COVID-19 Vaccination: Guidance for Ethical, Informed Consent in a National Context

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ABSTRACT: This Guidance addresses the essential elements of informed consent to novel, provisionally registered COVID-19 vaccines which conform to the current definition of an investigational vaccine namely, lacking requirements for approval for full registration. [1] First, it addresses the ethical obtaining of informed consent in a setting of short and long term knowns and unknowns, by structuring the personal nature of informed consent into its twelve component parts. Second, as a guidance for family physicians, it explores reasonable medical concerns arising for individuals from both knowns and unknowns about COVID-19 disease and vaccines.

Where there are waves of pandemic pressure impelling political, economic, social and public health forces to promote vaccination to health care providers and their patients, the necessary constituents of valid informed consent can be sublimated and possibly forfeited. This context of informed consent for COVID-19 vaccines is not unique to Australia. The analysis and presentation of international data by Aus-

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[1] Council for International Organizations of Medical Sciences. Cumulative Pharmacovigilance Glossary Version 1.0 <https://cioms.ch/wp-content/uploads/2021/03/CIOMS-Cumulative-PV-Glossary-v1.0.pdf>.

tralian Government agencies is a process occurring in all countries. Therefore, the Australian experience of consenting for vaccination is relevant to informed consent across the globe.

The purpose of this Guidance is to assist personalised risk-benefit assessment for the informed consent of the vaccinee. Its aim is not to give a therapeutic guide nor to draw conclusions which can only rightly be drawn pertaining to each individual recipient in discussion with a health care provider. This is especially true in the setting of incomplete research where the many unknowns may be more significant for some than others. Since data is changing over time, national tables have not been used for specifics which the vaccine provider should access at the time of consultation.

While we recommend the Guidance be read in conjunction with Government issued information, this Guidance will address specific fields relevant to informed consent which may not be addressed in those communications, but which a consenting individual as a person with their own values and experiences may wish to know.

Aim: To address the requirements of ethical informed consent of the individual adult in the context of reasonable concerns pertaining to the unknowns and incomplete research attending novel, provisionally registered COVID-19 vaccines.

Methodology: To elucidate what might be reasonable concerns for individuals considering vaccination, Public Assessment Reports of regulatory authorities (Food and Drug Administration and Therapeutic Goods Administration) and published trials of currently available vaccines were reviewed. International Covid-19 vaccine safety discussions were observed for peer-reviewed and, if necessary, pre-print references base. These references were studied for potential relevance to vaccine recipients. Vaccine Development Guidelines were also reviewed for pre-clinical requirements and compared with pre-clinical data presented at licensing. Missing information was requested from the Therapeutic Goods Administration (TGA).

Pertinent unknowns were thereby identified as issues potentially relevant to fully informed consent, and compared with the content of standard Government-issued vaccine consent advice forms. Disparities were selected as relevant unknowns or reflecting incomplete research.

Pertinent issues were incorporated into a twelve point structure for reasonable consideration to guide ethical inform consent. Paediatric COVID disease and vaccination are mentioned briefly due to paediatric vaccination being unapproved in Australia at the time of writing in under 12-year-olds, and exclusion of minors from phase III safety and efficacy trials.

Conclusion: **The provision of ethically obtained, fully informed consent is very pertinent to an investigational vaccine notwithstanding the pandemic context. To ascertain informed consent to the best of our ability, the gap between officially delivered information and reasonable concerns generated by knowns and relevant unknowns, can be addressed in a structured manner by physicians. Consent should not be coerced but be free of inducements and reprisals, respecting declarations of human rights, particularly given the investigational nature of COVID-19 vaccines. Each recipient requires adequate information to make their own judgment. The process of validly informed consent will therefore include discussion of concerns and of relevant information we do and do not yet have. Ethical informed consent should address those concerns as best is possible.**

Background

A programme for vaccination against COVID-19 disease commenced in Australia in 2021. The Therapeutic Goods Administration (TGA) provisionally approved the Pfizer/BioNTech mRNA vaccine BNT162b2 ('Comirnaty') and the University of Oxford/AstraZeneca viral vector vaccine ChAdOx1 nCoV-19 (AZD1222) in February. Provisional, not full, registration was granted as both vaccines are investigational. Additionally, another mRNA vaccine, Moderna, is provisionally registered to become available later in 2021. Australia has determined a fourth vaccine 'Novavax', a protein vaccine with completed phase 3 trials, is eligible to apply for provisional registration in the Australian Register of Therapeutic Goods.

Initially, the Pfizer vaccine has been limited to certain population groups and, ultimately, all adults will have access to a COVID-19 vaccine with an AstraZeneca vaccine safety caveat for those under 60 years of age, for whom the 'Pfizer' vaccine is now preferred. Phase III trials on the currently used vaccines, Pfizer and AstraZeneca, are published and accessible.[2,3]

The fast-tracking of anti-COVID-19 disease vaccine development has resulted in products with more known unknowns, and unknown unknowns, than any other vaccine in common usage.[4] While short term safety follow-up involves direct electronic

[2] Fernando P. Polack, et al, 'Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine' (2020) 383 New England Journal of Medicine 2603 <https://www.nejm.org/doi/full/10.1056/NEJMoa2034577>.

[3] M Voysey et al, 'Safety and Efficacy of the ChAdOx1 nCoV-19 Vaccine (AZD1222) Against SARS-CoV-2; An Interim Analysis of Four Randomised Controlled Trials in Brazil, South Africa and the UK' (2021) 397 Lancet (10269) 111 <https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32661-1/fulltext>.

[4] See, eg, Peter Doshi, 'Clarification: Pfizer and Moderna's "95% effective" vaccines—We Need More Details and the Raw Data' BMJ Opinion (Blog Post, 5 February 2021) <https://blogs.bmj.com/bmj/2021/02/05/clarification-pfizer-and-modernas-95-effective-vaccines-we-need-more-details-and-the-raw-data/>.

patient contact on Day 3 post vaccination and mandatory healthcare provider reporting of Adverse Events Following Immunization (AEFI), longer term safety information will rely more heavily on the recognition and voluntary reporting of adverse events by General Practitioners, nurses, hospital officers, and patients.[5] These unknowns, together with a lack of knowledge of long term consequences of COVID-19 infection, make the consent process more complex.

The Australian Government has produced a consent form for COVID-19 vaccination and providers of medical indemnity have produced information on how to obtain informed consent for such vaccines.[6] We are concerned these documents are inadequate for informed consent due to missing or unclear information, specifically:

As of August 6th 2021 there is no reference on government issued vaccine consent forms to:

- the investigational nature of the provisionally registered vaccines and unknowns arising therefrom (see section 3.f);
- Developmental And Reproductive Toxicity (DART) studies which do not give access to ovarian and testicular histology reports (see section 3.j);
- cluster reports eg myocarditis associated with mRNA vaccines; new onset menstrual irregularities with AstraZeneca and Pfizer vaccines etc., as yet unexplained (see section 3.e):

Also, there is unclear vaccine consent form information:

- incomplete short term safety data, and consent form internet links to government downloads to which a person may not have ready access or comprehension and,
- the absence of long term safety data and knowledge of potential outcomes.

