recorded with Covid-19.[1 2] Cities and countries all around the world went into lockdown, hospitals were at total capacity, face masks became compulsory, and pharmaceutical companies were rapidly trying to produce a vaccine to help protect the world. The first case was confirmed in NZ, Aotearoa 28th February 2020, and the entire country went into lockdown on the 25th of March 2020.[3 4] The New Zealand government went for the elimination strategy; the borders to the rest of the world were closed, vaccine passes were created, and mandates were put in place.[5 6] New Zealand implemented legislation for a Covid-19 Public health response (vaccination order) 2021 and all health and disability, education, and prison staff had to have their first dose of the Covid-19 vaccination by the 15th of November 2021 and be fully vaccinated with two doses by the 1st of January 2022.[7]

I am a registered nurse with 20 years of experience. I was working in the busiest emergency department in the southern hemisphere when the Covid-19 pandemic started. During NZ's last and Auckland's most prolonged lockdown in 2021, I had my first positive pregnancy test at the age of 40. Vaccinations for Covid-19 had only been available since December 2020, and no data was available for pregnant women having the Pfizer-BioNTech, as it had only been tested on pregnant rats. The mandate in NZ to be vaccinated as a nurse became compulsory on the 15th of November 2021. I reluctantly declined the Pfizer-BioNTech vaccination due to my age, first pregnancy and no human studies being completed and published on the safety and efficacy of the vaccination during pregnancy; this decision was not easily made. I made an informed decision with what evidence-based information was available then. I had one more year to complete my Master's, for which I had been awarded a scholarship from the Victoria League. With the University's approval, I could continue my studies externally, with this dissertation being the last paper to complete my Master's in Nursing. I could understand the hesitancy in 2021 with the Pfizer-BioNTech vaccination during pregnancy. This background is how my review question came about; What is the safety and efficacy of the Pfizer-BioNTech (BNT162b2, Comirnaty, Tozinameran) vaccination during pregnancy? Numerous studies have been published worldwide, and some are still in progress regarding the safety and efficacy of the different Covid-19 vaccinations during pregnancy. However, this systematic review and meta-analysis specifically focused on the Pfizer-BioNTech, as this vaccination was first available, widely provided, and used in NZ. By completing this systematic review and meta-analysis, I hope all those hapu mamas (pregnant women) can make an informed decision about getting vaccinated during pregnancy, and future hesitancy and reluctance can be addressed or help answer some of those concerning questions. Due to giving birth to my daughter in mid-2022, halfway through completing my dissertation, I was granted a suspension. When I started this dissertation in semester one of 2022, no systematic reviews and meta-analyses were published about the safety and efficacy of Covid-19 vaccinations during pregnancy. However, when I restarted in semester one, 2023, some reviews had been published but combined mRNA, Pfizer-BioNTech, and Moderna (mRNA-1273) vaccinations in their results. The Moderna mRNA vaccine was not available in NZ, only the Pfizer-BioNTech mRNA vaccination. Therefore there was a gap in the literature research with no reviews reporting only on the Pfizer-BioNTech vaccination, which New Zealanders could use to make an informed decision regarding vaccination, and health professionals could utilise for their evidence-based practice. I therefore continued and completed this systematic review and meta-analysis for my dissertation.

This systematic review and meta-analysis is organised in the following way:

- Background: is broken down into nine small sections for simplicity, including what is coronavirus, angiotensin-converting enzyme 2 (ACE-2) receptors, transmission, Covid-19 vaccinations, how Covid-19 affects the body, pregnant women were excluded from vaccination trials, pregnant women's advice and hesitancy towards the Covid-19 vaccination, Pfizer-BioNTech vaccination timeline and why it was necessary to carry out this systematic review and meta-analysis.

- Method: includes the objective, search strategy (protocol, key search terms and databases searched), selection criteria (types of studies, participants, intervention, and outcomes), data collection (selection of studies and data extraction and management), risk of bias assessment and data analysis.
- Results: includes six forest plots of maternal safety outcomes, fifteen safety outcomes for foetal and neonatal outcomes and three forest plots for efficacy outcomes.
- Discussion: includes key messages, comparison with previous reviews, strengths, limitations, publication bias and clinical and research implications.
- Conclusion
- Appendices: Appendix One – the study protocol, Appendix Two – table of risk of bias for individual studies.

3 BACKGROUND

3.1 WHAT IS CORONAVIRUS

Coronaviruses come from the Coronaviridae family and the subfamily Coronavirinae.[8 9] Coronaviruses have the largest genome size compared to all other RNA viruses.[10] Covid-19 was the third zoonotic coronavirus transmission from animal to human in the last two decades.[9] Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) 2003 in Asia and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) 2012 in the Middle East were transmitted from civets and camels, respectively. However, both coronaviruses are believed to originate from bats. [8 9 11]

Coronavirus infections in humans and animals are generally transmitted by respiratory and oral-faecal routes causing respiratory or intestinal infections. The four human coronaviruses (HCoVs), HCoV229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, usually cause only mild upper respiratory disease, like a common cold, in immunocompetent adults. However, in the elderly, children or immunocompromised population, human coronaviruses can cause severe illness.[8 9] SARS-CoV and Covid-19 cause severe acute respiratory illnesses with high morbidity and mortality rates among infected people.[9] Globally, from the WHO dashboard on the 10th of May 2023, there were 765,903,278 confirmed cases of Covid-19 and 6,927,378 deaths.[12] In NZ, on the 10th of May 2023, there were 2,321,399 confirmed cases of Covid-19 and 2,792 deaths.[13]

Corona means crown in Latin, and coronaviruses get their name from the crown-like spikes on their outer surfaces.[9 14] Coronaviruses are large enveloped, positive single-stranded RNA viruses made up of four protein structures, the spike, membrane, envelope, and nucleocapsid. Covid-19 spike proteins bind to the host angiotensin-converting enzyme 2 (ACE-2) receptors to enter the host cell.[9 15-18] Covid-19 spike proteins bind ten times stronger than other coronaviruses. The spike protein is made up of two functional subunits, S1 which are responsible for binding to the host cell receptor, and S2 is involved in the fusion of the virus into the host cellular membranes.[16 18-20] The Covid-19 outer surface spike glycoprotein that binds to the host cell is the key target for vaccinations, therapies, and diagnosis.[16 20]

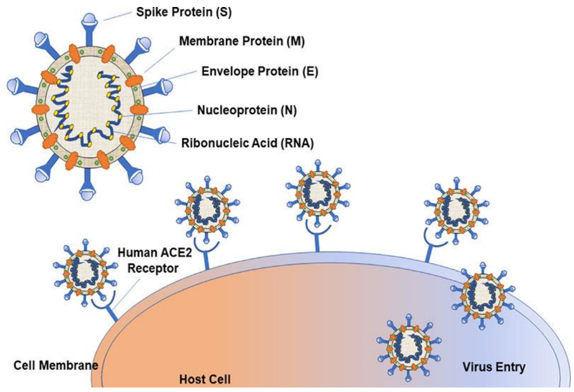

Figure 1. Covid-19 virus binds to ACE-2 receptors of the host cell to enter into the cell to replicate. Used with permission.[21]

3.2 ANGIOTENSIN-CONVERTING ENZYME 2 RECEPTORS

Covid-19 spike protein attaches to ACE-2 receptors to enter the host cell, where the virus RNA is released into the cytoplasm and replicates.[22 23] ACE-2 is highly expressed in type 2 pneumocytes in the lungs. When Covid-19 attaches to the ACE-2 and replicates, it decreases its function and oxygen exchange.[17 22] Covid-19 is not just isolated to the lungs and respiratory system, causing pneumonia or severe respiratory distress; it can affect multiple systems of the body, causing multiple organ dysfunction syndrome (MODS).[23-25] ACE-2 receptors are found throughout the body in the epithelial cells, endothelium and vascular smooth muscle cells, brain, retina, oral and nasal mucosa, nasopharynx, lungs, heart, gastrointestinal, liver, kidneys, gallbladder, and pancreas (Table 1).[18 23-26] The body responds with an immune response to the invasion of Covid-19. Sometimes an imbalanced immune response can result in a cytokine storm, which can lead to multiple organ dysfunctions as seen in numerous patients with Covid-19.[23 27 28] The body's innate immunity, including macrophages and neutrophils, first responds to the Covid-19 invasion.[23 28] Cytokines including interleukins, interferons, chemokines, and tumour necrosis factors predominantly activated by the macrophages regulate the inflammation response to Covid-19, either causing a pro or anti-inflammation response.[23 28 29] Inflammation is vital to maintain tissue homeostasis.[29] A cytokine storm occurs when a hyperactive innate immune response to the Covid-19 invasion and an uncontrollable excess release of cytokines occurs, which can cause local or systemic vasculitis throughout the body.[28 30 31] Covid-19 is a systemic inflammatory vascular disease and can cause thromboembolism in the blood vessels.[31 32] The excess pro-inflammatory response from the cytokines leads to hyperinflammation and vasculitis, which have an adverse effect and destroy healthy cells and cause endothelial and epithelium dysfunction, resulting in respiratory distress syndrome (ARDS), sepsis, coagulation impairment, leading to MODS and death.[28 30 32] Patients who have MODS may need haemodialysis or even require a kidney transplant and admission to an intensive care unit (ICU) for interventions including mechanical ventilation and extracorporeal membrane oxygenation (ECMO).[24 33]

3.3 TRANSMISSION

Covid-19 is now considered aerosol transmitted from person to person with small respiratory droplet nuclei.[16 17] WHO defines droplet transmission when the particles are greater than five micrometres and droplet nuclei when the particles are less than five micrometres.[34] At the start of the pandemic, there was debate and controversy about Covid-19 being droplet versus aerosol transmission amongst health authorities, WHO and CDC, and scientists, respectively.[35-38] On the 29th of March 2020, WHO declared that Covid-19 was transmitted through close contact, within one meter, by respiratory droplets, by an infected person with respiratory symptoms including coughing and sneezing. Transmission could also occur by indirect contact with contaminated surfaces from someone with Covid-19. WHO declared in the same statement that airborne transmission could be possible with medical procedures that cause aerosols, including endotracheal intubation, open suction, tracheostomy, nebulised treatments, and cardiopulmonary resuscitation.[34] The WHO tweeted on the same day, 29 March, stating that Covid-19 was not airborne.[39] The guidelines from WHO were droplet and contact precautions, but airborne precautions were advised when performing aerosol medical tasks.[34] A study published in March 2020 documented that Covid-19 was still viable in the air as aerosols after three hours.[40] In July 2020, 239 scientists wrote to the health authorities pleading that they recognise that Covid-19 was more likely to be airborne and that exposure could occur at distances greater than one to two meters apart from an infected person. The scientists stated that indoor aerosol particles could spread more than ten meters. The letter advised on precautions that should be taken to help reduce aerosol transmission, including having adequate and effective ventilation, air filtration, and avoiding overcrowding.[37] Numerous studies were carried out in 2020 suggesting that Covid-19 was more likely to be aerosol transmitted, including a study published in December 2020 on a group of infected people in an apartment building in Seoul, South Korea. The bathrooms in two vertical sets of apartments in a block of apartment buildings were connected with a single air duct, where a cluster of positive Covid-19 infections occurred in individuals who had no contact with each other, suggesting aerosol transmission.[41] Sixteen months into the pandemic and on the 30th of April 2021, WHO announced that Covid-19 could be transmitted by large respiratory droplets and smaller aerosols and recommended good ventilation.[35 36] Finally, on the 23rd of December 2021, nearly two years after the pandemic started, WHO stated on their website that Covid-19 could be transmitted by aerosol, also referred to as airborne transmission.[35 42] In May 2021, CDC documented on their web site that Covid-19 was transmitted by aerosol particles, and can remain in the air for minutes to hours, travelling further than two metres.[38]

3.4 COVID-19 VACCINATIONS

Covid-19 vaccinations were developed to protect against Covid-19 disease so the body's immune system could recognise the virus, activate an immune response, and help prevent Covid-19 infections.[43] The spike protein on the surface of the SARS-CoV-2 helps the virus enter human cells, and therefore these spikes were the target for Covid-19 vaccines.[16 20] The different types of Covid-19 vaccinations that have been produced are messenger RNA (mRNA), viral vector, protein subunit, and inactivated vaccine.[44] The Food and Drug Administration (FDA) has approved four Covid-19 vaccinations under the emergency use of authorisation (EUA), including Pfizer-BioNTech on 11 December 2020, Moderna (mRNA-1273) on 18 December 2020, Johnson and Johnson (Ad26.CoV2.S) on 27 February 2021 and Novavax (NVX-CoV2373) on 13 July 2022.[45] In NZ, the first available and widely used vaccination for Covid-19 was Pfizer-BioNTech, although later through the pandemic, the Johnson and Johnson, and Novavax vaccines became available.[46]

Pfizer-BioNTech and Moderna are both mRNA vaccinations. Researchers have been studying and working with mRNA vaccines for over 30 years for oncology and infectious diseases.[47-49] However, Pfizer-BioNTech and Moderna Covid-19 vaccinations were the first mRNA vaccines to be authorised by the FDA.[45] These Covid-19 mRNA vaccinations have more significant benefits than the other vaccines with shorter manufacturing times due to their synthetic nature, high potency, rapid development, and low cost.[48 50] mRNA vaccinations do not contain a live or inactivated virus and do not affect or interact with people's DNA because mRNA vaccines do not get into the nucleus of cells where DNA is stored.[43 51]

The Pfizer-BioNTech vaccination contains the genetic code for the spike protein on the outer surface of Covid-19.[19 44 52] Pfizer-BioNTech vaccines have four main ingredients, mRNA molecules for encoding Covid-19 spike protein, lipid nanoparticles to encapsulate, protect and transfer the mRNA into the cells, salt buffers to maintain the pH of the vaccine and sucrose to help the molecules to keep shape during freezing and storage.[44 53] Once the mRNA vaccine is administered intramuscularly and attaches to the host cells, it inserts the mRNA into the cytoplasm of the cell, not the nucleus, and the host cell replicates the spike protein, which activates the body's immune system to respond.[18 44] The body develops antibodies, causing both a humoral and cellular immune response, to protect against Covid-19. After being vaccinated with Pfizer-BioNTech, with any further exposure to Covid-19, the immune system will recognise the virus and help prevent infections or serious illness.[43 51]

The Johnson and Johnson and the AstraZeneca are both viral vector vaccines. The Johnson and Johnson vaccine has the gene for the SARS-CoV-2 spike protein combined with the DNA of a different human respiratory virus called adenovirus twenty-six.[54 55] Once the adenovirus is modified not to cause Covid-19 and administered intramuscularly, it enters the body cells and releases its viral DNA. The adenovirus DNA instructs the body's cells to copy and reproduce the spike protein, which activates the body's immune system to produce antibodies, causing a humoral and cell-mediated immune response.[54 55] In a person vaccinated and exposed to Covid-19, their immune system can recognise the virus and help prevent infections. The AstraZeneca viral vector vaccine uses a chimpanzee adenovirus, ChAdOx1, based on ChAdY25, and activates an immune response like the Johnson and Johnson vaccine.[44 56 55 57]

Novavax is a protein subunit vaccine. Subunit vaccines are composed of tiny amounts of virus particles, for example, protein or glycoprotein, which induce humoral and cellular immunity. Novavax is different from mRNA and vector vaccines in that it contains nanoparticles of the Covid-19 spike protein, which cannot cause the disease but stimulates a humoral and cell-mediated immune response.[44 58 59]

Sinovac (CoronaVac) is an inactivated vaccine made in China and not used in NZ. Sinovac uses inactivated Covid-19 virus particles to activate an immune response. Sinovac uses cultured African green monkey kidney Vero cells to replicate the Covid-19 virus and beta propiolactone to inactivate the virus, maintaining the antigen component that activates an immune response when administered.[44 60]

3.5 HOW COVID-19 AFFECTS THE BODY

Covid-19 enters the body through the respiratory system. It can cause mild symptoms like a common cold to severe respiratory distress, but it can also affect multiple organs and different systems in the body (Table 1).[61] The WHO stated that most people who contract Covid-19 will have mild to moderate respiratory symptoms and recover without treatment or hospitalisation.[62] However, some people may become seriously unwell, including the elderly and those with pre-existing medical conditions, such as cardiovascular disease, diabetes, chronic respiratory disease, and immunocompromised or oncology patients. According to the WHO, the most common symptoms are fever, cough, tiredness, and loss of taste or smell.[62] Serious symptoms include difficulty breathing, shortness of breath, loss of speech, decreased mobility, confusion, and chest pain. Less common symptoms include sore throat, headache, aches and pains, diarrhoea, a rash on the skin, or red or irritated eyes.[62]

Table 1. Where ACE-2 is expressed in the organs and systems of the body and the effects of Covid-19[23-25 27 28]

SYSTEMS/ORGANS	ACE-2 Expression	Multiple organ injuries caused by Covid-19
Respiratory - lungs	Highly expressed on the type 2 pneumocytes in the lower respiratory tract and upper respiratory airways goblet and ciliated epithelial cells	Acute respiratory distress syndrome (ARDS), pneumothorax, pneumonia, pulmonary embolism, pulmonary oedema, and decreased lung function
Vascular system	Expressed endothelial cells of small and large blood vessels, migratory angiogenic cells and vascular smooth muscle cells	Venous thromboembolic event, inflammatory cell infiltration, raised plasma D-dimer, disseminated intravascular coagulation, microvascular thrombosis, coagulation impairment, hypercoagulation, deep vein thrombosis, thrombocytopenia, endothelial dysfunction
Heart	Highly expressed in cardiomyocytes and pericytes, present in the cardio fibroblasts, endothelial cells, and epicardial adipose cells	Acute cardiac injury, Myocarditis, arrhythmias, heart failure, acute myocardial infarction, cardiac arrest, oedema of the myocardial stroma, atrophy of cardiac muscle fibres, acute coronary syndrome, cardiogenic shock
Renal system – kidneys	Highly expressed in the kidneys, especially in the proximal tubular epithelial cells. Present in the glomerular endothelial cells, podocytes, and kidney vasculature	Acute kidney injuries, raised creatinine, haematuria, proteinuria, focal necrosis, vasculitis of small veins, kidney failure
Gastrointestinal	Highly expressed in the small intestines, duodenum, jejunum, and ileum in the epithelial cells and enterocytes.	Diarrhoea, nausea, vomiting, irritable bowel syndrome, melena, anorexia, gastrointestinal bleeding, abdominal discomfort, gut dysbiosis

SYSTEMS/ORGANS	ACE-2 Expression	Multiple organ injuries caused by Covid-19
Liver	Highly expressed in the hepatocytes and cholangiocytes	Acute hepatic injury, liver dysfunction, elevated aminotransferases, elevated bilirubin
Pancreas	Highly expressed in the pancreatic islet beta cells	Focal inflammation, inflammation, Islet damage, elevated serum amylase, elevated lipase levels, pancreatitis, pancreatic tissue injury, insulin-dependent acute diabetes, hyperglycaemia, diabetic ketoacidosis
Gallbladder	Highly expressed in gallbladder epithelial cells	Cholangiocytes damage
Immune system		Cytokine storm, elevated inflammatory markers including interleukin, decreased lymphocytes, especially CD4 and CD8 T cells, adaptive immunity decreases, innate immunity increases
Central nervous system – brain, retina	Widely spread in the brain, the endothelium and vascular smooth muscle cells, and highly expressed in the neurons. In the retina, pigmented epithelial cells, road, and cone photoreceptor cells	Oedema, degeneration of neurons, olfactory and gustatory dysfunction, encephalitis, acute cerebrovascular disease, headache, dizziness, impaired concentration, Guillain-Barre syndrome
Thyroid glands	Thyroid follicular epithelial cells	Thyroid dysfunction
Skeletal muscle	Dystrophic muscles	Myofiber necrosis, atrophy, muscle weakness, elevated serum creatine kinases
Skin	Present in the basal cell layer of the epidermis, and keratinocytes	Purpuric lesions, petechiae, erythematous rash, urticaria

Pregnant women were categorised as high risk because of concerns about the effects of Covid-19 during pregnancy and the impact on the foetus and neonate.[63 64] During pregnancy, women undergo physiological changes, including cardiovascular, respiratory and immune system changes, which can make the pregnant women, foetus and neonatal more susceptible and change the body's response to Covid-19 compared to a non-pregnant woman.[65 66] During pregnancy, some adaptive immunity responses are decreased, including B cells and T cells, although the innate immunity, natural killer cells, monocyte and cytokine response is increased.[67] The most common symptoms of Covid-19 during pregnancy were fever and cough.[61 63 68] Other frequent symptoms included myalgia, fatigue, diarrhoea, dyspnoea, headache, and chest tightness.[61 69] Pregnant women were more susceptible to severe Covid-19.[64] Dyspnoea is a common symptom of Covid-19, and a common physiological response during pregnancy due to uterus enlarging, increasing the abdominal pressure and lifting the diaphragm, reducing lung capacity, functional residual capacity, and increased placenta and foetal oxygen demand.[64 69]

Pregnant women with Covid-19 have increased odds of delivering preterm, stillborn, preeclampsia, admission to ICU, and increased risk of maternal death compared to pregnant women without Covid-19.[63 65 70] Pregnant women with severe Covid-19 also have increased odds of preeclampsia, preterm birth, gestational diabetes, and low birth weight compared to pregnant women with mild Covid-19.[65 70] Pregnant women with pre-existing comorbidities and medical conditions including hypertension, diabetes, asthma, increased maternal age, high body mass index (BMI), and pregnancy-related medical conditions including gestational diabetes and pre-eclampsia and diagnosed with Covid-19 had increased risk of severe complications including admission to ICU, invasive ventilation and maternal death.[63 68] Neonates born to mothers with Covid-19 had increased odds of being admitted to the neonatal intensive care unit (NICU) compared to neonates without Covid-19-positive mothers.[63 65 70]

One systematic review concluded that Covid-19 clinical presentations in pregnancy were similar and not worse compared to the general population, with two maternal deaths out of 364 pregnant women with Covid-19 from severe pneumonia and multiple organ dysfunction.[61] One in four women between 15-49 years old hospitalised with Covid-19 were pregnant, although these admissions might have occurred due to having a lower threshold for admitting pregnant women.[68] Sixteen per cent of the pregnant women were admitted to ICU, and 8.5% needed invasive ventilation.[68] Symptomatic pregnant women with Covid-19 were three times more likely to have a preterm delivery compared to asymptomatic pregnant women.[68] Larger numbers of pregnant women in their third trimester were diagnosed with Covid-19.[61 64]

3.6 PREGNANT WOMEN WERE EXCLUDED FROM VACCINATION TRIALS

Pregnant women have always been an exclusion criterion for vaccination research, including Covid-19 vaccine trials.[70] Pregnant women were excluded from the first trials of Covid-19 vaccines, even with the knowledge from past viruses, including SARS-CoV and MERS-COV, that pregnancy increased illness severity and mortality, and about one-third of infected pregnant women died.[64 71] In 2016, the 21st Century Cures Act established the Pregnancy and Lactating Women (PRGLAC) Task Force to inform the gaps, knowledge and research on the safety and effectiveness of therapies, including vaccinations for pregnant and lactating women, to the Secretary of Health and Human Services.[72] The FDA Office of Women's Health (OWH) oversees pregnancy and lactation research and works with the PRGLAC Task Force.

However, pregnant women are still excluded from participating in clinical trials creating inequity and limiting access to potentially life-saving medications.[73] Pregnant women should be given the same choice and opportunity as non-pregnant women and other adults and decide if they want to be part of a clinical trial.[74] Pregnant women are usually excluded from clinical trials due to safety reasons and the unknown potential effects of clinical trial drugs on foetal growth and development if it crosses the placenta. During pregnancy, numerous physiologic changes, including maternal blood volume, alter pharmacokinetics, effects pharmacodynamics, bioavailability, absorption, distribution, metabolism, and excretion of medications. Therefore, it is easier to exclude pregnant women from clinical trials.[75] Throughout the pandemic, there have been gaps in research and information about the safety and efficacy of Covid-19 vaccines in pregnancy that led to global differences in guidance.[70]

3.7 PREGNANT WOMEN'S ADVICE AND HESITANCY TOWARDS THE COVID-19 VACCINATION

In January 2021, there was conflicting information from the Centers for Disease Control and Prevention (CDC), the WHO, Pfizer, the American College of Obstetricians and Gynaecologists (ACOG) and the Society of Maternal-Fetal Medicine (SMFM) regarding pregnant women and Covid-19 vaccination.[76] Organisations' statements included that Covid-19 vaccinations were unlikely to cause risks to pregnant women and the foetus (although actual risks are unknown), high-risk pregnant women including those in the medical professions were advised to have the vaccination and other pregnant women to withhold from doing so, to have the vaccination if the benefits outweigh the potential risks, to consult with your doctor, and that it is the individual pregnant women's personal choice.[76] Around the world, different countries had different policies and recommendations for pregnant women, including some countries recommending the vaccination, others recommending vaccination only for those at high risk of exposure, decisions left up to the individual's Doctor, that vaccination was contraindicated for pregnant and lactating women, and that there was insufficient information on safety and efficacy, while some countries prioritised pregnant women.[77] Covid-19 vaccine clinical trials excluded pregnant women, but then pregnant women were encouraged to have the vaccine before any clinical trials on pregnant women were completed.[49 71 73] Pregnant women's doctors, midwives or obstetricians had to weigh the risks of Covid-19 exposure with the risk and benefits of the Covid-19 vaccination with the limited research and data available on vaccination during pregnancy.[78]

Pfizer stated that data was insufficient to inform vaccination of Pfizer-BioNTech safety risks in pregnant women. However, developmental toxicity studies had been carried out on female rats administrating Pfizer-BioNTech with two doses before mating and two doses during pregnancy. These Pfizer studies showed no evidence of harm or vaccine-related adverse effects on female rat fertility, rat foetal development or postnatal rat development. Pfizer encouraged pregnant women vaccinated with Pfizer-BioNTech during pregnancy to register on the pregnancy exposure registrar.[79] However, there was very little information about the safety and efficacy of the Pfizer-BioNTech vaccine from the women who had the vaccination during the trials and became pregnant.[49 73]

Many pregnant women hesitated to be vaccinated against Covid-19, with concerns regarding the vaccine's safety.[66 71 80] Vaccine hesitancy during pregnancy is understandable, as women continued to be excluded from the trials. Social media, misinformation, statements about Covid-19 vaccinations around infertility, and concerns about unknown effects during pregnancy and long-term effects on the foetus and neonate led to vaccine hesitancy and acceptance.[49] Several studies have noted that vaccine hesitance in pregnant women also included concerns in the last two decades about the increased cases of autism.[66] Some pregnant women were fearful that the Covid-19 vaccination would harm the foetus and had increased apprehension at having the vaccination during the embryogenesis phase.[81 82] It is understandable that pregnant people were apprehensive and hesitant, given that thalidomide had been used in the 1950s and early 1960s to treat nausea in pregnant women, which caused severe congenital anomalies and deformities in thousands of children.[83] The leading reason for Covid-19 vaccination hesitancy and acceptance during pregnancy was a lack of information regarding safety during pregnancy and apprehensive of short and long-term effects on the foetus and neonate.[84] Another reason pregnant women refused the Covid-19 vaccination was because they had tested positive for Covid-19 infection.[84] Some pregnant women declined the vaccination while pregnant but planned to have it after giving birth.[84] A survey of 16 countries worldwide indicated that 52 per cent of pregnant women would accept the Covid-19 vaccination if it had a 90% efficacy.[80] A systematic review and meta-analysis of 19,219 pregnant women found that only 53.5 per cent would accept the Covid-19 vaccination.[85] Another systematic review and meta-analysis of 25,147 pregnant women found that only 49 per cent would accept a Covid-19 vaccination.[66] However, vaccine acceptance was higher in pregnant women with a medical history and comorbidities, those employed, those with higher education, and in the primigravida.[66]

3.8 PFIZER-BIONTECH VACCINATION TIMELINE

On the 2nd of December 2020, the United Kingdom was the first country to approve a Covid-19 vaccine under emergency use authorisation (EUA) called Pfizer-BioNTech, only seven months after clinical trials started.[86] There was no safety and efficacy data yet on pregnant women or children, which are often carried out once the safety and efficacy have been researched in healthy adults.[86]

On the 11th of December 2020, the United States Food and Drug Administration [87] announced the first Covid-19 vaccine, Pfizer-BioNTech, to be issued and used as a EUA (emergency use authorisation) against covid-19 disease for 16 years of age and over. The FDA evaluation from a clinical trial stated that the vaccine was 95% effective in preventing Covid-19 disease. However, this appears to be ambiguous, with follow-up statements saying there was no evidence that the vaccine would provide prevention of transmission of Covid-19 from person to person, and no data was available on how long the vaccination would provide protection.[87]

On the 19th of January 2021, the Israel Ministry of Health released a statement recommending and encouraging all pregnant women to receive the Covid-19 vaccination.[88] Women vaccinated before the government statement were in occupations of high-risk exposure, including medical and education staff.[81] Israel was one of the leading countries in the world, with 536 articles and studies regarding the Covid-19 vaccine published between January 2020 and June 2022. Eighty of the studies were highly cited papers, 36 were in the top 0.1% in the academic field, known as hot papers, and most of these analysed the safety and or efficacy of the Pfizer-BioNTech Covid-19 vaccine.[89]

On the 18th of February 2021, Pfizer announced the beginning of Pfizer-BioNTech Covid-19 vaccine studies in 4,000 healthy pregnant women over 18 years old.[90] The study was to look at the safety, tolerability, and immunogenicity of two doses of the Pfizer-BioNTech Covid-19 vaccination during 24 to 34 weeks gestation. Pfizer was continuing subpopulation research, including pregnant women, to potentially support using Pfizer-BioNTech during pregnancy. The clinical trials identifier number is NCT04754594.[90]

On the 3rd of February 2021, New Zealand's Medsafe provisionally approved the Pfizer-BioNTech Covid-19 vaccination.[46] The first batch of Pfizer-BioNTech vaccinations arrived in NZ on the 15th of February, and the first dose was administered on the 19th of February 2021.[91] [92] The rollout of the Pfizer-BioNTech vaccination for pregnant women in NZ started on the 10th of June 2021.[93] On the 23rd of August 2021, FDA announced that Pfizer-BioNTech was the first Covid-19 vaccination to be approved and not under EUA.[94] FDA commenced a pregnancy registry study to continue to evaluate pregnant women and infant outcomes.[94] On December 2021, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists stated that the mRNA Covid-19 vaccination was recommended for pregnant and breastfeeding women.[95] In NZ, Pfizer-BioNTech was the only Covid-19 vaccination approved for pregnant women.[96]

3.9 WHY WAS IT NECESSARY TO CONDUCT THIS SYSTEMATIC REVIEW AND META-ANALYSIS

It was necessary to carry out this systematic review and meta-analysis because there was a gap in the research with no safety and efficacy reviews of just the Pfizer-BioNTech vaccination alone during pregnancy. There were conflicting messages between different health authorities and the media, which led to hesitancy and decline of the Pfizer-BioNTech vaccination. It was essential to complete this systematic review and meta-analysis for evidence-based practice for health professionals to inform and educate pregnant women. Pregnant women then have the best available evidence, information, and statistical data to make an informed choice in accepting or declining the Pfizer-BioNTech vaccination. This review only included the Pfizer-BioNTech vaccine, the primary vaccination available and administered throughout NZ.

4 METHOD

4.1 OBJECTIVE

Conduct a systematic review and meta-analysis on the safety and efficacy of the Covid-19 Pfizer-BioNTech (also called BNT162b2, Comirnaty, or Tozinameran) vaccination during pregnancy, including the safety outcomes for the mother, foetus, and neonate.

4.2 SEARCH STRATEGY

4.2.1 Protocol

A protocol was written a priori, setting the objective of the systematic review and the search strategy, selection criteria, data collection and analysis (Appendix One).

4.2.2 Key Search Terms

The search terms below were used:

Population: Pregnant, Pregnancy, Pregnant women, first trimester, second trimester, third trimester

Exposure: Pfizer-BioNTech, Comirnaty, BNT162b2, Tozinameran

Safety: Severe adverse reactions, severe adverse effects, severe adverse events, miscarriages, spontaneous abortion, stillborn, stillbirth, birth defects, congenital abnormalities, deformities, teratogenic, premature birth, preterm birth, neonatal seizures, neonatal pulmonary haemorrhage, pre-eclampsia, eclampsia, maternal haemorrhage, placenta abruption, placenta calcification

Efficacy: Effectiveness benefits, transmission, spreading, transferring, hospitalisation, ICU admissions, High dependency unit (HDU) admissions, critical care, death, mortality

4.2.3 Databases searched

Five electronic databases were searched, Embase, Medline, Web of Science, PubMed, and Scopus, to the 4^{th} of February 2023. The reference lists of included published studies were hand searched for additional relevant studies.

4.3 SELECTION CRITERIA

4.3.1 Types of Studies

Studies included had to have a control or placebo group of pregnant women, so a comparison could be made between pregnant women receiving the Pfizer-BioNTech vaccination and pregnant women not receiving the Pfizer-BioNTech vaccination. Study designs that could be included were randomised controlled trials, case-control studies, or cohort studies. All studies had to be written in the English language and published.

4.3.2 Types of Participants

The participants had to be people who were pregnant at enrolment and in any trimester of their pregnancy.

4.3.3 Type of Intervention

The pregnant women had to be vaccinated with the Pfizer-BioNTech (BNT162b2, Comirnaty, Tozinameran) during their pregnancy. All studies were included irrespective of whether the women received one or two doses of the Pfizer-BioNTech vaccination.

4.3.4 Types of Outcomes

The outcomes of interest were the safety and efficacy of the Pfizer-BioNTech during pregnancy. The outcomes of interest for the safety of the Pfizer-BioNTech were miscarriages, stillborn, stillbirth, congenital anomalies, premature birth, damage to the placenta, pulmonary haemorrhaging, seizures in the neonate, pre-eclampsia, eclampsia, maternal haemorrhage and foetal, neonatal, or maternal death. The outcomes of interest in the efficacy of the Pfizer-BioNTech were stopping or reducing transmission, preventing or reducing hospitalisation, preventing or reducing severe illness, preventing or reducing ICU admissions, and preventing or reducing death.

4.4 DATA COLLECTION

4.4.1 Selection of Studies

References were imported and managed in EndNote (version 20.5) reference management software, and duplicates were removed. There were two stages to the screening process. The titles and abstracts of the studies were first screened to determine if they met the inclusion criteria. When there was uncertainty about whether the study met the inclusion criteria, they were kept for full-text screening. With the remaining studies, the entire study was screened to see if they met the inclusion criteria.

4.4.2 Data Extraction and Management

Data from the included studies were extracted into Microsoft Excel spreadsheets. A separate Microsoft Excel worksheet for each study was set up to summarise the study, including reference, title, country of study, year, aim, the method including study design, data collection, where, period, inclusion criteria and exclusion criteria, participants included total number pregnant women, control and Pfizer-BioNTech vaccination, subgroup analysis, first, second and third trimester, the intervention included one or two doses, results, conclusion, study strength and limitations, and risk of bias assessment. These worksheets were then summarised in two separate spreadsheets, one for the safety outcomes and one for the efficacy outcomes.

4.5 RISK OF BIAS ASSESSMENT

As there were no randomised controlled trials, the included studies were assessed using the Cochrane Risk of Bias in non-randomized studies of exposure (ROBINS-E). There were seven domains that each study was assessed against:

- **Domain one** - risk of bias due to confounding factors
- **Domain two** - risk of bias arising from the measurement of the exposure
- **Domain three** - risk of bias in the selection of participants for the study
- **Domain four** - risk of bias due to post-exposure interventions
- **Domain five** – risk of bias due to missing data
- **Domain six** – risk of bias arising from the measurement of outcomes
- **Domain seven** – risk of bias in selection of the reported results

The studies were categorised into four levels of risk of bias:

- **Low risk of bias** – low risk of bias in domain two to domain seven. Exception for domain one due to the nature of observational studies where confounding factors may occur.

- **Some concerns of risk of bias** - at least one domain was categorised as some concerns, but no domains were high risk or very high risk of bias.
- **High risk of bias** - at least one domain was at high risk of bias, but no domains were at very high risk of bias.
- **Very high risk of bias** - at least one domain was at very high risk of bias.[97]

4.6 DATA ANALYSIS

The data were meta-analysed using RevMan 5.4.1 to create forest plots for all outcomes with odds ratios (OR) and 95% confidence intervals (95%CI) reported. Six meta-analyses were for maternal safety outcomes, fifteen were for foetal and neonatal safety outcomes, and three were for efficacy outcomes. Statistical heterogeneity was used to assess the consistency of effects in the interventions between the different studies. Heterogeneity was not considered statistically significant when a P value was over 0.10.[98] The I^2 percentage was used to assess the proportion of heterogeneity due to chance: 0% to 40% heterogeneity was not considered to be important, 30% to 60% was considered to be moderate heterogeneity, 50% to 90% was considered to be substantial heterogeneity and 75% to 100% was significant heterogeneity.[98] The threshold for overall statistical significance for the treatment effects was a p-value of 0.05.[98]

5 RESULTS

5.1 STUDY SELECTION

One thousand four hundred and sixteen studies were initially identified and a further ten studies were identified by searching the reference lists of obtained studies and reviews. Five electronic databases were searched to the 4th of February 2023 (Figure 2); Embase (n=758), Medline (n=428), Web of Science (n=67), PubMed (n=109) and Scopus (n=54). Six hundred and forty-six duplicates were removed after import into Endnote. After screening the titles and abstracts, 630 studies were excluded. The full papers for 150 studies were obtained and screened for inclusion criteria. Overall ten studies met the inclusion criteria.