This Guidance therefore delves deeper into the process of facilitating fully informed consent utilising a 12 point structure appropriate to an investigational intervention, published and formerly used by the National Health and Medical Research Council.[7] Other authors have produced detailed documents to support the informed consent process for COVID-19 vaccination, including one example from the United Kingdom based on the Montgomery Judgement and General Medical Council (GMC) Guidelines.[8]

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[5] On-line reporting of problems or side effects can be made to the Australian Government Department of Health's Therapeutic Goods Administration at <https://www.tga.gov.au/reporting-problems>.

[6] See, eg, 'Consent Form for Covid Vaccination', Australian Government, Department of Health (Web Page) <https://www.health.gov.au/sites/default/files/documents/2021/02/covid-19-vaccination-consent-form-for-covid-19-vaccination_2.pdf>; 'Novel Covid-19' MIGA (Web Page, updated 1 April 2021) <https://www.miga.com.au/coronavirus>.

[7] National Health and Medical Research Council, 'General Guidelines for Medical Practitioners on Providing Information to Patients' (1993).

[8] Letter from UK Medical Freedom Alliance to the Medicines and Healthcare Products Regulatory Agency and the Joint Committee on Vaccination and Immunisation, 23 November 2020 <https://uploads-ssl.webflow.com/5fa5866942937a4d73918723/5fbd13488af2de09d68bd61c_UKMFA_Letter_to_MHRA_JCVI.pdf COVID-19_Consent_Form_v3.pdf>.

Upholding this informed consent process with provision of relevant information for an investigational vaccine is consistent with our professional values of beneficence, non-maleficence, justice, veracity, fidelity and autonomy.[9] The Australian Government strongly supports vaccination[10] under appropriately trained supervision of COVID-19 vaccine eligibility and contraindications. However, with the exception of certain health care workers, vaccination is not mandatory and individuals may choose not to vaccinate. This is consistent with the Universal Declaration of Human Rights provision for the right to bodily integrity.[11] This Guidance provides detailed information to enhance personal risk-benefit assessment to determine the suitability of vaccination, or alternative measures, case by case.

Three Questions to Address During Shared Decision Making:

1. Capacity—Is the patient able to make this decision?

Generally, a patient has capacity to make a decision if they can understand, retain and evaluate the information relevant to the decision, and communicate their decision and understanding. The level of capacity required relates to the seriousness of the proposed intervention. Consent for a patient with diminished capacity for example, an aged care resident with dementia, may be obtained via a substitute decision-maker (medical power of attorney).[12, 13]

2. Voluntariness—Is the patient making this decision freely?

Has the decision been pressured or coerced by other interests? Patients must give their consent freely and have the right to refuse treatment or seek another opinion.[14]

3. Information—Does the patient have enough?

Doctors have a legal obligation to inform patients of the important or 'material' risks involved in a proposed procedure or treatment. The emphasis is on the particular

[9] New South Wales Government, Health, Education and Training (Webpage) <https://www.heti.nsw.gov.au/>.

[10] Australian Covid-19 Vaccination Policy', Australian Government, Department of Health (Policy, August 2020) <https://www.health.gov.au/sites/default/files/documents/2020/12/covid-19-vaccination-australian-covid-19-vaccination-policy.pdf>.

[11] Universal Declaration of Human Rights, GA Res 217A (III), UN GAOR, UN Doc A/810 (10 December 1948). See specifically, International Covenant on Political and Civil Rights, opened for signature 16 December 1966, UNTS 999 (entered into force 23 March 1976) art 7.

[12] Xavier Symons, 'Covid Vaccine Consent for Aged Care Residents' Royal Australian and New Zealand College of General Practitioners GP News (Blog Post, 24 February 2021). <https://www1.racgp.org.au/newsgp/clinical/covid-vaccine-consent-for-aged-care-residents?utm_source=racgpnewsgpnewsletter&utm_campaign=newsgpedm&utm_medium=email>. See also,

[13] Consent: The Essentials' Avant Mutual (Web Page, 15 August 2019) <https://www.avant.org.au/Resources/Public/consent-essentials/>.

[14] Avant Mutual (n 13).

and the individual—what is material to one patient may not be to another. The particular circumstances of the individual patient will ultimately determine which risks are considered to be material by the patient and, ultimately, by the medical practitioner.[15]

Twelve Points to Cover on Information:

a) the possible or likely nature of the condition i.e. COVID-19;
b) the proposed approach to management i.e. vaccination;
c) what the proposed approach entails;
d) the expected benefits i.e. protection against infection;
e) common side effects and material risks;
f) whether the intervention is investigational (experimental) or conventional;
g) other options for management;
h) the degree of uncertainty of the outcome;
i) the likely consequences of not choosing the proposed procedure, or of not having any procedure at all;
j) any significant long term physical, emotional, mental, social, sexual or other outcome that may be associated with the proposed procedure;
k) the time involved; and
l) the cost involved, including out of pocket costs.

Results

3. a) The Possible or Likely Nature of the Condition i.e. COVID-19;

The symptoms of COVID-19 can range from those of a mild flu-like illness to those of pneumonia and acute respiratory distress and thromboembolic disorders. Patients with severe COVID-19 disease have laboured, difficult breathing and progressive hypoxia requiring hospitalization and often need mechanical ventilatory support.

In a New South Wales (Australia) setting, following up all cases of confirmed COVID-19 between April and July 2020 with regular 3 weekly interviews (excluding those who remained hospitalized or in a residential aged care facility), 80% of all confirmed COVID-19 cases reported recovery from symptoms within a month, but about 5% continued to experience symptoms 3 months later.[16]

The common COVID-19 symptoms are fever, cough, sore throat and shortness of breath. Other symptoms can include runny nose, blocked nose (congestion), headache, muscle or joint pains, nausea, diarrhoea, vomiting, loss of sense of smell, altered sense of taste, loss of appetite and fatigue.[17] The long term sequelae of COVID-19 disease and their duration are currently unknown. Recent literature has mentioned newly described

[15] Ibid.

[16] B Liu et al, 'Whole of Population-based Cohort Study of Recovery Time from COVID-19 in NSW Australia' (2021) 12 The Lancet Regional Health-Western Pacific 100193 <https://www.thelancet.com/action/showPdf?pii=S2666-6065%2821%2900102-4>

[17] 'What you Need to Know about Corona Virus (Covid-19)', Australian Government, Department of Health (Web Page, last updated 6 April 2021) <https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/what-you-need-to-know-about-coronavirus-covid-19#symptoms>.