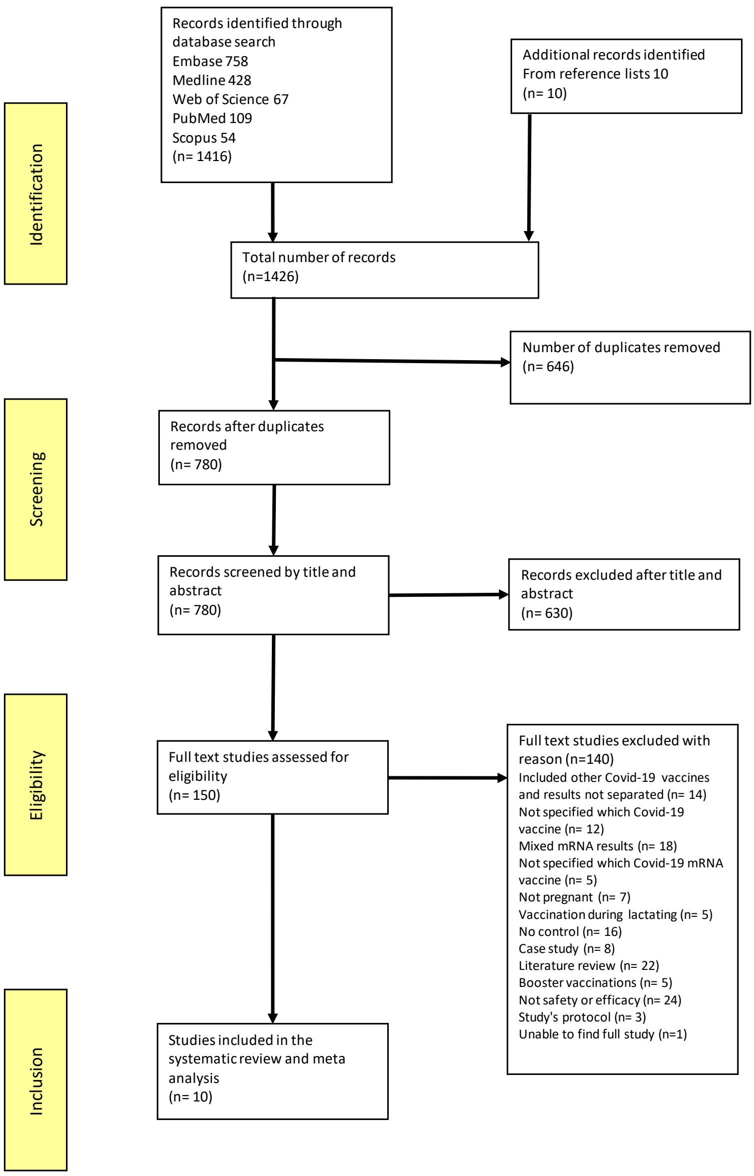

Figure 2. PRISMA flowchart of the studies selected for the systematic review and meta-analysis

5.2 DESCRIPTIVE CHARACTERISTICS OF THE STUDIES

The ten studies were all cohort designs and either observation, retrospective or population-based, published in 2021 or 2022 (Table 2). Nine studies were included in the safety outcomes,[81 84 99-105] three studies were included in the efficacy outcomes,[84 99 106] and two studies were included in both safety and efficacy outcomes.[84 99] Eight studies were carried out in Israel, one in Canada and one in Romania. Data for eight of the studies were collected by computerised electronic health database services from different medical centres, hospitals, or health services. Two studies used self-reporting questionnaires and survey forms sent through email, Facebook, or WhatsApp.[84 104] The study periods for all of the studies were between December 2020 to January 2022. This systematic review included a total pool of 44,883 pregnant women who received one or two doses of Pfizer-BioNTech vaccination during pregnancy compared to the combined control group of 34,988 unvaccinated pregnant women. Four thousand and forty-eight (9%) vaccinated pregnant women had a body mass index greater than thirty compared with 3,493 (10%) in the control group.

The inclusion criteria for the study's participants were pregnant women with the Pfizer-BioNTech vaccination during pregnancy compared to the control group of unvaccinated pregnant women. All studies included only singleton pregnancies. One study had pregnant women 15 to 49 years old,[104] another 16 years and older,[106] and three studies stated the ages were 18 years and older.[100 102 103] The mean age for Pfizer-BioNTech vaccinated pregnant women group was 30.7 years, and the control group was 30.0 years. The mean age for gestation in weeks for the vaccinated pregnant women was 39.2 weeks, and for the control group, 39.3 weeks. Four studies had pregnant women vaccinated in any of the three trimesters.[81 84 99 106] One study only included vaccinations in the first trimester and focused on spontaneous abortions as an outcome.[100] Two studies only had a vaccination in the third trimester.[102 105] Two studies did not state in which trimester the pregnant women received the vaccination.[103 104] One study noted that pregnant women received the vaccination in the second and third trimesters but did not state how many were vaccinated in each trimester.[101] Five of the studies included pregnant women vaccinated with one and two doses of Pfizer-BioNTech,[84 99 101 104 105] two studies only included pregnant women vaccinated with two doses,[102 103] and three studies did not state how many doses were given.[81 100 106] The two studies that had self-reporting questionnaires and survey, participants had to have a valid email address, Facebook, or WhatsApp account.[84 104]

The main exclusion criteria for the studies included multiple gestations. Five studies excluded pregnant women who tested positive for Covid-19 with a polymerase chain reaction (PCR) test.[99 102 103 105 106] Two of the studies excluded women who only had one Pfizer-BioNTech vaccination.[102 103] Other exclusion criteria included pregnant women that did not provide consent, those who had terminations, vaccinated pre-pregnancy and unknown vaccination status.

In the nine studies that covered the safety of the Pfizer-BioNTech during pregnancy, the maternal outcomes included antepartum haemorrhage, postpartum haemorrhage, placenta abruption, meconium-stained amniotic fluid, gestational diabetes and combined pregnancy-related hypertension, pre-eclampsia, and eclampsia. Foetal and neonatal outcomes included miscarriage, stillborn, infant death, preterm delivery with subgroups <32 weeks, <35 weeks and <37 weeks of gestation, heart malformations, congenital anomalies, neonatal intensive care unit admissions, neonatal seizures, neonatal respiratory complications, neonatal meconium aspiration syndrome, abnormal foetal heart rate, one minute neonate Apgar scores ≤7, five minutes neonate Apgar scores ≤7, small for gestational age (SGA) and neonatal birthweight outcomes in grams.

Table 2. Description of characteristics of studies (n=10)

AUTHOR, YEAR, and COUNTRY	STUDY PERIOD and STUDY DESIGN	WHERE and DATA COLLECTION	INCLUSION CRITERIA	GROUP SIZE		NUMBER OF PFIZER DOSES	TRIMESTER OF PFIZER-BIONTECH VACCINATION	MATERNAL AGE YEARS (yrs) *GESTATIONAL AGE WEEKS (wks)*		OUTCOMES	CONCLUSION
				PFIZER	CONTROL	ONE/TWO DOSES	1st - 2nd -3rd	PFIZER	CONTROL		
Bleicher,[84] 2021, Israel	January and February 2021. A prospective observational cohort study.	The first questionnaire was sent on the 10th of January, and the second, one month later, to participants who answered the first questionnaire. The primary investigator sent online Google questionnaire forms using her Facebook and WhatsApp accounts.	Medical groups only to start with, however, a few days after distributing questionnaires, the vaccine became available to all pregnant women, and then any pregnant women were included. Participants had to complete the first and second questionnaires correctly and have an email address and Facebook or WhatsApp account.	202	124	78/124	36 - 110 - 56	31.7 ± 3.9yrs	30.2 ± 5.09yrs	Safety and effectiveness. Primary outcomes included antepartum bleeding, pregnancy loss, foetal growth restriction, hypertension, gestational diabetes, preterm birth, and foetal malformations noted on the first or second anatomy scan. Secondary outcomes included vaccine side effects and diagnosis of Covid-19 since the last questionnaire.	Pfizer-BioNTech vaccination during any trimester of pregnancy does not appear to increase pregnancy complications, and the risk of Covid-19 infection was reduced significantly. Thirteen patients with similar ID numbers were excluded from the analysis because they could not match the answers with the first and second questionnaires.
Citu,[100] 2022, Romania	January 2020 to January 2022. Data collection for the control group began in January 2020 and for Pfizer-BioNTech in January 2021. An observational retrospective cohort.	Obstetrics and Gynaecology Timisoara Municipal Emergency Hospital. Computerised database.	>18 years old and pregnant, Pfizer-BioNTech or Moderna vaccination in the 1st trimester.	638	2167		638 - 0 - 0	29.5 ± 7.3yrs	31.6 ± 5.6yrs	Safety. The risk of spontaneous abortions after receiving an mRNA vaccination (Pfizer-BioNTech or Moderna - data separated) during the first trimester of pregnancy.	The risk of spontaneous abortion after Pfizer-BioNTech vaccination during the first trimester of pregnancy is similar with no statistically significant difference to non-vaccinated pregnant women, odds ratio of 1.04 (95% CI 0.91-1.12).

AUTHOR, YEAR, and COUNTRY	STUDY PERIOD and STUDY DESIGN	WHERE and DATA COLLECTION	INCLUSION CRITERIA	GROUP SIZE		NUMBER OF PFIZER DOSES	TRIMESTER OF PFIZER-BIONTECH VACCINATION	MATERNAL AGE YEARS (yrs) *GESTATIONAL AGE WEEKS (wks)*		OUTCOMES	CONCLUSION
				PFIZER	CONTROL	ONE/TWO DOSES	1st - 2nd -3rd	PFIZER	CONTROL		
Dagan,[106] 2021, Israel	20 December 2020 to 3 June 2021. An observational cohort study.	Clalit Health Services database.	Pregnant women, 16 years and older, no history of Covid-19 infection, vaccinated between 20th December 2020 - 3 June 2021.	10861	10861		2814 - 5242 - 2805	30yrs	30yrs	Effectiveness. Documented infections with Covid-19, Covid-19 related hospitalisation, severe illness, and death.	Pfizer-BioNTech vaccine during pregnancy is as effective as the general population against the original Covid-19 strain and the Alpha variant. From 7-56 days after the second dose of Pfizer-BioNTech, it was 96% effective from documented infections.
Kugelman,[101] 2022, Israel	1 February 2021 to 31 July 2021. A retrospective equivalence cohort study.	Computerised medical records from Carmel Medical Centre, Haifa.	Singleton pregnancy, > 23 weeks gestations, admitted to Carmel Medical Centre delivery room, Haifa.	930	964	51/879	2nd or 3rd	32 (29-35)yrs *39.6 (38.7-40.3)wks*	31 (28-35)yrs *39.7 (38.7-40.4)wks*	Safety. Perinatal outcomes included preterm delivery <35 weeks gestation, intrauterine foetal death > 23 weeks gestation, intrauterine growth restriction, 5-min Apgar scores <7, and neonatal care unit admission.	There was no statistically significant difference in adverse foetal and neonatal outcomes with Pfizer-BioNTech vaccination in the second and third trimesters compared to the control group of non-vaccinated pregnant women.

AUTHOR, YEAR, and COUNTRY	STUDY PERIOD and STUDY DESIGN	WHERE and DATA COLLECTION	INCLUSION CRITERIA	GROUP SIZE		NUMBER OF PFIZER DOSES	TRIMESTER OF PFIZER-BIONTECH VACCINATION	MATERNAL AGE YEARS (yrs) *GESTATIONAL AGE WEEKS (wks)*		OUTCOMES	CONCLUSION
				PFIZER	CONTROL	ONE/TWO DOSES	1st - 2nd -3rd	PFIZER	CONTROL		
Goldshtein,[99] 2021, Israel	19 December 2020 to 28 February 2021. Follow-ups finished on 11 April 2021. A retrospective Cohort study.	Maccabi Health Care Service represents 26.7% of Israel's population. A comprehensive database of electronic health records.	Pregnant women who joined the fund more than one -year preconception, tested negative for Covid-19 infection with a polymerase chain reaction (PCR) test, and anyone vaccinated during pregnancy with a first dose of Pfizer-BioNTech between 19 December 2020 to 28 February 2021.	7530	7530	1904/5626	21% - 46% - 33%	31.1 ± 5.01yrs *39 (38-40)wks*	31.0 ± 4.85yrs *39 (38-40)wks*	Safety and effectiveness. To see if the Pfizer-BioNTech helped reduce the risk of Covid-19 infection during pregnancy. Maternal and neonatal outcomes included stillborn, intrauterine growth restriction, abortion (spontaneous and induced), pre-eclampsia, maternal death, and obstetric pulmonary embolism.	Pregnant women vaccinated with Pfizer-BioNTech had a lower risk of Covid-19 infection, especially 28 days after their first vaccination. There was no statistically significant difference in the maternal and neonatal outcomes between the vaccinated and unvaccinated groups.

AUTHOR, YEAR, and COUNTRY	STUDY PERIOD and STUDY DESIGN	WHERE and DATA COLLECTION	INCLUSION CRITERIA	GROUP SIZE		NUMBER OF PFIZER DOSES	TRIMESTER OF PFIZER-BIONTECH VACCINATION	MATERNAL AGE YEARS (yrs) *GESTATIONAL AGE WEEKS (wks)*		OUTCOMES	CONCLUSION
				PFIZER	CONTROL	ONE/TWO DOSES	1st - 2nd -3rd	PFIZER	CONTROL		
Goldshtein,[81] 2022, Israel	1 March to 31 September 2021. Follow-up ending 31 October with a minimum of one month. Population-based cohort study	Maccabi Healthcare Services has a 2.5 million member state health fund, including 26.7 per cent of Israel's population. A comprehensive computerised electronic database.	Singleton live births from 1 March to 31 September 2021.	16697	7591		2134 - 9364 - 5199	31.61 (5.22)yrs	30.49 (5.67)yrs	Safety. To see if Pfizer-BioNTech vaccination during pregnancy had associated adverse effects on neonatal outcomes, including preterm birth, small for gestation age and infant death. A subgroup analysis of pregnant women who had the Pfizer-BioNTech vaccination during their first trimester compared to the control group of non-vaccinated pregnant women, including the above outcomes and congenital anomalies.	There was a statistically significant difference in neonatal outcomes for all trimesters of Pfizer-BioNTech vaccination for preterm <32 weeks gestation with a risk ratio (RR) of 0.52(95% Cl 0.33-0.82) and very low birth weight <1500g with a RR 0.44(95% Cl 0.27-0.70), in favour of the vaccine. There were no statistical differences for all other outcomes. In the subgroup of Pfizer-BioNTech vaccination in the first trimester, preterm <32 weeks gestation RR 0.39(95% Cl 0.15-0.88), major heart malformations RR 0.53(95% Cl 0.29-0.90) and very low birth weight <1500g RR 0.41(95% Cl 0.15-0.09) were statistically significant in favour of the vaccine.

AUTHOR, YEAR, and COUNTRY	STUDY PERIOD and STUDY DESIGN	WHERE and DATA COLLECTION	INCLUSION CRITERIA	GROUP SIZE		NUMBER OF PFIZER DOSES	TRIMESTER OF PFIZER-BIONTECH VACCINATION	MATERNAL AGE YEARS (yrs) ***GESTATIONAL AGE WEEKS (wks)***		OUTCOMES	CONCLUSION
				PFIZER	CONTROL	ONE/TWO DOSES	1st - 2nd -3rd	PFIZER	CONTROL		
Rottenstreich,[102] 2021, Israel	19 January to 27 April 2021. A multicentre retrospective cohort database study.	Shaare Zedek and Bikur Holim Medical Centres are two university-affiliated Medical Centres in Jerusalem that have 16% of all deliveries in Israel. Computerised database.	Pregnant women, 18 years and older, delivered > 24 weeks gestations, full records of Covid-19 disease and vaccine status, women who received two doses of Pfizer-BioNTech vaccine during their third trimester and Covid-19 PCR test negative.	712	1063	0/712	0 - 0 - 712	30.6 ± 5.8yrs ***39.1 ± 1.6wks***	29.5 ± 6yrs ***39.4 ± 1.6wks***	Safety. To assess the adverse maternal and neonatal outcomes of the Pfizer-BioNTech vaccination during the third trimester of pregnancy. Maternal outcomes included postpartum haemorrhage, placental abruptions, meconium-stained amniotic fluid, and neonatal outcomes included intrauterine foetal death, Apgar score at one and five minutes scoring <7, admission to neonatal ICU, meconium aspiration syndrome, neonatal seizures and respiratory complications.	Postpartum haemorrhage was statistically significant in favour of the Pfizer-BioNTech vaccine in pregnant women, with a P-value of 0.05. There were no statistically significant differences in the other maternal outcomes. Combined neonatal adverse outcomes were lower in the Pfizer-BioNTech vaccinated pregnant women than in the control group; however, there were no statistically significant differences for individual outcomes.

AUTHOR, YEAR, and COUNTRY	STUDY PERIOD and STUDY DESIGN	WHERE and DATA COLLECTION	INCLUSION CRITERIA	GROUP SIZE		NUMBER OF PFIZER DOSES	TRIMESTER OF PFIZER-BIONTECH VACCINATION	MATERNAL AGE YEARS (yrs) *GESTATIONAL AGE WEEKS (wks)*		OUTCOMES	CONCLUSION
				PFIZER	CONTROL	ONE/TWO DOSES	1st - 2nd -3rd	PFIZER	CONTROL		
Rottenstreich, [103] 2022, Israel	28 August to 31 December 2021. A retrospective cohort study	Two university-affiliated Medical Centres in Jerusalem that have 16% of all deliveries in Israel. Computerised medical record database updated in real-time during labour and delivery.	Eighteen years and older, no history of Covid-19 PCR positive tests during pregnancy or before pregnancy, delivered between 28th August and 31 December 2021, full records of Covid-19 infection and vaccination status.	1094	863	0/1094	Not stated	28.9 ± 5.7yrs *39.4 ± 1.4wks*	28.4 ± 6.2yrs *39.4 ± 1.5wks*	Safety. The adverse effects of maternal and neonatal outcomes with three Covid-19 vaccination doses and compared with two doses and no vaccination in pregnant women. Data for two doses and no vaccinations were included.	In maternal outcomes, there was a reduction in placental abruption and meconium-stained amniotic fluid in the Pfizer-BioNTech vaccinated group compared to the control group. In neonatal outcomes, there was a reduction in SGA, Apgar scores at 1- and 5-minute scores <7, Meconium aspiration syndrome, and respiratory complications in the Pfizer-BioNTech vaccinated group, and a small increase in neonatal seizures (0.1%) and intrauterine foetal death (0.5%) in the vaccinated group compared to the control group.

AUTHOR, YEAR, and COUNTRY	STUDY PERIOD and STUDY DESIGN	WHERE and DATA COLLECTION	INCLUSION CRITERIA	GROUP SIZE		NUMBER OF PFIZER DOSES	TRIMESTER OF PFIZER-BIONTECH VACCINATION	MATERNAL AGE YEARS (yrs) *GESTATIONAL AGE WEEKS (wks)*		OUTCOMES	CONCLUSION
				PFIZER	CONTROL	ONE/TWO DOSES	1st - 2nd -3rd	PFIZER	CONTROL		
Sadarangani, [104] 2022, Canada	Study enrolment started on 22 December 2020. Observational cohort study	Seven Canadian provinces and territories, including Ontario, Quebec, British Columbia, Alberta, Nova Scotia, Yukon, and Prince Edward Island, covers over 75% of the country's population. Self-reported survey, and telephone follow-up for pregnant women who reported any medical events. The survey information was collected in a secure research electronic data capture (REDCap) database.	The first dose of any mRNA (Pfizer-BioNTech or Moderna mRNA-1273 - data is separated) Covid-19 vaccination within the previous seven days. Both groups, the vaccinated and the control group, needed an active email address, telephone number, able to speak English or French and aged between 15 and 49 years old.	5306	339	3414/1892		15-29yrs 51 30-49yrs 288	15-29yrs 1218 30-49yrs 4088	Safety. Significant health events seven days post mRNA vaccination, one and two doses in pregnant women. Control pregnant women had to email any health problems in the previous seven days. Outcomes included a first-dose Pfizer-BioNTech vaccination subgroup, including miscarriage or stillborn, vaginal haemorrhage, abnormal foetal heart rate and hypertension.	The study had separate results for mRNA vaccination. Combined results for miscarriage and stillborn in the second trimester, unable to use results. There were no significant health events difference between one or two doses of Pfizer-BioNTech.

AUTHOR, YEAR, and COUNTRY	STUDY PERIOD and STUDY DESIGN	WHERE and DATA COLLECTION	INCLUSION CRITERIA	GROUP SIZE		NUMBER OF PFIZER DOSES	TRIMESTER OF PFIZER-BIONTECH VACCINATION	MATERNAL AGE YEARS (yrs) *GESTATIONAL AGE WEEKS (wks)*		OUTCOMES	CONCLUSION
				PFIZER	CONTROL	ONE/TWO DOSES	1st - 2nd -3rd	PFIZER	CONTROL		
Wainstock,[105] 2021, Israel	January to June 2021. Retrospective cohort study	Soroka University Medical Centre. Computerised Clalit database.	Pregnant women, singleton deliveries between January - June 2021 at Soroka University Medical Centre, no history of Covid-19.	913	3486	155/758	0 - 0 - 913	30.6 ± 5.3yrs *38.9 ± 1.4wks*	28.2 ± 5.7yrs *39 ± 1.9wks*	Safety. The effects of Pfizer-BioNTech vaccination in the third trimester during pregnancy, delivery, and any newborn complications.	Pfizer-BioNTech vaccination during the third trimester had no adverse effects during the last pregnancy trimester, during delivery and neonatal outcomes. No differences in the two groups in gestational age, small for gestational age, and newborn respiratory complications. Pregnant women with two doses had a lower risk for meconium-stained amniotic fluid, and their babies had a higher gestational age and birth weight.

5.3 RISK OF BIAS ASSESSMENT

Following the Cochrane ROBINS-E tool and completing the seven domains for each of the ten studies, four studies were classified as low risk,[81 99 100 106] four studies were classified as having some concerns, [101-103 105] and two studies were classified as high risk of bias.[84 104] None of the studies were classified as very high risk of bias (Table 2). See Appendix two for individual study results with the seven domains using the ROBINS-E tool for risk of bias.

Table 3. Risk of bias using the ROBINS-E tool

First author	Bias due to confounding	Bias arising from measurement of the exposure	Bias in the selection of participants	Bias due to post-exposure interventions	Bias due to missing data	Bias arising from the measurement of outcomes	Bias in selection of the reported results	Overall risk of bias
Bleicher[84] 2021 #*	Concerns	Low	High	Low	Concerns	Concerns	Concerns	High
Citu[100] 2022 #	Low	Low	Low	Low	Low	Low	Low	Low
Dagan[106] 2021 *	Low	Low	Low	Low	Low	Low	Low	Low
Goldshtein[99] 2021 #*	Low	Low	Low	Low	Low	Low	Low	Low
Goldshtein[81] 2022 #	Low	Low	Low	Low	Low	Low	Low	Low
Kugelman[101] 2022 #	Concerns	Low	Concerns	Low	Low	Low	Low	Concerns
Rottenstreich[102] 2021 #	Concerns	Low	Concerns	Low	Low	Low	Low	Concerns
Rottenstreich[103] 2022 #	Concerns	Concerns	Low	Low	Low	Low	Low	Concerns
Sadarangani[104] 2022 #	Concerns	High	Concerns	Low	Concerns	Concerns	Concerns	High
Wainstock[105] 2021 #	Concerns	Low	Concerns	Low	Low	Low	Low	Concerns

Note: The study's outcomes are Safety # and efficacy *. The risk of bias is classified into four groups, low risk, some concerns, high risk, or very high risk. None of the studies were classified as very high risk of bias.

The four studies classified as low risk had a low risk for all seven domains.[81 99 100 106] The four studies classified as having some concerns of bias, all had some concerns of bias for domain one due to confounding factors.[101-103 105] For example, the maternal characteristics or results section does not include pregnant women's medical history, socioeconomic status, education, prenatal care, or smoking status. One of the studies had some concerns of bias for domain two arising from measurement of the exposure of the Pfizer-BioNTech vaccination and not being able to report on the week of gestation or trimester the vaccination was given to the pregnant women.[103] Three of the studies had some concerns of bias for domain three for the selection of participants into the study. For example, two of the studies only included pregnant women with Pfizer-BioNTech vaccination in their third trimester,[102 105] and one study only included pregnant women over 23 weeks of gestation.[101] This has the potential for risk of bias for not including and selecting pregnant women in all trimesters. All the other four domains in these four studies were classified as low risk.

One study was judged at high risk of bias for domain three, in the selection of participants into the study, because the primary investigator used her private Facebook and WhatsApp accounts to send out the questionnaire forms for the study.[84] Therefore, the pregnant women had to have social media and have some connection with the primary investigator to receive these questionnaire forms to be included in the study. A second study was judged at high risk of bias for domain two arising from measurement of the exposure and only including events that happened seven days after the Covid-19 vaccination and the control of pregnant women any events that occurred in the previous seven days.[104] The same study was judged at some concerns for domain three, in the selection of participants into the study because the participants had to have an active email address and telephone, speak English or French and had a first dose of Covid-19 vaccination within the previous seven days.[104] Not everyone has an active email address. Both studies were judged as having some concerns of bias for domain one and did not address confounding factors, including education, socioeconomics, medical history, prenatal care, or smoking. Both studies were also judged as having some concerns of bias for domain five with missing data; in one of the studies, 25 per cent of participants did not respond to the second questionnaire.[84] The other study did not document how many participants were vaccinated in each trimester or how many participants had a severe or serious health event in each trimester.[104] However the study did show a breakdown of significant health events in each trimester.[104] Domain six, arising from the measurement of the outcome, both studies had some concerns with relying on self-reporting for surveys and questionnaires. Domain seven in the selection of the reported results of both studies were some concerns, one of the studies combined miscarriage and stillborn for the second trimester,[104] and in the other study, the number of pregnant women in both groups did not add up to the total number of pregnant women who completed the survey, with more women added to the control group.[84]

5.4 MATERNAL SAFETY OUTCOMES

Eight studies included different maternal outcomes of the Pfizer-BioNTech vaccination during pregnancy and compared it to the control group of unvaccinated pregnant women.[81 84 99 101-105] The six following forest plots show the maternal outcomes, including antepartum haemorrhage, postpartum haemorrhage, placenta abruption, meconium-stained amniotic fluid, and gestational diabetes and combined pregnancy-related hypertension, pre-eclampsia, and eclampsia. There were no records of maternal deaths in any of the studies, and therefore, no meta-analysis was produced. The protocol included placenta calcification, but no study reported this maternal outcome.

Meconium-stated amniotic fluid was included in the maternal outcomes because three of the studies reported that the group of pregnant women who had the Pfizer-BioNTech vaccination had a reduction in meconium-stated amniotic fluid compared to the control group. Gestational diabetes was included to the maternal outcome to see if having the Pfizer-BioNTech vaccination during pregnancy increases or decreases gestational diabetes rates.

5.4.1 Antepartum Bleeding

Combining the two studies' [84 104] results indicated a 55% reduction (OR 0.45, 95% CI 0.17 to 1.24) in the odds of antepartum bleeding in the pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women, but the difference was not statistically significant. Heterogeneity was not statistically significant, with a P value of 0.38, indicating a consistency of effect across the two studies. The I^2 was 0% indicating an unimportant heterogeneity.

	Pfizer-BioNTech vaccine		Control			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Bleicher 2021	4	202	7	124	82.4%	0.34 [0.10, 1.18]
Sadarangani 2022	10	3414	1	339	17.6%	0.99 [0.13, 7.78]
Total (95% CI)		**3616**		**463**	**100.0%**	**0.45 [0.17, 1.24]**
Total events	14		8			
Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 1.55 (P = 0.12)						

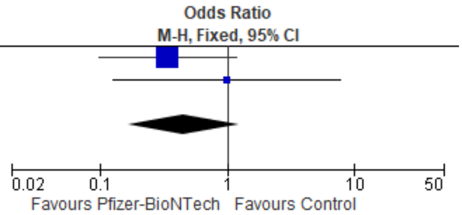

Figure 3. Forest plot of odds ratio for antepartum bleeding in pregnant women.

5.4.2 Postpartum Haemorrhage

Combining the three studies'[102 103 105] results indicated a 12% reduction (OR 0.88, 95% CI 0.70 to 1.09) in the odds of postpartum haemorrhage in the pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women, but the difference was not statistically significant. Heterogeneity was not statistically significant, with a P value of 0.23, indicating a consistency of effect across the three studies. The I^2 was 32% indicating an unimportant level of heterogeneity above chance.

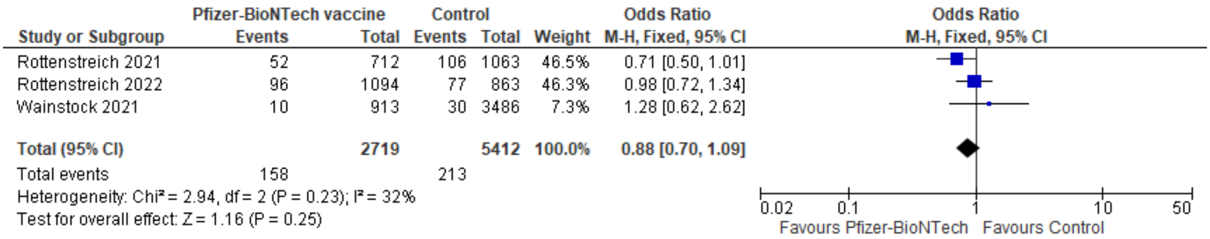

Figure 4. Forest plot of odds ratio for postpartum haemorrhage in pregnant women

5.4.3 Placental Abruption

Combining the three studies[102 103 105] results indicated a 55% reduction (OR 0.45, 95% CI 0.27 to 0.75) in the odds of placental abruption in the pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women. The reduction was statistically significant, with a p-value of 0.002. Heterogeneity was not statistically significant, with a P value of 0.33, indicating a consistency of effect across the three studies. The I^2 was 11% indicating an unimportant level of heterogeneity above chance.

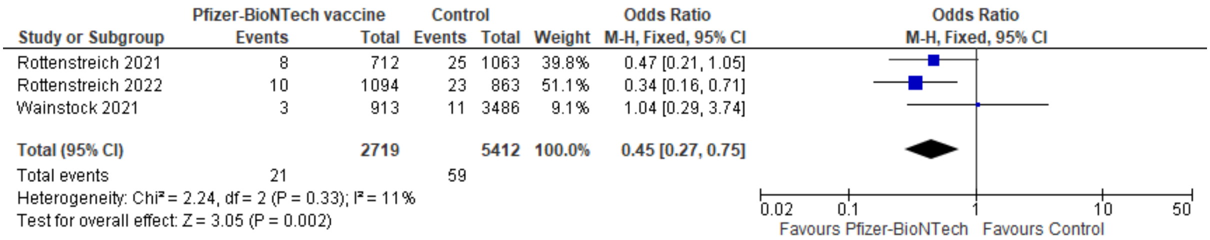

Figure 5. Forest plot of odds ratio for placental abruption in pregnant women

5.4.4 Meconium-Stained Amniotic Fluid

Combining the three studies[102 103 105] results indicated a 25% reduction (OR 0.75 95% CI 0.64 to 0.88) in the odds of meconium-stained amniotic fluid in the pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women. The reduction was statistically significant, with a p-value of 0.0003. Heterogeneity was not statistically significant, with a P value of 0.34, indicating consistency of effect across the three studies. The I^2 was 8% indicating an unimportant level of heterogeneity above chance.

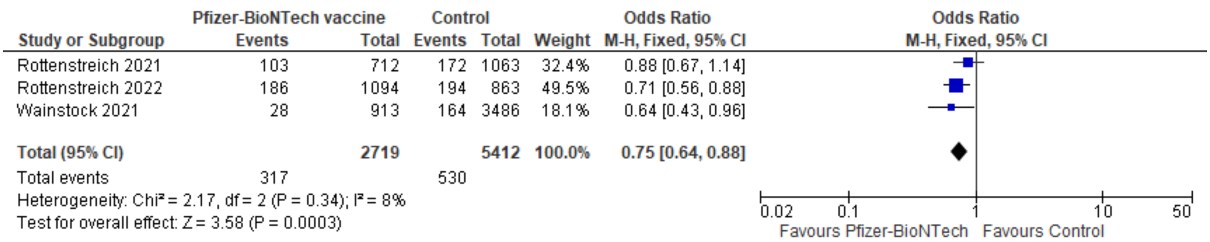

Figure 6. Forest plot of odds ratio for meconium-stained amniotic fluid in pregnant women

5.4.5 Gestational Diabetes

Two studies combined pregnant women with diabetes and gestational diabetes results together; therefore, they were excluded from this forest plot.[102 103] Combining the three studies'[81 101 105] results indicated a 1% increase (OR 1.01, 95% CI 0.87 to 1.18) in the odds of gestational diabetes in the pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women, but the difference was not statistically significant. Heterogeneity was not statistically significant, with a P value of 0.14, indicating a consistency of effect across the three studies. The I^2 was 50% indicating a moderate level of heterogeneity above chance.

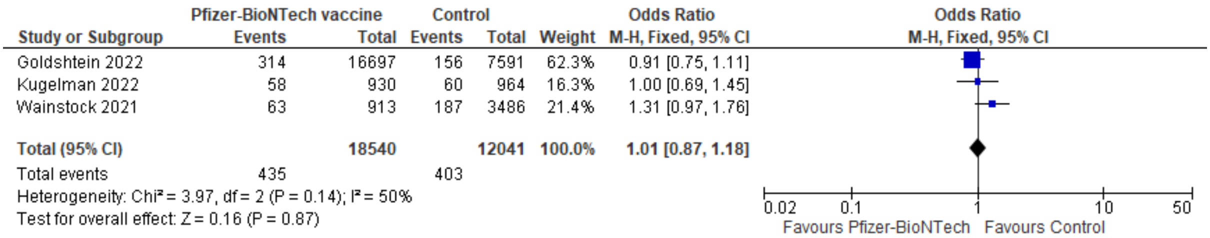

Figure 7. Forest plot of odds ratio for gestational diabetes in pregnant women

5.4.6 Pregnancy-Related Hypertension

Pregnancy-related hypertension includes pre-eclampsia and eclampsia. Combining the five studies[99 102-105] results indicated a 6% increase (OR 1.06, 95% CI 0.82 to 1.37) in the odds of pregnancy-related hypertension, pre-eclampsia, and eclampsia in the pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women, but the difference was not statistically significant. Heterogeneity was not statistically significant, with a P value of 0.90, indicating a consistency of effect across the five studies. The I^2 was 0% indicating an unimportant heterogeneity.

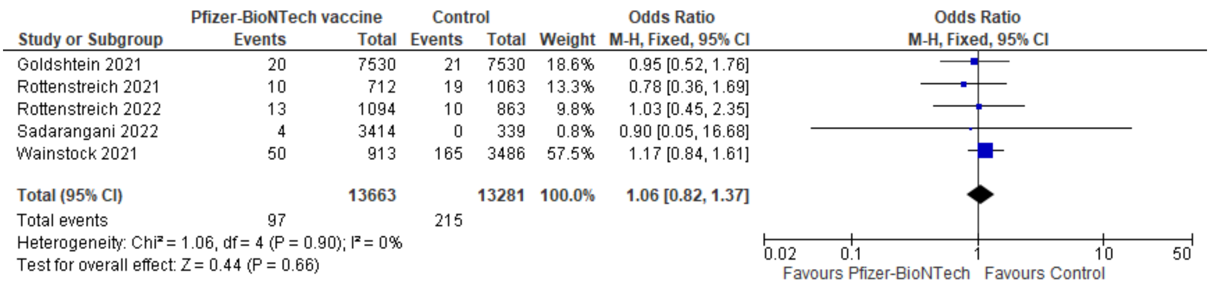

Figure 8. Forest plot of odds ratio for pregnancy-related hypertension in pregnant women

5.5 FOETAL AND NEONATAL SAFETY OUTCOMES

Nine studies included different foetal and neonatal outcomes after pregnant women had the Pfizer-BioNTech vaccination during pregnancy compared to the control group of unvaccinated pregnant women.[81 84 99-105] The following 15 forest plots show the foetal and neonatal outcomes, including miscarriage, stillborn, infant death, preterm delivery <37 weeks of gestation, heart malformations, congenital anomalies, neonatal care unit admissions, seizures, respiratory complications, meconium aspiration syndrome, abnormal foetal heart rate, neonatal one minute Apgar scores ≤7, neonatal five minutes Apgar scores ≤7, small for gestational age (SGA) and neonatal birthweight outcomes in grams.