'Long Covid' symptomatology including 'brain fog' and fatigue.[18] Long Covid refers to a COVID-like illness lasting more than 12 weeks of yet to be defined pathogenesis and diagnostic criteria. Lung injury and neuronal injury contributing to Long Covid have been postulated and neurodegenerative disease also theorized as a future possibility.[19] Because the pandemic has been ongoing for less than 18 months, long term outcomes are uncertain. The possibility of COVID-19 disease being followed by pulmonary fibrosis and impaired lung function has been suggested by follow-up of SARS-CoV-1 patients from 2003, and might result from diffuse alveolar damage and diffuse thrombotic alveolar microvascular occlusion. Central and peripheral nervous systems might also show longer term neurological sequelae.[20] Coronaviruses SARS-CoV-1 and SARS-CoV-2 could enter the brain via alteration to the blood-brain barrier by the viral S protein. Concerns have also been raised about symptoms of Long Covid in children. The incidence is difficult to assess at this time. While one very small study suggests 30.9% of children had one to two persisting symptoms >120 days post COVID-19 infection,[21] a much larger study[22] of a randomly selected population based cohort, with 6 months follow up of over 1,350 of children and adolescents, found 4% of seropositive 6 to 16 year-olds reported one or more persisting symptoms, compared with 2% of seronegative children. This suggests a low prevalence of symptoms compatible with long COVID, the authors claim. While this Guidance focuses on adult vaccination for the reasons stated in methodology, early Italian experience[23] has suggested the incidence of multisystem inflammatory syndrome in children (MIS-C), which shows a significant overlap with other hyperinflammatory syndromes such as Kawasaki disease, may be 2.3%. However, this was a small study of 129 children. Consistency of diagnostic criteria is unclear. In a systematic review of MIS-C cases in children, by World Health Organization case definition, 68% required critical care.[24]

The Brighton Collaboration describes SARS-CoV-2 as an infection associated with a spectrum of disease that varies from asymptomatic infection to severe lung disease with acute respiratory distress syndrome and a fatal multi-organ disease with inflammatory, cardiovascular, hematologic and coagulation dysregulation. Post-infectious,

[18] 'COVID-19 Rapid Guideline: Managing the Long Term Effects of COVID-19', NICE Guideline [NG188] (Web Page, published 18 December 2020) <https://nice.org.uk/guideline/ng188>.

[19] F Wang, R Kream and G Stefano, 'Long -Term Respiratory and Neurological Sequelae of COVID-19' (2020) Medical Science Monitor (1 November 2020) <https://www.medscimonit.com/abstract/index/idArt/928996>.

[20] CMS Singal, P Jaiswal and P Seth, 'SARS-CoV-2, More Than a Respiratory Virus: Its Potential Role in Neuropathogenesis' (2020) 11(13) ACS Chemical Neuroscience 1887-99 <https://pubs.acs.org/doi/pdf/10.1021/acschemneuro.0c00251>.

[21] D Buonsenso et al, 'Preliminary Assessment on Long COVID in Children' Acta Paediatrica (2021) 110. doi: 1111/apa.15870 <https://onlinelibrary.wiley.com/doi/epdf/10.1111/apa.15870>.

[22] T Radke et al, 'Long-term Symptoms After SARS-CoV-2 Infection in School Children: Population-based Cohort with 6 Months Follow-up' MedRxiv doi: <https://doi.org/10.1101/2021.05.16.21257255>.

[23] D Buonsenso et al (n 21).

[24] T Radia et al, 'Multisystem Inflammatory Syndrome in Children and Adolescents (MIS-C): A Systematic Review of Clinical Features and Presentation' (2021) 38 Paediatric Respiratory Review 51-57 <https://pubmed.ncbi.nlm.nih.gov/32891582/>.

possibly immune-mediated systemic disease, has also been described, particularly the multi systemic inflammatory syndrome in children (MIS-C) and adults (MIS-A) which is of unclear pathogenesis at this time.[25]

In October 2020, the global COVID-19 infection fatality rate was estimated to be 0.15-0.20% (0.03-0.04% in those <70 years), with large variability across locations with different age-structure, institutionalization rates, socioeconomic inequalities, population-level clinical risk profile, public health measures, and health care.[26]

Case fatality data from January 25th to December 10th 2020 (encompassing two waves of COVID-19 cases) from Victoria, Australia, where there was ready access to standard care, give the observed case fatality risk of a confirmed COVID-19 infection to be: 0% to age 19, 0.02% in 20 to 29 year-olds, 0.06% in 30 to 39 year-olds, 0.04% in 40 to 49 year-olds. This increased to 0.63% in 50 to 59 year-olds and 2.16% in 60 to 69 year-olds. Thereafter, it increased more steeply to 14.41% in 70 to 79 year-olds, 31.90% in 80 to 89 year-olds, and 40.03% in those over 90[27] many of whom died in aged care facilities. This Victorian data of a completed outbreak is a valuable resource worldwide, since its data series ended on December 10th 2020, when the state had experienced 42 consecutive days with zero COVID-19 cases and COVID-19 was therefore officially eliminated.[28] These results therefore avoid right censoring of data as occurs from a population where cases are still active and accord with other Australian research.[29] The SARS-CoV-2 Delta variant was not present in Australia at this time.

3. b) The Proposed Approach to Management (Vaccination);

Vaccination has the potential to curb the SARS CoV2 pandemic. COVID-19 vaccines aim to prevent a person from becoming ill or dying from the SARS-Co-V2 virus.

Current anti-viral vaccines are essentially protein-based or gene-based. Gene-based vaccines are nucleic acid (mRNA and DNA) vaccines and viral vector vaccines. The provisionally licensed COVID-19 vaccines in Australia are both totally new, gene-

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[25] L I Jiang et al, 'COVID-19 and Multisystem Inflammatory Syndrome in Children and Adolescents (2020) 20 (11) Lancet Infectious Diseases doi.org/10.1016/51473-3099(20)30651-4.

See also, 'Covid-19 Symptom Checker', HealthDirect (Web Page) <https://www.healthdirect.gov.au/symptom-checker/tool/disposition/8768060/203/7>.

[26] John P A Ioannidis, 'Global Perspective of COVID-19 Epidemiology for a Full-Cycle Pandemic' (2020) European Journal of Clinical Information doi.org/10.1111/eci.13423 <https://onlinelibrary.wiley.com/doi/10.1111/eci.13423>.

[27] IC Marschner, 'Estimating Age-Specific COVID-19 Fatality Risk and Time to Death by Comparing Population Diagnosis and Death Patterns: Australian Data' (2021) 21 BMC Medical Research Methodology 126 (21 June 2021) <https://doi.org/10.1186/s12874-021-01314w>.

[28] T Blakely et al, 'The Probability of the 6 Week Lockdown in Victoria Achieving Elimination of Community Transmission of SARS-CoV-2' (2020) 213 Medical Journal of Australia 349-51. <https://www.mja.com.au/journal/2020/213/8/probability-6-week-lockdown-victoria-commencing-9-july-2020-achieving>.

[29] K Macartney, 'Thrombosis and Thrombocytopoenia Syndrome Associated with COVID-19 Vaccine AstraZeneca' (Presentation, Australian Health Protection Principal Committee, Australian Technical and Advisory Group on Immunization, 12 April 2021).

based vaccines, as is the pending Moderna vaccine.[30] They carry genetic instructions for the host cells to make antigen to induce an immune response.

The other vaccine accepted by the TGA to seek provisional registration is NVX-CoV2373 ('Novavax').[31] It is a protein-based vaccine. It differs from gene-based vaccines as it formulates the coronavirus spike protein as nanoparticles which stimulate the immune system.

The AstraZeneca vaccine is a chimpanzee adenovirus which enters host cells but has been modified to prevent replication. It is a double strand DNA vaccine carrying a gene encoding the SARS Co-V-2 spike protein surface glycoprotein. The product contains genetically modified organisms.[32]

The Pfizer vaccine contains single strand messenger RNA (mRNA) encoding the SARS-CoV-2 spike protein antigen which, after administration, is delivered into host cells. The spike protein is subsequently expressed, stimulating neutralising antibody and cellular immune responses.[33] Moderna mRNA vaccine works similarly, encapsulated in a lipid nanoparticle and encoding the spike glycoprotein.[34]

3. c) What the Proposed Approach Entails;

Vaccination with the AstraZeneca COVID-19 vaccine requires an intramuscular injection of 0.5 mls into the upper arm. It consists of two doses given 4 to 12 weeks apart. In Australia a 12 week interval is recommended.[35]

Vaccination with the Pfizer vaccine requires an intramuscular injection through a needle in the arm. It consists of two doses (30 microg, 0.3 mL each) administered intramuscularly, three weeks apart.[36]

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[30] LR Baden et al, 'Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine' (2021) 384 New England Journal of Medicine 403-416 <https://www.nejm.org/doi/full/10.1056/nejmoa2035389>.

[31] 'TGA Grants Additional Provisional Determination for a COVID-19 Vaccine' Australian Government, Department of Health, Therapeutic Goods Administration (Web Page, 20 January 2021) <https://www.tga.gov.au/tga-grants-additional-provisional-determination-covid-19-vaccine>.

[32] See, Australian Product Information Covid-19 Vaccine AstraZeneca, Australian Government, Department of Health, Therapeutic Goods Administration (Web Page) <https://www.tga.gov.au/sites/default/files/auspar-chadox1-s-covid-19-vaccine-astrazeneca-210215-pi.pdf>.

[33] Information for Healthcare Professionals on Pfizer BioNTech Covid-19 Vaccine', Government of the United Kingdom, Medicines and Healthcare Products Regulatory Authority (Web Page, 31 March 2021) <https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine>.

[34] LR Baden (n 30).

[35] COVID-19 vaccine: AstraZeneca ChAdOx1-S', Australian Government, Department of Health, Therapeutic Goods Administration (Web Page, 26 March 2021) <https://www.tga.gov.au/covid-19-vaccine-astrazeneca-chadox1-s>.

[36] See, Australian Product Information COMIRNATY™ (BNT162b2 [mRNA]) Covid-19 Vaccine Australian Government, Department of Health, Therapeutic Goods Administration (Web Page) <https://www.tga.gov.au/sites/default/files/auspar-bnt162b2-mrna-210125-pi.pdf>.

3. d) The Expected Benefits i.e. Protection Against Infection.

Re Oxford/AstraZeneca Vaccine ChAdOx1-S (AZD1222)

There is currently limited data available for the efficacy and safety in individuals over 65 years of age. Only 12% of those assessed for efficacy were over 55 years. However, the vaccine has been shown to create an immune response in this group and can be used based on the efficacy and safety demonstrated in the general clinical trial population.[37]

Vaccine effectiveness against primary symptomatic COVID-19 was 62.1% in the randomized controlled phase III trial tested group who received standard dosing, and 90.0% effective in those who received a half dosage (protocol error) followed by a standard dosage.[38] However, those who received this half dose were younger on average and vaccines are more effective in younger persons.

Emerging "real world" data from Scotland claimed the first dose of AstraZeneca vaccine was 94% effective against hospitalization (95% CI 73-99).[39] It is noted however, that this is pre-print research without peer review. It does not define indications for hospitalization, and vaccine effects against other outcomes of interest (such as ICU admission, death etc) were not estimated. In other pre-print research, two doses of the AstraZeneca vaccine had only 10% effectiveness against mild to moderate infections due to the South African variant B.1.351 (known as Beta variant).[40] Effectiveness of two doses against illness from the Delta variant has been given as 67%.[41]

Re the Pfizer vaccine (BNT162b2)

The percentage of people who get protection from symptomatic infection after 2 doses of the Pfizer vaccine in a randomized controlled trial with 21,720 vaccinated individuals has been estimated at 95%.[42] The probability of >30% vaccine efficacy is 99.99%.[43] For comparison, the modern influenza vaccine reduces infections by 40-60%.[44]

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[37] Australian Government, Department of Health, Therapeutic Goods Administration (n 32).

[38] Mervyn Voysey et al (n 3).

[39] E Vasileiou et al, 'Effectiveness of First Dose of COVID-19 Vaccines against Hospital Admissions in Scotland: National Prospective Cohort Study of 5.4 million People', (advance, Lancet, posted 19 February 2021 <https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3789264>.

[40] S A Madhi et al, 'Safety and Efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 Vaccine Against the B.1.351 Variant in South Africa' Posted February 12, 2021, MedRxiv doi: <https://doi.org/10.1101/2021.02.10.21251247>. Pre-print. Not peer reviewed. WHO Target Product Profile, World Health Organization (Web Page, 9 April 2020).

[41] JL Bernal et al, 'Effectiveness of Covid-19 Vaccines Against the B.1.617.2 (Delta) Variant' (2021) 385 New England Journal of Medicine 585-594 <https://www.nejm.org/doi/full/10.1056/NEJMoa2108891>.

[42] Fernando Polack (n 2).

[43] 'Australian Public Assessment Report for BNT162b2 (mRNA)' Australian Government, Department of Health, Therapeutic Goods Administration, (Web Page, January 2021) <https://www.tga.gov.au/sites/default/files/auspar-bnt162b2-mrna-210125.pdf>.

[44] 'Vaccine Effectiveness: How well do the Flu Vaccines Work?'Centers for Disease Control and Prevention (Web Page, last reviewed 16 December 2020) <https://www.cdc.gov/flu/vaccines-work/vaccineeffect.htm>.

Although vaccination is expected to reduce hospitalisations and deaths from COVID-19, the Pfizer phase III trial data albeit limited, does not confirm this.[45] The preprint Scottish study quoted above suggests an 85% reduction in hospitalisation following vaccination with the Pfizer vaccine (compared with a 94% reduction for the AstraZeneca vaccine).

A recent study of 596,000 vaccinated and matched unvaccinated persons gave similar results to the phase 3 trial quoted above.[46] It is noted that this study excluded health care workers and nursing home residents. 'Matched' vaccinated persons were therefore younger than the eligible population and had a lower prevalence of chronic conditions. Vaccines are known to be more effective in younger recipients.