5.5.1 Miscarriage

Two studies' results were not included in the forest plot below because one study combined spontaneous and induced abortion, and the other combined miscarriage and stillborn in the second trimester.[99 104] Combining the three studies'[84 100 104] results indicated a 2% increase (OR 1.02, 95% CI 0.79 to 1.31) in the odds of miscarriages in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of unvaccinated pregnant women, but the difference was not statistically significant. Heterogeneity was not statistically significant, with a P value of 0.54, indicating a consistency of effect across the three studies. The I^2 was 0% indicating an unimportant heterogeneity.

	Pfizer-BioNTech vaccine		Control			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Bleicher 2021	2	202	1	124	1.0%	1.23 [0.11, 13.71]
Citu 2022	84	638	271	2167	88.6%	1.06 [0.82, 1.38]
Sadarangani 2022	47	3414	7	339	10.4%	0.66 [0.30, 1.48]
Total (95% CI)		**4254**		**2630**	**100.0%**	**1.02 [0.79, 1.31]**
Total events	133		279			

Heterogeneity: Chi² = 1.23, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)

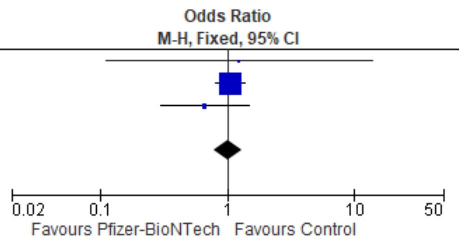

Figure 9. Forest plot of odds ratio for miscarriage

5.5.2 Stillborn

Stillborn included stillbirth and intrauterine foetal death >23 weeks of gestation. Combining the three studies'[99 102 103] results indicated a 13% increase (OR 1.13, 95% CI 0.77 to 1.65) in the odds of stillborn, including stillbirth and intrauterine foetal death >23 weeks of gestation in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women, but the difference was not statistically significant.

Heterogeneity was not statistically significant, with a P value of 0.73, indicating a consistency of effect across the three studies. The I^2 was 0% indicating an unimportant heterogeneity.

Study or Subgroup	Pfizer-BioNTech vaccine Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Goldshtein 2021	1	7530	2	7530	4.0%	0.50 [0.05, 5.51]
Rottenstreich 2021	5	712	5	1063	8.1%	1.50 [0.43, 5.19]
Rottenstreich 2022	58	1094	41	863	87.9%	1.12 [0.74, 1.69]
Total (95% CI)		**9336**		**9456**	**100.0%**	**1.13 [0.77, 1.65]**
Total events	64		48			

Heterogeneity: Chi² = 0.64, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)

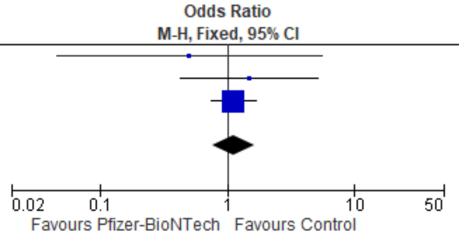

Figure 10. Forest plot of odds ratio for stillborn

5.5.3 Infant Death

The study[81] results indicated a 25% increase (OR 1.25, 95% CI 0.56 to 2.81) in the odds of infant death in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women, but the difference was not statistically significant. Heterogeneity was not applicable as only one study was included in this forest plot. The study in the forest plot above did not specify the causes of infant deaths, only the total during their study period.[81]

Study or Subgroup	Pfizer-BioNTech vaccine Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Goldshtein 2022	22	16697	8	7591	100.0%	1.25 [0.56, 2.81]
Total (95% CI)		**16697**		**7591**	**100.0%**	**1.25 [0.56, 2.81]**
Total events	22		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)

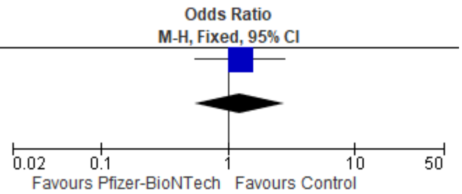

Figure 11. Forest plot of odds ratio for infant death

5.5.4 Preterm Delivery with Subgroups <32, <35 and <37 weeks of Gestation

The forest plot below includes three subgroups for preterm delivery, <32, <35 and <37 weeks of gestation with subtotals only because of the double counting of population groups and the simplicity of presentation. In the first subgroup, the study[81] results indicated a 43% reduction (OR 0.57, 95% CI 0.39 to 0.83) in the odds of preterm delivery <32 weeks of gestation in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women. The reduction was statistically significant, with a p-value of 0.003. Heterogeneity was not applicable as only one study included participants with this outcome. The second subgroup, combining the three studies'[101-103] results indicated a 5% increase (OR 1.05, 95% CI 0.70 to 1.60) in the odds of preterm delivery <35 weeks of gestation in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women, but the difference was not statistically significant. Heterogeneity was not statistically significant, with a P value of 0.44, indicating a consistency of effect across the three studies. The I^2 was 0% indicating an unimportant heterogeneity. The third subgroup, combining the five studies'[81 99 102 103] results indicated a 1% increase (OR 1.01, 95% CI 0.90 to 1.14) in the odds of preterm delivery <37 weeks of gestation in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women, but the difference was not statistically significant. Heterogeneity was not statistically significant, with a P value of 0.55, indicating a consistency of effect across the five studies. The I^2 was 0% indicating an unimportant heterogeneity.

	Pfizer-BioNTech vaccine		Control			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
3.17.1 < 32 weeks of gestation						
Goldshtein 2022	60	16697	48	7591	100.0%	0.57 [0.39, 0.83]
Subtotal (95% CI)		**16697**		**7591**	**100.0%**	**0.57 [0.39, 0.83]**
Total events	60		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.92 (P = 0.003)						
3.17.2 < 35 weeks of gestation						
Kugelman 2022	12	930	15	964	33.5%	0.83 [0.39, 1.78]
Rottenstreich 2021	20	712	30	1063	53.8%	1.00 [0.56, 1.77]
Rottenstreich 2022	12	1094	5	863	12.7%	1.90 [0.67, 5.42]
Subtotal (95% CI)		**2736**		**2890**	**100.0%**	**1.05 [0.70, 1.60]**
Total events	44		50			
Heterogeneity: Chi² = 1.65, df = 2 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.25 (P = 0.80)						
3.17.3 < 37 weeks of gestation						
Bleicher 2021	0	202	0	124		Not estimable
Goldshtein 2021	77	1387	85	1427	14.0%	0.93 [0.68, 1.27]
Goldshtein 2022	730	16697	315	7591	73.4%	1.06 [0.92, 1.21]
Rottenstreich 2021	27	712	40	1063	5.5%	1.01 [0.61, 1.66]
Rottenstreich 2022	36	1094	37	863	7.1%	0.76 [0.48, 1.21]
Subtotal (95% CI)		**20092**		**11068**	**100.0%**	**1.01 [0.90, 1.14]**
Total events	870		477			
Heterogeneity: Chi² = 2.11, df = 3 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						

Test for subgroup differences: Chi² = 8.39, df = 2 (P = 0.02), I² = 76.2%

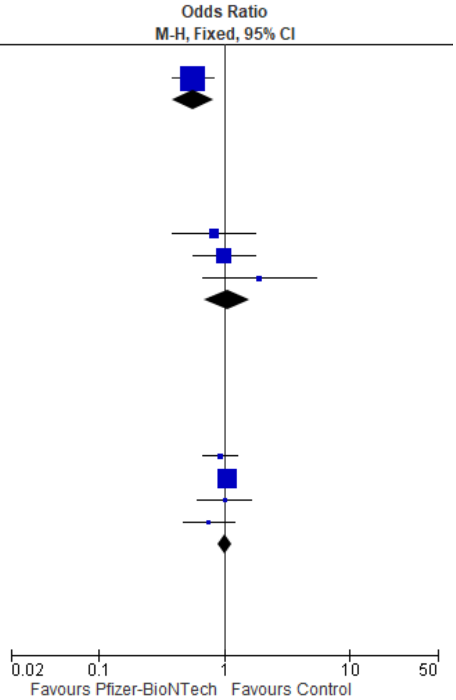

Figure 12. Forest plot of odds ratio for preterm delivery with subgroups <32, <35 and <37 weeks of gestation

5.5.5 Heart Malformation

The study[81] results indicated a 28% reduction (OR 0.72, 95% CI 0.50 to 1.03) in the odds of neonatal heart malformation in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the pregnant women control group, but the difference was not statistically significant. Heterogeneity was not applicable as only one study was included in this forest plot. Heart malformation was only included in one study as a subgroup analysis of neonatal outcomes for pregnant women who had the Pfizer-BioNTech vaccination in their first trimester.[81]

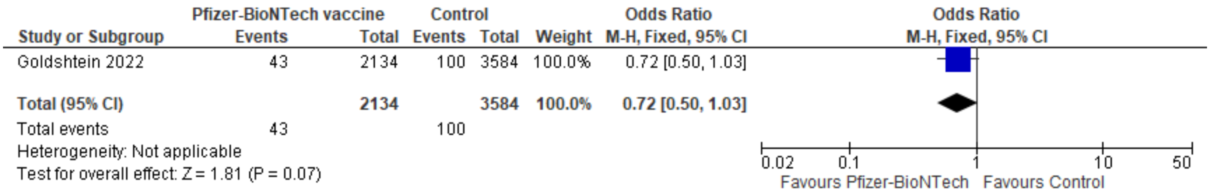

Figure 13. Forest plot of odds ratio for heart malformation

5.5.6 Congenital Anomalies

Combining the two studies'[81 84] results indicated a 16% reduction (OR 0.84, 95% CI 0.59 to 1.18) in the odds of neonatal congenital abnormalities in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the pregnant women control group, but the difference was not statistically significant. Heterogeneity was not statistically significant, with a P value of 0.86, indicating consistency of effect across the two studies. The I^2 was 0% indicating an unimportant heterogeneity. Congenital anomalies were included in one study as a subgroup analysis of neonatal outcomes for pregnant women who had the Pfizer-BioNTech vaccination in their first trimester,[81] one study included congenital anomalies reported on the anatomy scan during the first and second trimesters.[84]

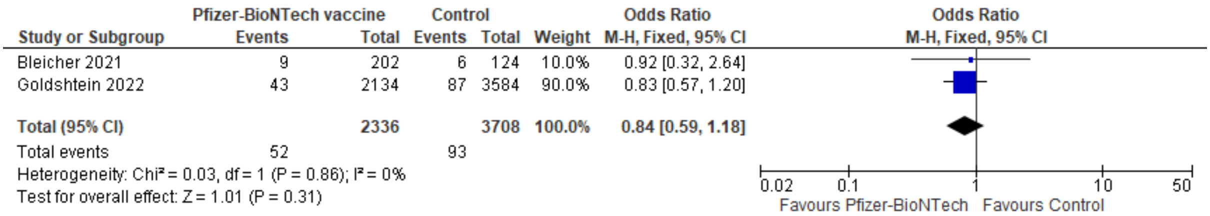

Figure 14. Forest plot of odds ratio for congenital anomalies

5.5.7 Neonatal Intensive Care Unit Admission

Combining the three studies'[101-103] results indicated a 23% reduction (OR 0.77, 95% CI 0.57 to 1.05) in the odds of neonatal intensive care unit admissions in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women, but the difference was not statistically significant. Heterogeneity was not statistically significant, with a P value of 0.41, indicating a consistency of effect across the three studies. The I^2 was 0% indicating an unimportant heterogeneity.

Study or Subgroup	Pfizer-BioNTech vaccine Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kugelman 2022	43	930	63	964	61.5%	0.69 [0.47, 1.03]
Rottenstreich 2021	29	712	48	1063	38.5%	0.90 [0.56, 1.44]
Rottenstreich 2022	0	1094	0	863		Not estimable
Total (95% CI)		**2736**		**2890**	**100.0%**	**0.77 [0.57, 1.05]**
Total events	72		111			

Heterogeneity: Chi² = 0.67, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.66 (P = 0.10)

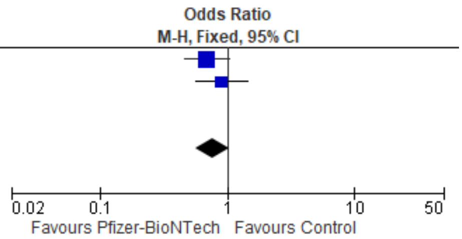

Figure 15. Forest plot of odds ratio for neonatal intensive care unit admission

5.5.8 Neonatal Seizures

Combining the two studies'[102 103] results indicated a 32% reduction (OR 0.68, 95% CI 0.15 to 3.03) in the odds of neonatal seizures in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women, but the difference was not statistically significant. Heterogeneity was not statistically significant, with a P value of 0.38, indicating a consistency of effect across the two studies. The I^2 was 0% indicating an unimportant heterogeneity.

Study or Subgroup	Pfizer-BioNTech vaccine Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Rottenstreich 2021	1	712	4	1063	74.2%	0.37 [0.04, 3.34]
Rottenstreich 2022	2	1094	1	863	25.8%	1.58 [0.14, 17.44]
Total (95% CI)		**1806**		**1926**	**100.0%**	**0.68 [0.15, 3.03]**
Total events	3		5			

Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)

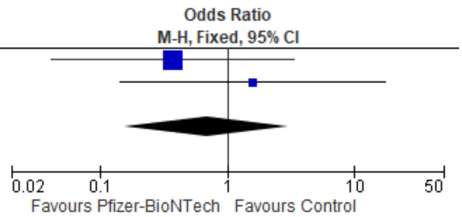

Figure 16. Forest plot of odds ratio for neonatal seizures

5.5.9 Neonatal Respiratory Complications

Neonatal respiratory complications included apnoea, dyspnoea, tachypnoea, respiratory distress, syndrome, transient tachypnoea, asphyxia, and mechanical ventilation. Combining the three studies'[102 103 105] results indicated a 35% reduction (OR 0.65, 95% CI 0.43 to 0.99) in the odds of respiratory complications in pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women. The reduction was statistically significant, with a p-value of 0.05. Heterogeneity was not statistically significant, with a P value of 0.19, indicating a consistency of effect across the three studies. The I^2 was 40% indicating an unimportant or possibly moderate level of heterogeneity above chance.

Study or Subgroup	Pfizer-BioNTech vaccine Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Rottenstreich 2021	8	712	32	1063	42.6%	0.37 [0.17, 0.80]
Rottenstreich 2022	9	1094	8	863	14.9%	0.89 [0.34, 2.31]
Wainstock 2021	14	913	62	3486	42.5%	0.86 [0.48, 1.54]
Total (95% CI)		**2719**		**5412**	**100.0%**	**0.65 [0.43, 0.99]**
Total events	31		102			
Heterogeneity: Chi² = 3.35, df = 2 (P = 0.19); I² = 40%						
Test for overall effect: Z = 2.00 (P = 0.05)						

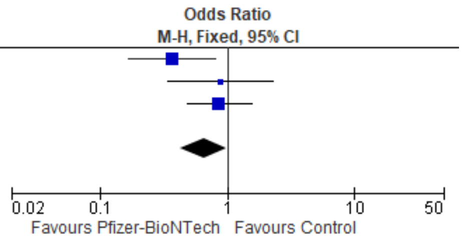

Figure 17. Forest plot of odds ratio for neonatal respiratory complications

5.5.10 Neonatal Meconium Aspiration Syndrome

Combining the two studies'[102 103] results indicated a 48% reduction (OR 0.52, 95% CI 0.31 to 0.90) in the odds of neonatal meconium aspiration syndrome in the group of pregnant women with the Pfizer-BioNTech vaccine compared to the control group of pregnant women. The reduction was statistically significant, with a p-value of 0.02. Heterogeneity was not applicable due to only one study with participants with this outcome.

Study or Subgroup	Pfizer-BioNTech vaccine Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Rottenstreich 2021	0	712	0	1063		Not estimable
Rottenstreich 2022	23	1094	34	863	100.0%	0.52 [0.31, 0.90]
Total (95% CI)		**1806**		**1926**	**100.0%**	**0.52 [0.31, 0.90]**
Total events	23		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.36 (P = 0.02)						

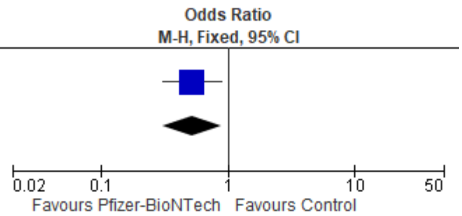

Figure 18. Forest plot of odds ratio for neonatal meconium aspiration syndrome

5.5.11 Abnormal Foetal Heart Rate

Combining the two studies'[104 105] results indicated a 36% reduction (OR 0.64, 95% CI 0.46 to 0.90) in the odds of abnormal foetal heart rate in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women. The reduction was statistically significant, with a p-value of 0.009. Heterogeneity was not statistically significant, with a P value of 0.71, indicating a consistency of effect across the two studies. The I^2 was 0% indicating an unimportant heterogeneity.

Study or Subgroup	Pfizer-BioNTech vaccine Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Sadarangani 2022	1	3414	0	399	0.9%	0.35 [0.01, 8.63]
Wainstock 2021	42	913	243	3486	99.1%	0.64 [0.46, 0.90]
Total (95% CI)		**4327**		**3885**	**100.0%**	**0.64 [0.46, 0.90]**
Total events	43		243			
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 2.61 (P = 0.009)						

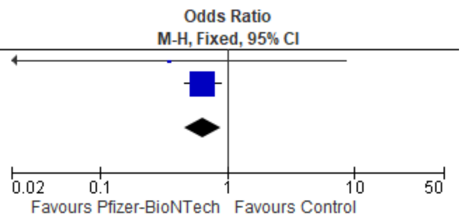

Figure 19. Forest plot of odds ratio for abnormal foetal heart rate

5.5.12 Neonatal One Minute Apgar Scores ≤7

Combining the two studies'[102 103] results indicated a 19% reduction (OR 0.81, 95% CI 0.59 to 1.12) in the odds of neonatal one minute Apgar scores ≤7 in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the pregnant women control group, but the difference was not statistically significant. Heterogeneity was not statistically significant, with a P value of 0.48, indicating a consistency of effect across the two studies. The I^2 was 0% indicating an unimportant heterogeneity.

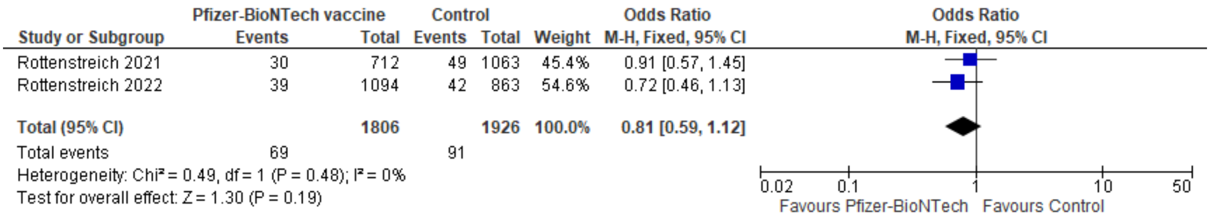

Figure 20. Forest plot of odds ratio for neonatal one minute Apgar scores ≤7

5.5.13 Neonatal Five Minutes Apgar Scores ≤7

Combining the four studies'[101-103 105] indicated a 26% reduction (OR 0.74, 95% CI 0.51 to 1.06) in the odds of neonatal five minutes Apgar scores ≤7 in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the pregnant women control group, but the difference was not statistically significant. Heterogeneity was not statistically significant, with a P value of 0.18, indicating a consistency of effect across the four studies. The I^2 was 39% indicating an unimportant or possibly moderate level of heterogeneity above chance.

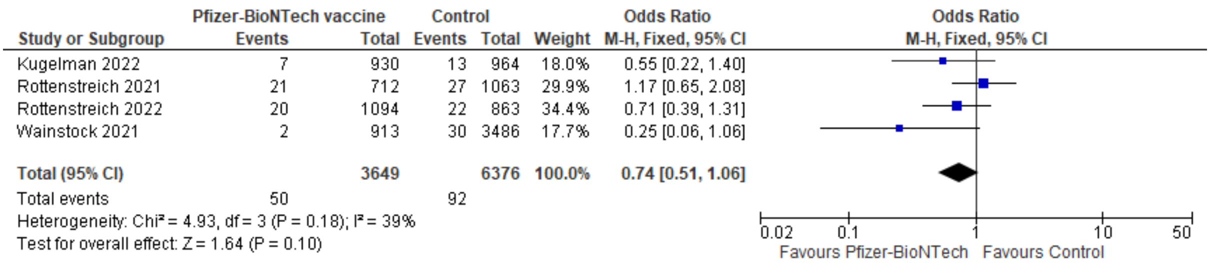

Figure 21. Forest plot of odds ratio for neonatal five minutes Apgar scores ≤7

5.5.14 Small for Gestational Age

Small for gestational age (SGA) included intrauterine growth restriction (IUGR) and birth weight less than the 10^{th} percentile. Combining the seven studies'[81 84 99 101-103 105] results indicated a 1% reduction (OR 0.99, 95% CI 0.91 to 1.09) in the odds of neonatal SGA in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women, but the difference was not statistically significant. Heterogeneity was not statistically significant, with a P value of 0.41, indicating a consistency of effect across the seven studies. The I^2 was 3% indicating an unimportant level of heterogeneity above chance.

Study or Subgroup	Pfizer-BioNTech vaccine Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bleicher 2021	3	202	0	124	0.1%	4.37 [0.22, 85.29]
Goldshtein 2021	36	7530	38	7530	4.2%	0.95 [0.60, 1.50]
Goldshtein 2022	1040	16697	468	7591	66.6%	1.01 [0.90, 1.13]
Kugelman 2022	83	930	94	964	9.3%	0.91 [0.67, 1.24]
Rottenstreich 2021	81	712	98	1063	7.7%	1.26 [0.93, 1.73]
Rottenstreich 2022	59	1094	55	863	6.4%	0.84 [0.57, 1.22]
Wainstock 2021	26	913	131	3486	5.8%	0.75 [0.49, 1.15]
Total (95% CI)		**28078**		**21621**	**100.0%**	**0.99 [0.91, 1.09]**
Total events	1328		884			

Heterogeneity: Chi² = 6.16, df = 6 (P = 0.41); I² = 3%
Test for overall effect: Z = 0.13 (P = 0.90)

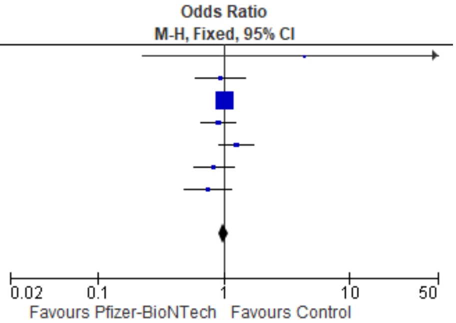

Figure 22. Forest plot of odds ratio for neonatal small for gestational age

5.5.15 Neonatal Birthweight

Combining the four studies'[101-103 105] results indicated a 2.27 grams (gm) lower (95% CI 25.18 gm lower to 20.64 gm higher) neonatal birthweight outcomes in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women, but the difference was not statistically significant. Heterogeneity was not statistically significant, with a P value of 0.55, indicating a consistency of effect across the four studies. The I^2 was 0% indicating an unimportant heterogeneity.

Study or Subgroup	Pfizer-BioNTech vaccine Mean [grams]	SD [grams]	Total	Control Mean [grams]	SD [grams]	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kugelman 2022	3,275	0	930	3,305	0	964		Not estimable
Rottenstreich 2021	3,317.8	517.8	712	3,339.5	466.3	1063	23.5%	-21.70 [-68.95, 25.55]
Rottenstreich 2022	3,311.4	449.2	1094	3,298.3	459.4	863	31.8%	13.10 [-27.50, 53.70]
Wainstock 2021	3,224	472	913	3,227	465	3486	44.6%	-3.00 [-37.29, 31.29]
Total (95% CI)			**3649**			**6376**	**100.0%**	**-2.27 [-25.18, 20.64]**

Heterogeneity: Chi² = 1.20, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)

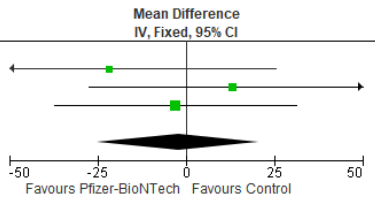

Figure 23. Forest plot of odds ratio for neonatal birthweight outcomes in grams

5.6 EFFICACY OUTCOMES

Only three studies evaluated the effectiveness of the Pfizer-BioNTech vaccination in pregnant women and had a control group of pregnant women.[84 99 106] The pool of pregnant women for efficacy outcomes in total included 18,593 Pfizer-BioNTech vaccinated pregnant women compared to the control group of 18,515 unvaccinated pregnant women. The following three forest plots show the results of the effectiveness of the Pfizer-BioNTech vaccination in pregnant women versus the control group, including documented Covid-19 infection, hospitalisation of Covid-19, and severe or critical Covid-19 or ICU admission with Covid-19.

No pregnant women died of Covid-19 in either the Pfizer-BioNTech vaccinated or control group.[99 106]

5.6.1 Documented Covid-19 Infection

Combining the three studies'[84 99 106] results indicated a 44% reduction (OR 0.56, 95% CI 0.48 to 0.65) in the odds of documented Covid-19 infections in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women. The difference was statistically significant with a p-value of <0.00001. Heterogeneity was not statistically significant, with a P value of 0.38, indicating a consistency of effect across the three studies. The I^2 was 0% indicating an unimportant heterogeneity. The pregnant women had to have a positive polymerase chain reaction (PCR) test result to be documented as having a Covid-19 infection.

	Pfizer-BioNTech vaccine		Control			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Bleicher 2021	3	202	8	124	2.2%	0.22 [0.06, 0.84]
Dagan 2021	131	10861	235	10861	52.7%	0.55 [0.45, 0.68]
Goldshtein 2021	118	7530	202	7530	45.1%	0.58 [0.46, 0.73]
Total (95% CI)		**18593**		**18515**	**100.0%**	**0.56 [0.48, 0.65]**
Total events	252		445			

Heterogeneity: Chi² = 1.96, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 7.38 (P < 0.00001)

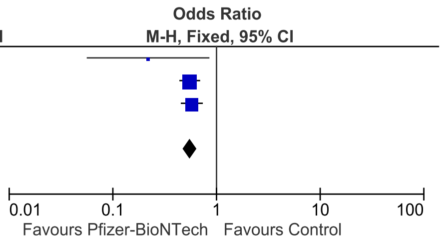

Figure 24. Forest plot of odds ratio for documented Covid-19 infection in pregnant women

5.6.2 Hospitalised with Covid-19

Combining the two studies'[99 106] results indicated a 50% reduction (OR 0.50, 95% CI 0.31 to 0.82) in the odds of hospitalisation with Covid-19 in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women. The reduction was statistically significant, with a p-value of 0.006. Heterogeneity was not statistically significant, with a P value of 0.62, indicating a consistency of effect across the two studies. The I^2 was 0% indicating an unimportant heterogeneity.

	Pfizer-BioNTech vaccine		Control			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Dagan 2021	11	10861	25	10861	52.1%	0.44 [0.22, 0.89]
Goldshtein 2021	13	7530	23	7530	47.9%	0.56 [0.29, 1.12]
Total (95% CI)		**18391**		**18391**	**100.0%**	**0.50 [0.31, 0.82]**
Total events	24		48			

Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.78 (P = 0.006)

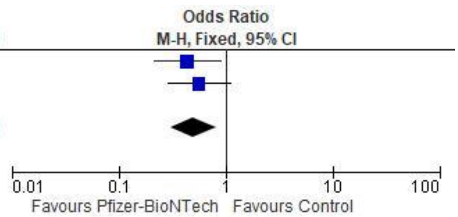

Figure 25. Forest plot of odds ratio for hospitalised with Covid-19 in pregnant women

5.6.3 Severe, Critical or ICU Admission with Covid-19

The study[106] results indicated a 89% reduction (OR 0.11, 95% CI 0.01 to 2.06) in the odds of severe, critical or ICU admission with Covid-19 in the group of pregnant women who had the Pfizer-BioNTech vaccine compared to the control group of pregnant women, but the difference was not statistically significant. Heterogeneity was not applicable as only one study included this outcome. Severe or critical Covid-19 illness was defined as pregnant women with oxygen saturations <94 per cent on room air, respiration rate >30 breaths per minute, respiratory failure, septic shock and or multiple organ dysfunction.

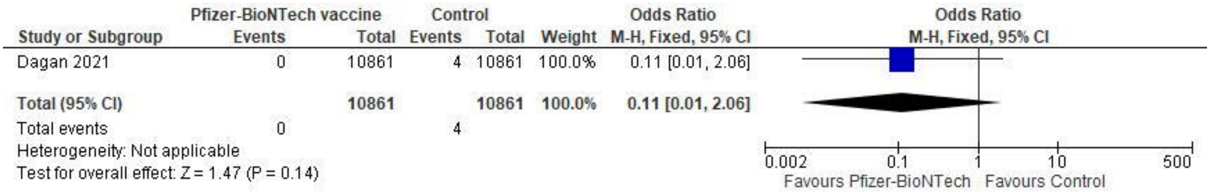

Figure 26. Forest plot of odds ratio for severe, critical or ICU admission with Covid-19 in pregnant women

5.7 SUMMARY OF RESULTS

In the six meta-analyses with maternal outcomes, only two of the outcome's placenta abruption and meconium-stained amniotic fluid had any statistically significant difference between the two groups of pregnant women favouring the group of pregnant women who had the Pfizer-BioNTech vaccination during pregnancy. Pregnant women who were vaccinated with Pfizer-BioNTech during pregnancy had a 55% reduction (OR 0.45, 95% CI 0.27 to 0.75) in the odds of placental abruption and a 25% reduction (OR 0.75 95% CI 0.64 to 0.88) in the odds of meconium-stained amniotic fluid compared to the control group of pregnant women. The four outcomes, antepartum haemorrhage, postpartum haemorrhage, gestational diabetes, and pregnancy-related hypertension had no statistically significant differences between the two groups. The results from these eight studies, with the above six meta-analyses, suggest no increased harm to pregnant women who have the Pfizer-BioNTech vaccination during pregnancy and benefits in terms of reducing placental abruption and meconium-stained amniotic fluid.

Of the fifteen meta-analyses with foetal and neonatal outcomes, three of the outcome's neonatal respiratory complications, neonatal meconium aspiration syndrome and abnormal foetal heart rate and one of the subgroups of preterm delivery, <32 weeks of gestation, had statistically significant differences between the two groups of pregnant women favouring the group who had the Pfizer-BioNTech vaccination during pregnancy. Pregnant women who were vaccinated with Pfizer-BioNTech during pregnancy had a 35% reduction (OR 0.65, 95% Cl 0.43 to 0.99) in the odds of neonatal respiratory complications, a 48% reduction (OR 0.52, 95% Cl 0.31 to 0.90) in the odds of neonatal meconium aspiration syndrome, 64% reduction (OR 0.36, 95% CI 0.46 to 0.90) in the odds of abnormal foetal heart rate and a 43% reduction (OR 0.57, 95% CI 0.39 to 0.83) in the odds of preterm delivery <32 weeks of gestation. All the other twelve outcomes had no statistically significant differences. The results from these nine studies, with the above 15 meta-analyses, suggest no increased harm to the foetus or neonate when the pregnant women have had the Pfizer-BioNTech during pregnancy.

In the three meta-analyses with efficacy outcomes, two of the outcomes, pregnant women with documented Covid-19 infection and pregnant women hospitalised with Covid-19, were statistically significant, favouring the pregnant women who had the Pfizer-BioNTech vaccination during pregnancy. Pregnant women vaccinated with Pfizer-BioNTech during pregnancy had a 44% reduction in the odds of documented Covid-19 infection and a 50% reduction in the odds of hospitalisation with Covid-19 compared to the control group of pregnant women. The results suggest that the Pfizer-BioNTech vaccination during pregnancy is beneficial and effective for pregnant women in reducing infection and hospitalisation.

6 DISCUSSION

6.1 KEY MESSAGES

To the best of my knowledge, this is the first systematic review and meta-analysis of the safety and efficacy of the Pfizer-BioNTech Covid-19 vaccination alone when used during pregnancy. Pfizer-BioNTech vaccination administered during pregnancy is safe and effective for the maternal, foetus, and neonate. Pregnant women vaccinated with Pfizer-BioNTech were half as likely to have Covid-19 or be hospitalised. In the maternal safety outcomes, there were no significant differences in antepartum haemorrhage, postpartum haemorrhage, gestational diabetes, or pregnancy-related hypertension. However, pregnant women were half as likely to have a placental abruption and 25% less likely to have meconium-stained amniotic fluid (indicating a stressed neonate). In the foetal and neonatal safety outcomes, there were no significant differences in miscarriage, stillborn, infant death, preterm delivery <35 and <37 weeks of gestation, heart malformation, congenital anomalies, NICU admissions, neonatal seizures, neonatal one and five minute Apgar scores ≤7, SGA and birth weight in grams. However, neonates were about 35% less likely to have respiratory complications or an abnormal foetal heart rate, 43% less like to have a preterm delivery <32 weeks of gestation and about half as likely to have meconium respiratory aspiration syndrome.

6.2 COMPARISON WITH PREVIOUS REVIEWS

To date, several systematic reviews and meta-analyses have been published regarding the safety and efficacy of Covid-19 vaccinations during pregnancy. However, all the reviews combined different Covid-19 vaccine results in their meta-analyses and did not report a breakdown of each vaccine's individual safety and efficacy during pregnancy. Combining all types of Covid-19 vaccines in the outcomes can mask vaccines that might be more beneficial or increase harm. This review included only one Covid-19 vaccine, Pfizer-BioNTech, when assessing the safety and efficacy during pregnancy because this was the primary and widely used vaccination in NZ.

Six systematic reviews and meta-analyses included six to twenty-three studies with different Covid-19 vaccinations in their safety and efficacy outcomes, including mRNA (Pfizer-BioNTech, Moderna) and viral vector (AstraZeneca, Johnson and Johnson),[107-112] and one review also included inactivated vaccine Sinovac.[111] Compared to my review, which focused solely on the Pfizer-BioNTech vaccination during pregnancy. The limitations of combining vaccinations in the analyses only gives an overview of the sum of all vaccinations and not the specific individual vaccine. Two reviews included studies with non-pregnant women as the control group,[108 111] and one of the reviews included studies without a control group.[111] In comparison to my review, I only included studies with a control group of pregnant women to have an appropriate comparison to the Pfizer-BioNTech vaccinated pregnant women group. There were no language restrictions for three reviews,[108-110] however in my review and in three other reviews, only English studies were included.[107 111 112] No new studies were identified from the reviews with no language restrictions. Five reviews had two people searching databases for study selection, assessing the risk of bias, and consulting with a third if a discrepancy occurred.[108-112] One review had three people and a fourth for any discrepancy.[107] Compared to my review, only one person searched the databases for study selection and assessed the studies for risk of bias because this was a dissertation, that a supervisor closely monitored.

Two reviews included analysis of placental abruption, but there was no statistically significant difference, [107 108] unlike my review, where there was a statistically significant reduction in odds ratio in favour of the Pfizer-BioNTech vaccination. This could potentially be due to the other two reviews combining the different Covid-19 vaccinations in the analysis. In my review, there was a statistically significant reduction in meconium-stained amniotic fluid in favour of the Pfizer-BioNTech vaccination. In comparison, two reviews had no statistically significant difference in meconium-stained amniotic fluid, possibly due to low power in the analyses because only two studies were included with a smaller population size.[107 112]

In one review, there was a statistically significant difference in premature delivery with a 12% reduction in odds ratio (OR 0.88, 95% Cl 0.78 to 0.98) in vaccinated pregnant women.[107] The heterogeneity was not statistically significant.[107] However, there was no definition of weeks for premature delivery. Compared to this review, my review used subgroups of preterm delivery and found it was only the <32 weeks gestational age that had a reduction (OR 0.57, 95% CI 0.39 to 0.83) in the odds of preterm birth, a finding that was not replicated in the <35 or <37 week groups. There may have been no statistically significant difference in the preterm birth subgroups of <35 weeks and <37 weeks gestation because of the number of participants included in the studies. The subgroup of <32 weeks gestation had more population and more power to find a difference, but it is unclear why a difference exists. Two other reviews had no statistically significant difference with preterm delivery.[108 109] However in one review, preterm delivery heterogeneity was statistically significant, with heterogeneity P value <0.001, indicating an inconsistent effect across the seven studies included.[109] The other review had no statistically significant difference in preterm delivery subgroups <32 weeks, <34 weeks, and <37 weeks of gestation.[108] However, in the <37 weeks gestation analysis, the heterogeneity was statistically significant, likely due to the control group including non-pregnant women.