More recent Israeli research showed adjusted estimates of vaccine effectiveness at 7 days or longer after the second dose to be 95·3% against SARS-CoV-2 infection (95% CI 94·9–95·7; incidence rate 91·5 per 100 000 person-days in unvaccinated *vs* 3·1 per 100 000 person-days in fully vaccinated individuals), 97·0% against symptomatic COVID-19 (95% CI 96·7–97·2; 32·5 *vs* 0·8 per 100 000 person-days), 97·2% against COVID-19-related hospitalisation (95% CI 96·8–97·5; 4·6 *vs* 0·3 per 100 000 person-days), 97·5% against severe or critical COVID-19-related hospitalisation (95% CI 97·1–97·8; 2·7 *vs* 0·2 per 100 000 person-days), and 96·7% against COVID-19-related death (95% CI 96·0–97·3; 0·6 *vs* 0·1 per 100 000 person-days).[47]

Vaccine effectiveness against asymptomatic infection, estimated at 91.5% (95% CI 90.7-92.2; 40.9 vs 1.8 per 100,000 person-days), could not be reliably calculated. The authors identified four factors which could have over-estimated vaccine effectiveness against asymptomatic infection: differing national testing protocols for vaccinated and unvaccinated study arms; vaccinated persons were exempt from the testing required of unvaccinated persons at times of risk such as re-entry to the country from abroad or after contact with a confirmed case; possible inclusion of pre-symptomatic vaccinated individuals with asymptomatic vaccinated individuals at the point of interview; possible concealment of symptoms at interview for fear of being blamed for infecting others. The authors noted that further studies were needed to confirm the magnitude of vaccine effectiveness against asymptomatic infection.

A vaccinated person may develop asymptomatic infection and still be infectious for the virus i.e. the vaccine may not prevent a person from contracting and transmitting COVID-19. This could be of concern since it has been estimated that 50% of transmis-

[45] See, Sara E Oliver et al, 'The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine—United States, December 2020' (2020) 69 (50) Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Reports 1922 <https://www.cdc.gov/mmwr/volumes/69/wr/mm6950e2.htm?s_cid=mm6950e2_w>.

[46] Noa Dagan et al, 'BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting' (2021) New England Journal of Medicine DOI: 10.1056/NEJMoa2101765. <https://www.nejm.org/doi/10.1056/NEJMoa2101765>.

[47] EJ Haas et al, 'Impact and Effectiveness of mRNA BNT262b2 Vaccine Against SARS-CoV-2 Infections and COVID-19 Cases, Hospitalizations and Deaths Following a Nationwide Vaccination Campaign in Israel: An observational study using national surveillance data (2021) 397 Lancet 1819.

sion of SARS CoV2 occurs from people who do not have symptoms.[48] Other research, however, suggests vaccinated carriers do have a reduced viral load.[49]

Duration of protection from the Pfizer vaccine is unknown. There is incomplete data on Pfizer vaccine effectiveness against emerging variants or strains. However, it appears to be reduced.[50] The effectiveness of two doses of the Pfizer vaccine against illness from the Delta variant is given as 88%.[51]

Comment:

Both vaccines exceed the minimum efficacy of 50% in their target product profile, as required by the WHO.[52] New variants are continually emerging and will require testing to confirm effective immunity and protection.[53] Moderna was estimated to be 94% effective against COVID-19 illness, including severe disease.[54]

COVID-19 vaccination has been recommended in previously infected individuals based on a large 2020 Danish study which did not directly compare vaccinated and unvaccinated individuals.[55] By contrast, a Cleveland Clinic preprint study dated June 5, 2021, which found that vaccination was associated with a significantly lowered risk of SARS-CoV-2 infection among those not previously infected (HR 0.031, 95% CI 0.015 to 0.061) but not among those previously infected (HR 0.313, 95% CI 0 to infinity), has provided evidence that vaccination with up to 5 months of follow-up does not add protection to those who were previously infected.[56] This is consistent with earlier observational studies which found very low rates of reinfection over several months among

[48] Michael A Johannson et al, 'SARS-CoV-2 Transmission from People without COVID-19 Symptoms' (2021) 4(1) JAMA Network Open e2035057. doi:10.1001/jamanetworkopen.2020.35057 <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2774707>.

[49] N K Jone et al, 'Single Dose BNT162b2 Vaccine Protects Against Asymptomatic SARS-CoV-2 Infection' eLife; 8 April 2021; DOI: 10.7554/eLife. 68808.

[50] See e.g. 'About the Pfizer/BioNTech COVID-19 Vaccine', Australian Government, Department of Health (Web Page, last updated 18 March 2021) <https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/about-covid-19-vaccines/about-the-pfizerbiontech-covid-19-vaccine>; See also, Noa Dagan et al (n 42).

[51] JL Bernal (n 41).

[52] WHO Target Product Profile, World Health Organization (Web Page, 9 April 2020) <https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines>.

[53] 'About the Pfizer BioNTech Covid-19 Vaccine,' Australian Government, Department of Health (Web Page, last updated 18 March 2021) <https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/about-covid-19-vaccines/about-the-pfizerbiontech-covid-19-vaccine>.

[54] LR Baden (n 30)

[55] C H Hansen, D Michlmayr, SM Gubbels et al. Assessment of protection against infection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. Lancet 2021;1204-12.

[56] K. Nabin et al. 'Necessity of Covid Vaccine in Previously Infected Individuals' Medrxiv (preprint, 5 June 2021) <https://www.medrxiv.org/content/10.1101/2021.06.01.21258176v2> Preprint. Not peer-reviewed.

survivors of COVID-19.[57] Cleveland Clinic authors conclude that previously infected individuals are unlikely to benefit from vaccination.

Since vaccines are not 100% effective, COVID-19 vaccines may not usher in the desired return to normal life. Social distancing, hand sanitizing, and masks may still be advised or required[58] on this basis by various health advisors and governments. Ultimately, requirements for social distancing will be determined by local governments and can be expected to change with alteration in the local incidence of infection.

3. e) Common Side Effects and Material Risks;

Re Oxford/AstraZeneca ChAdOx1 S (AZD1222)

The TGA states the side effects of the AstraZeneca vaccine to be headaches, fatigue (>50%), malaise (>40%), fever, chills, nausea and painful joints and muscles. Analgesics and anti-pyretic treatment may be required.[59]

Since those with severe cardiac, gastrointestinal, liver, renal, endocrine, metabolic and neurological illness were excluded from the vaccine trials, vaccine adverse effects in people with these conditions are unknown. As stated in the Product Information, there is limited data available for the efficacy and safety in individuals with significant co-morbidities.

Safety and efficacy in the frail, elderly, and immune suppressed is also unknown. Safety in those under 18 years has not been studied.

Very rare events of demyelinating disorders (transverse myelitis and multiple sclerosis) have been reported following vaccination with the AstraZeneca vaccines. A causal relationship has not been established.[60] ATAGI advises the first dose of COVID-19 vaccine has been found to be associated with Immune Thrombocytopoenic Purpura (ITP) and cautions about other serious but rare adverse events being reported, such as Guillane Barre Syndrome and capillary leak syndrome, [61] although a causal association has not been confirmed.

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[57] M M Sheehan et al, 'Reinfection Rates among Patients who Previously Tested Positive for Coronavirus Disease 2019: a Retrospective Cohort Study' (2021) Clinical Infectious Diseases (15 May 2021) <https://doi.org/10.1093/cid/ciab234>; S Pilz, et al, 'SARS-CoV-2 Re-infection Risk in Austria' (2021) European Journal of Clinical Investigation 51:e13520; S F Lumley et al, 'Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers' (2021) 384 New England Journal of Medicine 533.

[58] See, 'Continue to Wear a Face Mask, Practice Social Distancing After Being Vaccinated for Covid-19' News Network Mayo Clinic (Web Page, 2 February 2021) <https://newsnetwork.mayoclinic.org/discussion/continue-to-wear-a-mask-practice-social-distancing-after-being-vaccinated-for-covid-19/>; 'Good Hygiene for Coronavirus (COVID-19)' Australian Government Department of Health (Web Page, 29 April 2021) <https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/how-to-protect-yourself-and-others-from-coronavirus-covid-19/good-hygiene-for-coronavirus-covid-19>.

[59] Australian Government, Department of Health, Therapeutic Goods Administration (n 32).

[60] Ibid.

[61] 'Covid-19 Vaccination Training Program', Australian Government, Department of Health (Web Page, Updated 6 August 2021) <https://www.health.gov.au/covid-19-vaccination-training-program>.

Thrombosis with Thrombocytopoenia Syndrome (TTS):[62] The AstraZeneca vaccine has been suspended in many European and Scandinavian countries and, although re-instated in Germany, Italy, Philippines and Spain, it remains discontinued in Denmark due to coagulation disorder diagnoses. Features of this phenomenon have also included Disseminated Intravascular Coagulation (DIC) and Central Venous Sinus Thrombosis (CVST) with fatalities. While venous thromboembolic disorder (VTE) has been reported with COVID-19 disease, this is a different diagnostic entity to TTS. Among hospitalized and ICU patients with COVID-19 the incidence of VTE is 17.3%, with two thirds being deep vein thromboses (DVTs).[63] TTS has not to date been associated with COVID-19 disease.

The European Medicines Agency ('EMA') states most of these occurred in those under 55 and mostly in women.[64] The EMA reports that, based on pre-COVID figures, less than one reported case of DIC might have been expected by 16th March 2021, among people under 50 within 14 days of receiving the vaccine whereas, 5 cases had been reported. Similarly, on average, one case of CVST might have been expected among this age group whereas, by the same cut-off date, 12 cases had been reported. The EMA has advised physicians about cases of thrombosis and thrombocytopoenia, presenting as venous or arterial clotting, splanchnic/mesenteric vessels and cerebral vein/cerebral venous sinus thrombosis in persons who had recently received this vaccine, mostly within 14 days after vaccination.

ATAGI suggests a *TTS* rate of 2.6 per 100,000 persons vaccinated under age 50 and 1.6 per 100,000 over age 50.[65] Patients should be aware of the remote possibility of such syndromes and vaccine recipients who develop symptoms of these conditions should seek immediate medical attention. These symptoms are listed as dyspnoea, chest pain, stomach pain, swelling or coldness in an arm or leg, severe or worsening headache or blurred vision after vaccination, persistent bleeding, multiple small bruises, reddish or purplish spots, or blood blisters under the skin. Information on these cases is to be added to the Product Information.

The EMA has not, however, identified an overall association with this vaccine and thromboembolic disorders. It has meanwhile revised the summary of product character-

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[62] See, 'ATAGI, Statement on AstraZeneca Vaccine in Response to New Vaccine Safety Concerns' Australian Government, Department of Health (Web Page, 8 April 2021) <https://www.health.gov.au/news/atagi-statement-on-astrazeneca-vaccine-in-response-to-new-vaccine-safety-concerns>.

[63] D Jimenez et al, 'Incidence of VTE ad Bleeding Among Hospitalized Patients with Coronavirus Disease 2019 A Systematic Review and Meta-analysis' (2021) 159(3) CHEST 1182-1196 <https://doi.org/10.1016/j.chest.2020.11.005>.

[64] See, 'AstraZeneca's COVID-19 Vaccine: EMA Finds Possible Link to Very Rare Cases of Unusual Blood Clots With Low Blood Platelets' European Medicines Agency, (Web Page, 7 April 2021) <https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood>.

[65] 'ATAGI Update Following Weekly COVID-19 Meeting—26 May 202', Australian Government, Department of Health (Webpage, 21 May 2021) <https://health.gov.au/news/atagi-update-following-weekly-covid-19-meeting-26-may-2021>.

istics and listed thrombocytopenia as a 'common' side effect (i.e. 1 in 100 to 1 in 10) of AstraZeneca.[66] The EMA still advocates the benefits of this vaccine outweigh the risks.[67]

Interactions with other medications have not been studied and are unknown. No carcinogenicity or genotoxicity (mutagenicity) studies were performed. Genotoxicity tests are in vitro and in vivo tests designed to detect compounds that induce genetic damage by various mechanisms. These tests enable hazard identification with respect to damage to DNA and its fixation.[68] While not routinely done for vaccines, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, International Council for Harmonization (ICH) Guideline S5(R3) Detection of Toxicity to Reproduction for Human Pharmaceuticals 6.4, 18th February 2020, suggests additional testing strategies where there are novel active ingredients. This becomes more important as novel nucleic acid vaccines are introduced. The risk of integration or infection into host cell DNA is thought to be negligible, despite the absence of genotoxicity studies.

Dosages of excipients e.g. polysorbate have been omitted from the Product Information. The Australian Public Assessment Report for ChAdOx1-S-COVID-19 Vaccine AstraZeneca states:

> …one of the major limitations in the phase 3 study is the short and variable duration of follow up. The duration of follow up, and reasons for missing data in follow up, are important in determining efficacy. Lower duration of follow up may be from drop outs, but may also arise due to censoring of cases. Longer duration of follow up increases the time of exposure and increases the opportunity for true effectiveness (or non-effectiveness) to be demonstrated.[69]

Fertility, pregnancy and the newborn (also see section (3.j below): Developmental And Reproductive Toxicology study was published in July 2021.[70] This study concluded that AZD1222 has no adverse effects on female fertility, embryofetal development or postnatal development in mice.

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[66] See, Hamid Merchant, 'CoVID-19 Post-Vaccine Menorrhagia, Metrorrhagia or Postmenopausal Bleeding and Potential Risk of Vaccine-induced Thrombocytopoenia in Women (2021), 373 BMJ 373:n958, doi://doi.org/10.1136/bmj.n958 (published 14 April 2021).