Similar to my review, one review found neonatal respiratory complications had a statistically significant reduction in odds (71% and 35%, respectively) in favour of vaccinated mothers.[108] However, my review combined apnoea, dyspnoea, tachypnoea, respiratory distress, syndrome, transient tachypnoea, asphyxia, and mechanical ventilation into neonatal respiratory complications outcome where Prasad, et al. [108] only included Asphyxia but both analyses indicated a statistically significant difference. Like Carbone, et al. [107] my review found that abnormal foetal heart rate outcome had a statistically significant reduced odds (31% and 36%, respectively) in favour of vaccinated mothers. No other reviews included neonatal meconium aspiration syndrome in their analyses, whereas my review did and found a statistically significant reduction in favour of the Pfizer-BioNTech vaccination.

NICU admissions in two reviews had a statistically significant reduction in the odds ratio (OR 0.88, 95% CI 0.80 to 0.97)[109] and (OR 0.85, 95% CI 0.81 to 0.90)[112] in favour of a Covid-19 vaccination during pregnancy. Stillborn in two reviews had a statistically significant difference with a reduction in odds ratio (OR 0.73, 95% CI 0.57 to 0.94)[109] and (OR 0.85, 95% CI 0.73 to 0.99)[108] in favour of a Covid-19 vaccination during pregnancy. However, in one review[108] heterogeneity for stillborn was statistically significant, possibly because the control group included non-pregnant women. In my review, NICU admission and stillborn were not statistically significant; however, there was no adverse risk in pregnant women vaccinated with Pfizer-BioNTech in these two outcomes.

One review entered incorrect data into the miscarriage analysis, which has the potential to misinform.[111] The review included Rottenstreich, et al. [102] induction of labour results in the miscarriage analysis, and Magnus, et al. [113] study for miscarriage was entered wrong into the analysis, with vaccinated pregnant women in the control group and unvaccinated pregnant women entered in the experimental events group. The analysis resulted in a 12% increase (OR 1.12 95%CI 1.00 to 1.27) in odds ratio of miscarriage in the group of pregnant women who had the Covid-19 vaccination compared to the control group, and the difference was statistically significant with a p-value of 0.05. The outcome of the miscarriage analysis with the incorrect data entries is misleading and could be used to misinform health professionals and pregnant women.

Four reviews had statistically significant differences for documented Covid-19 infections. Three reviews had reductions in odds ratios[109 110 112] and one review had a reduction in hazard ratio[108] with combined Covid-19 vaccinations, supporting my review in favour of vaccination during pregnancy in reducing infection. Two reviews included the same two studies of pregnant women hospitalised with Covid-19 in their analysis as my review, therefore, we had the same findings.[110 112] There was a statistically significant reduction in odds ratio (OR 0.50, 95% CI 0.31 to 0.82) in hospitalisation with Covid-19 in favour of a Covid-19 vaccination compared to the control group.[110 112] The results from these reviews suggest that the Pfizer-BioNTech and other Covid-19 vaccinations during pregnancy are beneficial and effective for pregnant women in reducing infection and hospitalisation.

One systematic review's primary outcome was the dose and time effectiveness of Covid-19 vaccines which included four studies.[111] However, in each analyses, the outcomes documented infection and symptomatic infections were combined for mRNA vaccines, and symptomatic infections and severe Covid-19 infection outcomes were combined for inactive virus vaccines, in each dose and time of effectiveness. Combining the different infection types of results from the four studies into one analysis has the potential to mislead the efficacy of the Covid-19 vaccine.

From the reviews mentioned above and my review, the maternal, foetal and neonatal safety outcomes placental abruption, meconium-stained amniotic fluid, preterm delivery, neonatal respiratory complication, abnormal foetal heart rate, meconium aspiration syndrome, NICU admission and stillborn, and efficacy outcomes documented Covid-19 infection and hospitalised with Covid-19 all had statistically significant differences with reductions in odds ratio in favour of the Pfizer-BioNTech or a Covid-19 vaccinations during pregnancy. To my knowledge no reviews had any adverse events or increased risk of maternal, foetal, or neonatal outcomes with a Covid-19 vaccination during pregnancy.

Studies are still ongoing and in progress for the safety and efficacy of the Pfizer-BioNTech vaccine during pregnancy; these outcomes are yet to be published. Pfizer has not published the results of the safety, tolerability and immunogenicity of 4,000 healthy pregnant women vaccinated with Pfizer-BioNTech, even though the study was announced on the 18th of February 2021.[90] Phase two was to include approximately 200 pregnant women vaccinated with Pfizer-BioNTech at 27 to 34 weeks gestation with a control group of pregnant women vaccinated with saline as a placebo. Phase two was to assess the safety until seven days after the second dose. The second dose was twenty-one days after the first dose. Phase three of the study was to assess the safety, tolerability, and immunogenicity of the Pfizer-BioNTech vaccine between 24 to 34 weeks gestations. However, the clinical trials website states that the actual enrolment was only 349 pregnant women, and the study completion date was the 15th of July 2022, but the results still have not been published.[114]

Chambers, et al. [115] are conducting a study on pregnant women vaccinated with Pfizer-BioNTech during pregnancy to assess any risks of congenital malformations, spontaneous abortion, stillborn, preterm delivery, SGA, and infants who were exposed prenatally are small for their age at one year old compared to unvaccinated pregnant women. The data was to be collected from the Organization of Teratology Information Specialities Pregnancy Registry of the United States and Canada. The results are to be published in 2025. [115]

6.3 STRENGTHS

This systematic review had five main strengths. First, having the same vulnerable population in both the control and experimental group. To compare the safety and efficacy outcomes between pregnant women vaccinated with Pfizer-BioNTech to the control group of the same vulnerable population, pregnant women, unvaccinated. Assessing pregnancy outcomes against a control group of non-pregnant women is nonsensical, given that the risk of miscarriage would be zero in the non-pregnant comparison. Second, this review reports on one vaccination, Pfizer-BioNTech, because this is the primary and most widely used vaccination in NZ. Focusing solely on the Pfizer-BioNTech vaccination gives a clear report on its safety and efficacy in pregnant women. The Covid-19 vaccines available, mRNA, viral vector, protein subunits and inactivated vaccine are different and work differently, as explained in the background section, to create an immune response. Consequently combining the vaccinations in study results, systematic reviews and meta-analyses does not give a specific safety and efficacy outcome for that individual vaccine. If one type of Covid-19 vaccine has more adverse effects or more benefits on pregnancy outcomes it is masked by combining all the Covid-19 vaccinations. Third, this review included recent studies published to the 4th of February 2023 and had a short timeframe from the literature search to completion. Fourth, the studies were assessed for risk of bias with the ROBINS-E tool which provided a structured approach to assessing the risk of bias in the selected cohort studies. Fifth, this review included a range of safety outcomes with six maternal and fifteen foetal and neonatal outcomes of Pfizer-BioNTech vaccination during pregnancy.

6.4 LIMITATIONS

This review is subject to four limitations. First, only studies published in English were included. However, two other systematic reviews had no restrictions on language and found no other studies not already included in this dissertation.[109 110] Second, only one person searched and selected the studies for this review and assessed the studies for risk of bias using the ROBINS-E tool. However, this was because this review was a dissertation for partial fulfilment of a Master's in Nursing qualification and was guided by a supervisor. Third, this review did not report on the effectiveness of the Pfizer-BioNTech vaccine against the different variants of Covid-19, including Alpha, Beta, Gamma, Delta, or Omicron. However, the studies included in the review were carried out during the Alpha, Beta, Gamma, and Delta variants. The Pfizer-BioNTech vaccination during pregnancy was as effective as vaccinating the general population against the original SARS-CoV-2 variants, Alpha and Delta, with 96% effectiveness from day seven to fifty-six after the second dose.[106] WHO declared the new variant Omicron on the 26th

November 2021,[116] where this variant was only emerging at the end of two studies time periods.[100 103] Fourth, this review did not include the new Pfizer-BioNTech Bivalent Covid-19 vaccine as this vaccine only became available in NZ on the 1st March 2023.[117]

6.5 PUBLICATION BIAS

This dissertation did not assess for publication bias because fewer than ten studies were included in all of the meta-analyses. With fewer than ten studies, the tests for publication bias have a very low power to identify publication bias.[98]

6.6 CLINICAL AND RESEARCH IMPLICATIONS

Health professionals in NZ and worldwide where Pfizer-BioNTech is available can use this review as a reference for the safety and efficacy outcomes for evidence-based practice. To inform and educate future pregnant women with up-to-date research, that there are no adverse events or increased harm to the mother, foetus or neonate when the Pfizer-BioNTech vaccination is administered during pregnancy, and there are reductions in placental abruption, meconium-stained amniotic fluid, neonatal respiratory complications, abnormal foetal heart rate, and preterm delivery <32 weeks of gestation. Health professionals can discuss with pregnant women that having the Pfizer-BioNTech vaccination during pregnancy is beneficial and reduces the odds ratios of documented Covid-19 infection and hospitalisation with Covid-19. Hopefully, this dissertation and health authorities' advice and recommendations can be used to facilitate and improve the acceptance of the Pfizer-BioNTech vaccine among pregnant women.

Pregnant women have the right to equity and to be included in research if they choose to do so. Research in vaccines must include pregnant women when conducting clinical trials in order to forestall hesitancy and fears and increase support for vaccination in future pandemics. Research studies including pregnant women should also use pregnant women in the comparison groups. Covid-19 continues to mutate, and new Covid-19 vaccinations continue to be developed to fight against the viruses. Therefore, pregnant women need to be included in the clinical trials.

Further research is needed with larger cohort studies of the Pfizer-BioNTech administered during the different trimesters of pregnancy and with more extended follow-up periods for long-term outcomes of the Pfizer-BioNTech on the mother and foetus, and neonate in the future years. Future studies on the waning of the Pfizer-BioNTech vaccine effectiveness in pregnant women to assess if and when a booster Covid-19 vaccination is required would also be desirable.

7 CONCLUSION

This systematic review and meta-analysis show that receiving the Pfizer-BioNTech vaccination during any trimester of pregnancy is safe and effective for the mother and baby. No adverse effects or adverse events were found when the pregnant women had the Pfizer-BioNTech vaccination, and the women had reduced likelihood of having a placental abruption, meconium-stained amniotic fluid, foetal and neonatal respiratory complications, meconium aspiration syndrome, preterm delivery <32 weeks of gestation, or abnormal foetal heart rate. Pregnant women vaccinated with Pfizer-BioNTech had a reduced likelihood of having documented Covid-19 infection and hospitalised with Covid-19. The findings of this systematic review are broadly similar to those of other previous reviews, with results favouring the use of Covid-19 vaccines during pregnancy and reducing maternal, foetal, and neonatal outcomes.

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9 APPENDICES

9.1 APPENDIX ONE: PROTOCOL

Protocol information: What is the safety and efficacy of Covid-19 Pfizer-BioNTech (BNT162b2, Comirnaty, Tozinameran) vaccination in pregnancy?

1.0 Background

1.1 History and description of the condition

On the 31st of December 2019 in China, one of the World Health Organization's (WHO) offices noticed a media statement from the Wuhan Municipal Health Commission website about numerous cases of a 'viral pneumonia' and 'pneumonia of unknown cause' in Wuhan.[1] On the 1st of January 2020, WHO contacted Chinese authorities asking for information on the reported cluster of an 'atypical pneumonia' in Wuhan.[1] The virus was soon to be well-known as Coronavirus disease 2019 (Covid-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On the 21st of January 2020, the first confirmed case of the Covid-19 virus was detected in the United States of America (USA) and on the 24th of January, the first confirmed cases were detected in Europe, France.[1] By the 30th of January, 2020, this new virus had spread outside of China to eighteen different countries with ninety-eight cases.[2] On the 11th of March 2020, the WHO Director-General stated that the Covid-19 outbreak was declared a pandemic, with 114 countries detecting Covid-19 cases, with more than 118 000 confirmed cases and 4291 deaths recorded with Covid-19.[1 2] On the 5th of April 2022, according to the WHO worldwide statistics, 490 853 129 confirmed positive cases of Covid-19 and 6 155 344 deaths with Covid-19 had been reported to WHO.[118]

WHO stated that most people who contract Covid-19 have mild to moderate respiratory symptoms and recover without treatment or hospitalisation. Some people may become seriously unwell and need medical help, like older people and those with underlying medical conditions, for example, cardiovascular disease, diabetes, chronic respiratory disease, and cancer. However, any person at any age who gets infected with Covid-19 can get very unwell and may die. According to the WHO, the most common symptoms are fever, cough, tiredness, and loss of taste or smell. Severe symptoms include difficulty breathing, shortness of breath, loss of speech, mobility, confusion, and chest pain. Less common symptoms include sore throat, headache, aches and pains, diarrhoea, a rash on the skin, or red or irritated eyes.[62]

Historically pregnant women have always been an exclusion criterion for vaccination research, including Covid-19 vaccine trials.[70] Pregnant women were excluded from the first trials of Covid-19 vaccines. Still, with the knowledge of past viruses that cause pneumonia, including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-COV), which increase illness severity if pregnant.[71] Therefore, the Covid-19 vaccines were rolled out before the completion of clinical trials.[71] Zavala, et al. [70] discussed that pregnant women are at increased risk of severe illness, hospitalisation, and death if they become infected with Covid-19 compared to non-pregnant women. Pregnant women infected with Covid-19 are at higher risk of pre-eclampsia, preterm birth, stillborn, and having babies requiring intensive care than pregnant women not infected with Covid-19. Throughout the pandemic, there have been gaps in research and information about the safety and efficacy of Covid-19 vaccines in pregnancy, leading to global differences and guidance.[70] Many pregnant individuals are hesitant to be vaccinated against the Covid-19 virus with concerns regarding the vaccine's safety.[71]

Pfizer stated that the data was insufficient to inform vaccination of Pfizer-BioNTech safety risks in pregnant women. Developmental toxicity studies were carried out on female rats by administering Pfizer-BioNTech with two doses prior to mating and two doses during pregnancy. Pfizer stated studies showed no evidence of harm or vaccine-related adverse effects on female rat fertility, rat foetal development or postnatal rat development and encouraged pregnant women who were vaccinated with Pfizer-BioNTech during pregnancy to register on the pregnancy exposure registrar.[79]

The Covid-19 pandemic continues to show pregnant women's vulnerability to illnesses and ending up in intensive care units.[74] However, pregnant women continue to be excluded from clinical trials creating inequity and limited access to potentially life-saving medications. Pregnant women should be given the same choice and opportunity as other adults and decide if they want to be part of a clinical trial.[74] Though it is easier to exclude pregnant women from clinical trials because when pregnant women are included, there are not just concerns only for the pregnant woman's health and well-being but also for the growth and development of the foetus and neonate.[75] There are ethical concerns of equity when pregnant women are not included in clinical trials but also concerns of vulnerability and potential risks or harm from clinical trials to the pregnant women, foetus, and neonate. Pregnancy changes and affects drug pharmacodynamics and pharmacokinetics.[75]

1.2 Description of the Intervention

The following review looks at the Pfizer-BioNTech Covid-19 vaccination, also known or referred to as BNT162b2, Comirnaty or Tozinameran. This is the most commonly used vaccination in New Zealand.

On the 2nd of December 2020, the United Kingdom was the first country to approve a Covid-19 vaccine under emergency use authorisation (EUA) called Pfizer-BioNTech, only seven months after clinical trials started.[86] Ledford, et al. [86], stated there was no safety and efficacy data yet on pregnant women or children, which are often carried out once the safety and efficacy have been researched in healthy adults.

On the 11th of December 2020, the United States Food and Drug Administration announced the first Covid-19 vaccine, Pfizer-BioNTech, to be issued and used as a EUA against Covid-19 disease for 16 years of age and over.[87] The FDA evaluation from a clinical trial stated that the vaccine was 95% effective in preventing Covid-19 disease. However, this appears to be ambiguous with the following statements stating there was no evidence that the vaccine would provide prevention of transmission of Covid-19 from person to person and no data was available on how long the vaccination would provide protection.[87]

On the 18th of February 2021, Pfizer announced the beginning of Pfizer-BioNTech Covid-19 vaccine (BNT162b2) studies in healthy pregnant women over 18 years old. To carry out research and evidence on the safety and efficacy of the Pfizer-BioNTech and the potential to support the use of the vaccination in pregnant women.[90]

The rollout of the Pfizer-BioNTech vaccination for pregnant women in New Zealand started on the 10th of June 2021.[93]

1.3 Why it is important to do this review

Important for evidence-based practice to have the safety and efficacy of the Pfizer-BioNTech vaccination during pregnancy so pregnant mothers have the evidence and data to make an informed choice and give informed consent.

2.0 Objectives

To summarise the safety and efficacy of the Covid-19 Pfizer-BioNTech (BNT162b2, Comirnaty, Tozinameran) vaccination during pregnancy. This includes looking at the safety and efficacy of the mother, foetus, and neonate.

3.0 Search Strategy

3.1 Electronic Searches

The following databases will be searched for any studies relevant to the topic

- Embase (Ovid)
- Medline (Ovid)
- Web of Science
- Scopus
- PubMed
- Hand-searched articles from studies reference lists.

  Completed citations (including abstracts) will be imported into the reference manager EndNote Library for review.

4.0 Selection Criteria

4.1 Types of Studies

Must contain a control group or placebo group of participants so a comparison can be made between receiving the vaccination or not, including randomised and non-randomised controlled trials, case-control studies and or cohort studies.

4.2 Types of Participants

Pregnant women, any trimester.

4.3 Types of Intervention

Vaccinated with Pfizer-BioNTech (BNT162b2, Comirnaty, Tozinameran) during pregnancy.

4.4 Types of Outcomes

The safety and efficacy of the Pfizer-BioNTech.

SAFETY - adverse events, adverse reactions, adverse effects, including miscarriages, spontaneous abortions, stillborn, stillbirth, birth defects, effects on the foetus, congenital anomalies, damage to the placenta, placenta calcification, premature birth, pulmonary haemorrhaging, seizures in the neonate, pre-eclampsia, eclampsia, maternal haemorrhage and foetal, neonatal, or maternal death.

EFFICACY - benefits, including stopping or reducing transmission, preventing or reducing hospitalisation, preventing or reducing severe illness, preventing or reducing ICU admissions, preventing or reducing death.

5.0 Data Collection and Analysis

5.1 Key search terms

Pregnant, Pregnancy, Pregnant women, first trimester, second trimester, third trimester

Pfizer-BioNTech, Comirnaty, BNT162b2, Tozinameran

Coronavirus 2019, Covid-19, severe acute respiratory syndrome coronavirus two, SARS-CoV-2.