[67] 'COVID-19 Vaccine AstraZeneca: Benefits Still Outweigh the Risks Despite Possible Link to Rare Blood Clots with Low Blood Platelets' European Medicines Agency (Web Page, 18 March 2021) <https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots>.

[68] 'Guidance for Industry S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use, June 2021', U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research (June 2021) <https://www.fda.gov/media/71980/download#:~:text=Genotoxicity%20tests%20can%20be%20defined,to%20DNA%20and%20its%20fixation>.

[69] 'Australian Public Assessment Report for CgAdOx1-S-COVID-19 Vaccine Astra Zeneca' Australian Government, Department of Health, Therapeutic Goods Administration, (Web Page, February 2021) <https://www.tga.gov.au/sites/default/files/auspar-chadox1-s-covid-19-vaccine-astrazeneca-210215.pdf>.

[70] R Stebbings et al, 'Developmental and Reproductive Safety of AZD1222 (ChAdOx1 ncoV-10)' (2021) 104 Reproductive Toxicology 134-142 <https://doi.org/10.1016/j.reprotox.2021.07.010>.

Increasing reports of new onset menstrual irregularities are being notified in the UK Medicines and Health Care products Regulatory Agency (MHRA) adverse event reports following COVID-19 vaccinations. As of April 5, there were 958 cases notified, with twice as many notifications following AstraZeneca than Pfizer vaccine. As a British Medical Journal Editorial response states,

> It is anticipated that the actual numbers of cases are much higher than the numbers recorded in the pharmacovigilance systems as many women in different cultural contexts may have felt uncomfortable to talk about it, may not have thought it was vaccine related, or may not have been encouraged by their clinician to make an official report into the adverse events reporting system.[71]

Platelet counts would need to be extremely deficient to be associated with spontaneous bleeding disorders.[72] Injected polysorbate 80 vaccine excipient has a proven association with ovarian toxicity and uterine vascular anomalies in rats. A safe dose is not established, as all parenteral doses tested showed equal toxicity[73] and its effects resembled that of the diethylstilboestrol arm of the study.

It is present in the AstraZeneca vaccine and is chemically related to polyethylene glycol present in the Pfizer vaccine. Attention has previously been drawn to its possible association with notified cases of premature ovarian insufficiency following human papillomavirus vaccination (HPV) Gardasil ®.[74] Increased new onset menstrual irregularities have been reported following HPV vaccination.[75] What data on reproductive toxicity studies of COVID vaccines is currently submitted was not released by the TGA when requested by general practitioner vaccine providers. The TGA replied to practitioners' written request stating in an email that a Freedom of Information request was needed before it would consider release of information sought for patients of reproductive age who are considering vaccination with a novel investigational vaccine. Arguably, creating barriers for obtaining this data is inconsistent with respecting informed consent.

This vaccine is not routinely recommended in pregnancy in Australia due to its TTS risk in those under 60 years of age.[76] All available COVID-19 vaccines are now

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[71] Hamid Merchant (n 66).

[72] Sruthi Jinna and PB Khandhar, Thrombocytopoenia (National Centre for Biotechnology Information NCBI Resources COVID-19 Information, July 10th 2020). <https://www.ncbi.nlm.nih.gov/books/NBK542208/#:~:text=Spontaneous%20bleeding%20can%20occur%20with,with%20counts%20below%2050000%2FmicroL>.

[73] M Gajdova et al, 'Delayed Effects of Neonatal Exposure to Tween 80 on Female Reproductive Organs in Rats' (1993) 31 Food Chemical Toxicology 183.

[74] D Little and H Ward, 'Adolescent Premature Ovarian Insufficiency Following Human Papillomavirus Vaccination: A Case Series Seen in General Practice' (2014) 2 Journal of Investigative Medicine High Impact Case Reports doi: 10.1177/2324709614556129>.

[75] Li Gong et al, 'Human Papillomavirus Vaccine Associated Premature Ovarian Insufficiency and Related Adverse Events: Data Mining of Vaccine Adverse Event Reporting System' (2020) 10 (10762) Scientific Reports <https://doi.org/10.1038/s41598-020-67668-1>.

[76] 'ATAGI Statement on Revised Recommendations on the Use of COVID-19 Vaccine AstraZeneca, 17 June 2010, Australian Government, Department of Health (Web Page, 17 June 2021) <https://www.

available for pregnant women in Great Britain but noting exclusion of AstraZeneca vaccine from pregnancy safety studies underway in the USA.[77,78]

A risk to breastfed newborns and infants cannot be excluded. The duration of vaccine effectiveness is unknown.

The Pfizer vaccine (BNT162b2)

The most frequent adverse reactions in participants 16 years of age and older were injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia and chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%). These were usually mild or moderate in intensity and resolved within a few days after vaccination.[79] Severe local and systemic adverse reactions (grade ≥3, defined as interfering with daily activity) occur in 8.8% of vaccine recipients, more commonly after the second dose than the first, and are less prevalent in those >50 years. Serious adverse events are observed in 0.6%.[80] Safety in the frail elderly over 85 has not been assessed. Safety in children >16 years was not assessed in the original phase three trials. Publication of further research is awaited. Meanwhile, seven cases of acute myocarditis arising in newly vaccinated adolescents within 4 days of dose two of the Pfizer vaccine have been described and published.[81] Guillane-Barre occurring post the Pfizer vaccine has been notified and published.[82]

The occurrence of 'paroxysmal ventricular arrythmia' and 'cardiac arrest' in separate vaccine recipients in the phase 3 trial has not been fully researched. Furthermore, Israel Ministry for Health reports notifications of new onset myocarditis in young adults following Pfizer vaccination.[83] Most reported cases have occurred in men (55 out of 62). There had reportedly been two deaths of recipients aged 22 years (female) and 35 years (male). A causative link is not established. Myocarditis has also occurred with

health.gov.au/news/atagi-statement-on-revised-recommendations-on-the-use-of-covid-19-vaccine-astrazeneca-17-june-2021#:~:text=Home-,ATAGI%20statement%20on%20revised%20recommendations%20on%20the%20use%20of%20COVID,to%20new%20vaccine%20safety%20concerns>.

[77] Royal College of Obstetricians and Gynaecologists, 'Information Sheet and Decision Aid' (Web Page, Updated 20 July 2021) <https://www.rcog.org.uk/globalassets/documents/guidelines/2021-02-24-combined-info-sheet-and-decision-aid.pdf>.

[78] TT Shimabukuro et al, 'Preliminary Findings of mRNA COVID-19 Vaccine Safety in Pregnant Persons' (2021) 384(34) New England Journal of Medicine (published on line 21 April 2021) <https://pubmed.ncbi.nlm.nih.gov/33882218/>.

[79] Australian Government, Department of Health, Therapeutic Goods Administration (n 32).

[80] Sara E Oliver et al (n 45).

[81] M Marshall et al, 'Symptomatic Acute Myocarditis in Seven Adolescents Following Pfizer-BioNTech COVID-19 Vaccination' Pediatrics doi: 10.1542/peds.2021-052478.