Safety: adverse reactions, adverse effects, adverse events, miscarriages, spontaneous abortion, stillborn, stillbirth, deformity, teratogenic, congenital anomalies, premature birth, preterm birth, neonatal abnormalities, effects on the foetus, placenta abruption, placenta calcification, pulmonary haemorrhaging, neonatal seizures, pre-eclampsia, eclampsia, maternal haemorrhage, foetal death, neonatal death, maternal death.

Efficacy: benefits, effectiveness, transmission, prevents or reduces hospitalisation, prevents or reduces ICU admissions, prevents or reduces death.

5.2 Selection of Studies

Only English language studies will be included. Titles and abstracts will be first screened to determine if they meet inclusion criteria. When uncertainty is present, whether the studies meet the inclusion criteria will be kept for further screening. With the remaining studies, the full studies will be screened to see if they meet the inclusion criteria. The studies will be managed through Endnote referencing management.

5.3 Data extraction and management

Duplicates will be excluded using endnote, and any remaining duplicates will be manually extracted. Studies that do not meet the inclusion criteria will be excluded. An exclusion file will be created on Endnote referencing management.

5.4 Assessment of risk of bias

Must have a control and or placebo group. The studies will be assessed for risk of bias using the Cochrane risk of bias in non-randomised studies of exposure (ROBINS-E) tool.

5.5 Data analysis

The results will be analysed regarding the safety and efficacy of the Pfizer-BioNTech vaccination between the two groups, pregnant women who have received the vaccination, comparing the control/placebo group of pregnant women who have not received the vaccination. If possible systematic or meta-analysis approach will be used for the data to be analysed if this is not possible, a thematic analysis approach will be used.

5.6 Dealing with missing data

If data is missing from the published report, attempt to obtain further information by contacting the paper's author or, if applicable, from the trial registry.

9.2 APPENDIX TWO: RISK OF BIAS USING ROBINS-E TOOL

Reference	Risk of bias due to confounding	Risk of bias arising from the measurement of the exposure	Risk of bias in the selection of participants for the study	Risk of bias due to post-exposure interventions	Risk of bias due to missing data	Risk of bias arising from the measurement of the outcomes	Risk of bias in the selection of the reported results	OVERALL RISK OF BIAS
Bleicher,[84] 2021	**Some concerns.** Confounders not documented included education or socioeconomics, smoking, and prenatal care.	**Low risk.** The study had a range of participants who were vaccinated in the first, second and third trimesters, with some participants having one or two doses of Pfizer-BioNTech.	**High risk.** This self-reporting questionnaire was sent out by the primary investigator using her private Facebook and WhatsApp account, first to health professionals because the Pfizer-BioNTech vaccination was only available for pregnant health professionals. After distributing the first questionnaire, the vaccine became available to all pregnant women. Then the investigator opened the study for any pregnant women, using her private social media, Facebook, and WhatsApp account for people to share. Pregnant women had to be part of social media and have some sort of connection to the primary investigator for the questionnaire to reach the participants.	**Low risk.** No post-exposure interventions were documented.	**Some concerns.** Twenty-five per cent of the participants did not respond to the second questionnaire.	**Some concerns**. This study relied on self-reporting and answering a questionnaire, which could have increased the chances of bias compared to a computerised database. The study stated that because this study was a self-reported questionnaire, outcomes for miscarriage or stillborn could have been higher, however, due to a traumatic experience, participants may not have wanted to participate or complete the questionnaires.	**Some concerns.** In the second questionnaire, the study stated they had complete data on 313 participants, and this included 202 pregnant women who were vaccinated with Pfizer-BioNTech; therefore, 111 pregnant women should have been in the control group. However, the study documented 124 non-vaccinated pregnant women in the analysis of the results. The questionnaires were only distributed during a short time frame of one month apart, and one of the questions was if the participants had tested positive since the last questionnaire and concluded that the vaccine significantly reduces the risk of Covid-19 infection with an odds ratio of 4.5.	**High risk** overall because the participants had to have social media, including Facebook or WhatsApp, which was distributed through the primary investigator. A self-reported questionnaire could increase the chances of bias compared to a computerised database, and the number of participants in the results does not add up to the number of participants the study obtained the complete data from.

Reference	Risk of bias due to confounding	Risk of bias arising from the measurement of the exposure	Risk of bias in the selection of participants for the study	Risk of bias due to post-exposure interventions	Risk of bias due to missing data	Risk of bias arising from the measurement of the outcomes	Risk of bias in the selection of the reported results	OVERALL RISK OF BIAS
Citu,[100] 2022	**Low risk**. Confounding factors not addressed were education or socioeconomic status.	**Low risk.** Clearly stated Pfizer-BioNTech (or mRNA) vaccinations during the first trimester.	**Low risk**. Used the database from the outpatient clinic at Timisoara Municipal Hospital.	**Low risk**. No post-exposure interventions were documented.	**Low risk.** The study did not show how many doses of Pfizer-BioNTech were given in the first trimester, it only included the combined doses of mRNA (Pfizer-BioNTech and Moderna) given to the pregnant women.	**Low Risk.** Outcomes were collected from the computerised database at Timisoara Municipal Hospital.	**Low risk.** The selection of the reported results was in accordance with the study's focus to research whether pregnant women vaccinated with Pfizer-BioNTech or Moderna in the first trimester of pregnancy had higher chances of spontaneous abortions.	**Low risk** overall because the study collected data from the database at Timisoara Municipal Hospital. The study only focused on spontaneous abortions in the first trimester, however, in the discussion, the study stated its limitations were regarding not having the outcomes of pregnancies, including congenital malformations and stillborn in the pregnant women who received the Covid-19 vaccine in the first trimester.
Dagan,[106] 2021	**Low risk.** This study used the Clalit Health Services database to match the demographics and clinical characteristics of the Pfizer-BioNTech vaccinated pregnant women group to the control group. With the strict matching process, both groups ended up with few chronic medical conditions.	**Low risk.** Adjustments were made as some of the control group of pregnant women received the Pfizer-BioNTech vaccination during the study period.	**Low risk**. The study used the Clalit Health Service database and successfully matched 10861 Pfizer-BioNTech vaccinated pregnant women with unvaccinated pregnant women. Exclusion criteria included those with multiple gestations, pregnant women with terminations, and women who tested positive for COVID-19.	**Low risk.** No post-exposure interventions were documented.	**Low risk**. No data appeared to be missing.	**Low risk**. Information was collected from the Clalit Health Services database.	**Low risk.** Clearly reported the results of the aim of the study.	**Low risk** overall, the study collected the data from the Clalit Health Service database and matched the participant in both groups.

Reference	Risk of bias due to confounding	Risk of bias arising from the measurement of the exposure	Risk of bias in the selection of participants for the study	Risk of bias due to post-exposure interventions	Risk of bias due to missing data	Risk of bias arising from the measurement of the outcomes	Risk of bias in the selection of the reported results	OVERALL RISK OF BIAS
Goldshtein,[99] 2021	**Low risk**. The study addressed multiple confounding factors and matched a 1.1 ratio of Pfizer-BioNTech vaccinated pregnant women with non-vaccinated pregnant women as the control group. Maccabi Healthcare service represents 26.7% of Israel's population with similar socio-demographic characteristics throughout Israel.	**Low risk**. The study included a first dose exposure, however, by the end of the follow-up period (11 April 2021), 5626 pregnant women had their second Pfizer-BioNTech vaccination. Both groups of pregnant women were matched for their first, second and third trimester.	**Low risk**. The study used the Maccabi Healthcare Service's computerised database to select participants. The study matched 7530 Pfizer-BioNTech vaccinated pregnant women and matched 7530 unvaccinated pregnant women as the control group. Pregnant women who had a Pfizer-BioNTech dose from 19 December 2020 to 28 February 2021 were included, with 46% in their second and 33% in their third trimester. Exclusion criteria included clients who joined the health fund less than one year pre-conception, any previous positive PCR tests confirming Covid-19 infection, and any women vaccinated pre-pregnancy with Pfizer-BioNTech.	**Low risk**. No post-exposure interventions were documented.	**Low risk.** No data appeared to be missing.	**Low risk.** The outcomes were collected from the computerised database from Maccabi Healthcare Services.	**Low risk.** The results clearly reported the question and objective and followed the study method. The study had a table showing all the Pfizer-BioNTech pregnant women participants and matched control participants. Full results of the Covid-19 infections using statistics hazard rates and reported maternal and neonatal outcomes that were followed up until 11 April 2021.	**Low risk** overall because the study used a computerised database system for the selection of participants, results and matched a one-to-one ratio for the Pfizer-BioNTech vaccinated pregnant women to an unvaccinated pregnant woman.

Reference	Risk of bias due to confounding	Risk of bias arising from the measurement of the exposure	Risk of bias in the selection of participants for the study	Risk of bias due to post-exposure interventions	Risk of bias due to missing data	Risk of bias arising from the measurement of the outcomes	Risk of bias in the selection of the reported results	OVERALL RISK OF BIAS
Goldshtein,[81] 2022	**Low risk.** The study used stabilised inverse probability of treatment weighting (IPTW) to adjust for maternal age, the timing of conception, parity, socioeconomic status, pre-existing comorbidities and subgroup analysis. Maccabi Healthcare Service has a 2.5 million member state health fund representing 26.7 per cent of Israel's population.	**Low risk.** The study included pregnant women exposed to Pfizer-BioNTech in the first, second, and third trimesters and had a subgroup analysis of neonatal outcomes for pregnant women exposed in their first trimester.	**Low risk.** Data was collected from a computerised database system from the Maccabi Healthcare Service in Israel. Only singleton pregnancies were included because multiple pregnancy births are closely linked to higher outcomes of preterm birth and low infant weight, which would require a lot of adjustment and analyses. Records unable to link neonates and mothers were excluded because there was no way to find their prenatal exposure to the Pfizer-BioNTech vaccination.	**Low risk.** No post-exposure interventions were documented.	**Low risk.** No data appeared to be missing.	**Low risk.** The data was collected from the computerised electronic database system from the Maccabi Healthcare Service system in Israel.	**Low risk.** The study used stabilised IPTW and included pre- and post-IPTW results. The study combined all neonatal and early infant outcomes from the Pfizer-BioNTech vaccination given in all three trimesters. Also, the study had a subgroup analysis for the neonatal and early infant outcomes for the vaccination given in the first trimester.	**Low risk** overall because the study used a computerised electronic database system and used IPTW for the characteristics of the pregnant women and neonatal and early infant outcomes.

Reference	Risk of bias due to confounding	Risk of bias arising from the measurement of the exposure	Risk of bias in the selection of participants for the study	Risk of bias due to post-exposure interventions	Risk of bias due to missing data	Risk of bias arising from the measurement of the outcomes	Risk of bias in the selection of the reported results	OVERALL RISK OF BIAS
Kugelman,[101] 2022	**Some concerns.** The study did not mention maternal education, socioeconomics or prenatal care. However, there were no statistically significant differences between the Pfizer-BioNTech group and the control group of pregnant women in any maternal characteristics, including maternal age, BMI, smoking, previous c-section, primipara and gestational diabetes.	**Low risk.** The study used the database from Carmel Medical Centre, Haifa, Israel. One or two doses of Pfizer-BioNTech vaccination were combined because only 51 (5.5%) of the pregnant women had one vaccine, all the rest (879) had two doses, and there were no differences in the results of exposure doses.	**Some concerns.** The study used the database from Carmel Medical Centre to select the participants, including all singleton pregnancies over 23 weeks of gestation. The study did not include pregnant women vaccinated in the first trimester because their pregnancies were ongoing. Exclusion criteria included multiple gestations and pregnant women who had terminations.	**Low risk.** No post-exposure interventions were documented.	**Low risk.** Results were not shown for separate vaccination doses, because only 51 (5.5%) out of 930 vaccinated pregnant women had one dose of Pfizer-BioNTech, and there were no noticeable differences in the findings. The study did not specify how many pregnant women were vaccinated in the second or third trimester.	**Low risk.** The study used the computerised database from Carmel Medical Centre, Haifa, Israel, primary medical records for finding and reporting the results.	**Low risk.** The study clearly outlined in the method what the primary outcome was going to report, which focused on preterm delivery <35 weeks of gestation, intrauterine foetal death >23 weeks of gestation, intrauterine growth restriction, 5 minutes Apgar scores <7 and neonatal care unit admissions.	**Some concerns** overall because this study only included singleton pregnancies over >23 weeks gestation, excluding the first trimester and some confounding factors not included.

Reference	Risk of bias due to confounding	Risk of bias arising from the measurement of the exposure	Risk of bias in the selection of participants for the study	Risk of bias due to post-exposure interventions	Risk of bias due to missing data	Risk of bias arising from the measurement of the outcomes	Risk of bias in the selection of the reported results	OVERALL RISK OF BIAS
Rottenstreich,[102] 2021	**Some concerns.** The study could not report on participants' socioeconomic status due to the retrospective study design. Other confounding factors that were statistically significant were maternal age, previous miscarriages and fertility treatment were higher in the Pfizer-BioNTech vaccinated pregnant women group compared to the control group.	**Low risk.** The exposed group of pregnant women had two doses of Pfizer-BioNTech in their third trimester.	**Some concerns.** Participants were selected from a computerised database in two university-affiliated Medical Centres in Jerusalem, Israel. However, there could be a risk of bias in the selection of participants because this study only looked at women vaccinated in their third trimester, due to the urgency of the study to report on the safety of Pfizer-BioNTech during pregnancy and maternal and neonatal health outcomes. Exclusion criteria included pregnant women who only had one dose of Pfizer-BioNTech vaccination and tested positive for Covid-19 with a PCR test during pregnancy or delivery.	**Low risk.** No post-exposure interventions were documented.	**Low risk.** No data appeared to be missing.	**Low risk.** The results of this study were collected from a computerised real-time update database system.	**Low risk**. The selection of the reported results was in line with the objective and method of the study and clearly outlined the study's strengths and limitations.	**Some concerns** overall because the study only included women vaccinated in their third trimester, however, the study clearly states this in its objective due to the urgency of the study.

Reference	Risk of bias due to confounding	Risk of bias arising from the measurement of the exposure	Risk of bias in the selection of participants for the study	Risk of bias due to post-exposure interventions	Risk of bias due to missing data	Risk of bias arising from the measurement of the outcomes	Risk of bias in the selection of the reported results	OVERALL RISK OF BIAS
Rottenstreich,[103] 2022	**Some concerns.** The participants' socioeconomic status was unknown due to the study's computerised retrospective design. The study stated that the Pfizer-BioNTech vaccinations were free and easily accessible, and that the National Health Care system covers all healthcare in Israel.	**Some concerns.** The gestational week at the time of the Pfizer-BioNTech vaccination was not documented, only pregnant women who had two doses were included.	**Low risk.** Participants were selected through the computerised medical record database from two university-affiliated Medical Centres in Jerusalem, Israel. Exclusion criteria included pregnant women who had one dose of the Pfizer-BioNTech and had a history of testing positive for Covid-19 with a PCR test during or before pregnancy.	**Low risk.** No post-exposure interventions were documented.	**Low risk.** No data appeared to be missing.	**Low risk.** The results were recorded from the computerised medical record database, which was continuously updated in real-time during labour and delivery.	**Low risk.** Results were reported in accordance with the method, including maternal and neonatal outcomes.	**Some concerns** overall because of bias arising from the measurement of the exposure of the Pfizer-BioNTech and not being able to obtain the information for what gestational week the vaccination was administered to the pregnant women. The study noted this in its limitations and that this could be an important variable, which future studies could include to see if there is an effect in different trimesters on the outcomes for pregnant women or neonates.

Reference	Risk of bias due to confounding	Risk of bias arising from the measurement of the exposure	Risk of bias in the selection of participants for the study	Risk of bias due to post-exposure interventions	Risk of bias due to missing data	Risk of bias arising from the measurement of the outcomes	Risk of bias in the selection of the reported results	OVERALL RISK OF BIAS
Sadarangani,[104] 2022	**Some concerns.** Some confounding factors not addressed included education or socioeconomics, smoking and past medical history. Participants self-reported health status as excellent, very good, fair, poor, or unknown, which could be a risk of bias based on people's judgment.	**High risk.** The study only included events that happened seven days after the Covid-19 vaccination exposure. Or in the control group, any events that occurred in the previous seven days. The study included participants with one and two doses of the Pfizer-BioNTech vaccine versus the control group.	**Some concerns**. Selection for the study included participants who had an active email address, telephone, spoke English or French, and had a first dose of Covid-19 vaccination within the previous seven days.	**Low risk.** No post-exposure interventions were documented.	**Some concerns**. The study did not document how many participants were vaccinated in each trimester. No breakdown of trimester severe or serious health events, only significant health events for each trimester were reported.	**Some concerns**. Self-reporting in answering a survey could increase the chances of bias compared to a computerised database. The study only included outcomes seven days after the vaccination.	**Some concerns.** The study did not show how many participants were vaccinated in the first, second or third trimesters for vaccination doses one and two. This could have been useful when showing health events, however, the study only reported the breakdown for trimester significant health events and not for the severe or serious health events. The study combined miscarriage and stillborn together in the second trimester and only reported these results after the first vaccination dose and not after the second dose. Only reported on the pregnancy adverse outcomes after the first and not the second vaccination.	**High risk** overall because the data for the study was primarily collected from a self-reported survey and included events that only happened seven days after the Covid-19 vaccination was administered.

Reference	Risk of bias due to confounding	Risk of bias arising from the measurement of the exposure	Risk of bias in the selection of participants for the study	Risk of bias due to post-exposure interventions	Risk of bias due to missing data	Risk of bias arising from the measurement of the outcomes	Risk of bias in the selection of the reported results	OVERALL RISK OF BIAS
Wainstock,[105] 2021	**Some concerns.** Some confounding factors not addressed included medical history and smoking.	**Low risk.** Included participants that had one dose and two doses of Pfizer-BioNTech vaccination.	**Some concerns.** The study used the Clalit computerised Soroka University Medical Centre database to select participants. However, only vaccinated participants in their third trimester were included in the study. Exclusion criteria included pregnant women who tested positive for Covid-19 in the past, had multiple gestations and had an unknown vaccination status.	**Low risk.** No post-exposure interventions were documented.	**Low risk.** No data appeared to be missing.	**Low risk**. Outcomes were retrieved from the Soroka University Medical Centre database.	**Low risk**. The selection of the reported results was in line with the study's aim and objective. The study reported the results of one and two doses of the Pfizer-BioNTech vaccination and the odds ratio between one dose vs none, two doses vs none, and two vs one dose.	**Some concerns** overall because the study only included pregnant women vaccinated in their third trimester.