[82] Sadia Waheed et al, 'Neurological Complications of COVID-19: Guillain-Barre Syndrome Following Pfizer COVID-19 Vaccine' (2021) 13(2) Cureus e13426, doi:10.7759/cureus.13426 <https://www.cureus.com/articles/52295-neurological-complications-of-covid-19-guillain-barre-syndrome-following-pfizer-covid-19-vaccine>.

[83] 'Israel Assesses Myocarditis Cases Linked to Pfizer-BioNTech Covid-19 Vaccine', Pharmaceutical Technology News (Web Page, 26 April 2021) <https://www.pharmaceutical-technology.com/news/israel-myocarditis-pfizer-vaccine/>.

COVID-19 disease although it is reported as rare in COVID-19 autopsies,[84] performed at a median age of 75. Clinical myocarditis had a prevalence rate of 0.31% in 1597 athletes[85] after COVID-19 infection, and subclinical myocarditis a prevalence rate of 2.3% on routine cardiac MRI screening of the same group. Comparable routine cardiac MRI screening of a vaccinated cohort has not occurred. In one retrospective review of myocarditis post mRNA COVID-19 vaccination in members of the US military,[86] 23 male patients (22 serving, 1 retiree, median age 25 years) with acute onset of chest pain post vaccination, met CDC case definitions for probable myocarditis. Eight of these 23 had MRI findings consistent with myocarditis. No other aetiologies were identified. Symptoms commenced 12 to 96 hours after 2nd dose of vaccine in 20 patients, and followed the first dose in 3 patients, each of whom had previous SARS-CoV-2 infection more than 2 months prior. Cardiac symptoms resolved within one week for 16 of 23. Seven remained symptomatic at the time of the report. During that time 436,000 2nd doses had been administered to male military service members. In comparison, nearly 1% of highly fit athletes with mild COVID-19 infection have myocarditis on Cardiac MRI.[87,88] Other case reports of myocarditis post COVID-19 vaccine also followed the 2nd dosage,[89,90] and a series of 7 adolescents[91] developed myocarditis or myopericarditis

[84] MK Halushka and RS Vander Heide, 'Myocarditis is Rare in COVID-19 Autopsies: Cardiovascular Findings Across 277 Postmortem Examinations (2021) 50 Cardiovascular Pathology 107300. doi: 10.1016/j.carpath.2020.107300 <https://www.sciencedirect.com/science/article/abs/pii/S1054880720301046>.

[85] CJ Daniela, S Rajpal and JT Greenshields, 'Prevalence of Clinical and Subclinical Myocarditis in Competitive Athletes with Recent SARS-CoV-2 Infection Results from the Big Ten COVID-19 Cardiac Registry' (2021) JAMA Cardiology (published on line, 27 May 2021) doi: 10.1001/jamacardio.2021.2065 <https://jamanetwork.com/journals/jamacardiology/fullarticle/2780548>

[86] J Montgomery et al, 'Myocarditis Following Immunization with mRNA COVID-19 Vaccines in members of the US Military' (2021) JAMA Cardiology (published online June 29, 2021) doi:10.1001/jamacardio.2021.2833 <https://jamanetwork.com/journals/jamacardiology/fullarticle/2781601>.

[87] J Starekova et al, 'Evaluation for Myocarditis in Competitive Student Athletes Recovering from Coronavirus Disease 2019 with Cardiac Magnetic Resonance Imaging (2021) JAMA Cardiology (published online, 14 January 2021) doi:10.1001/jamacardio.2020.7444 <https://jamanetwork.com/journals/jamacardiology/fullarticle/2781601>.

[88] MW Martinez et al, 'Prevalence of Inflammatory Heart Disease Among Professional Athletes with Prior COVID-19 Infection who Received Systematic Return-to -Play Cardiac Screening (2021) JAMA Cardiology (published online, 4 March 2021) doi: 10.1001/jamacardio.2021.0565 <https://jamanetwork.com/journals/jamacardiology/fullarticle/2777308>.

[89] GJ Bautista, OP Pena and FJA Bonilla, 'Acute Myocarditis After Administration of the BNT162b2 Vaccine Against COVID-19' (2021) Revista Espanola Cardiologia (Engl Ed) (published online, 20 March 2021) doi:10.1016/j.rec.2021.04.005

[90] E Albert et al, 'Myocarditis Following COVID 19 Vaccination' (2021) 16(8) Radiology Case Reports 2142-2145 doi:10.1016/j.radcr.2021.05.033 <https://pubmed.ncbi.nlm.nih.gov/34025885/>.

[91] M Marshall et al, 'Symptomatic Acute Myocarditis in Seven Adolescents Following Pfizer BioNTech COVID-19 Vaccination' Pediatrics doi:10.1542/peds2021-052478 (published 2 June 2021) <https://pediatrics.aappublications.org/content/pediatrics/early/2021/06/02/peds.2021-052478.full.pdf>.

within 4 days of Pfizer vaccination. Related JAMA editorials,[92,93] commenting on the myocarditis case series post COVID-19 vaccine, note that cardiac injury after SARS-CoV-2 infection also occurs and may result in severe outcomes. They also note that public vaccine confidence includes transparency, with careful critical review and publication of possible links between vaccines and rare adverse events. Myocarditis is not referred to as a possible side effect on Australian Government COVID-19 vaccine consent forms.

Fertility, pregnancy and the newborn (also see section 3.j below):

Rat DART fertility studies were published May 28th 2021.[94] Only macroscopic examination and numbering of corpora lutea and implantation sites is presented. Authors state 'the lack of female fertility effects is consistent with the lack of microscopic effects in female reproductive organs in non-pregnant rats administered BNT162b2 in prior general toxicology studies (data not shown)'. The 'data not shown' is neither referenced nor cited. Pre-clinical gonad histology reports are not shown in accessible licensing documentation.[95] Freedom of Information Request (FOI) 2183 response from the TGA has redactions of organ histopathology in section 5.3.1 of the BIONTECH Investigator's Brochure.[96] The Brochure elsewhere states that section 5.3.1 contains microscopic evaluations of male and female reproductive tissues from the repeat-dose toxicity study. However, no such report is visible. The Investigator's Brochure summary, however, states there were no reported changes in these tissues. An email request made by vaccine providers to the TGA for access to available reproductive data was declined by the TGA without a Freedom of Information Request, which has since been lodged and rejected. Product Information states there were no effects on fertility or offspring following vaccination of rats before and during gestation. However, there is limited completed data of use in pregnant women.[97] An uncompleted USA study of Pfizer vaccine in pregnancy[98] found no short term ill effects from Pfizer vaccine given in the third trimester. Éarlier pregnancy outcomes are awaited. The authors conclude: 'Preliminary findings did not show obvious safety signals among

[92] DK Shay, TT Shimabukuro and F DeStefano, 'Myocarditis Occurring After Immunization with COVID-19 Vaccines' Editorial, JAMA Cardiology (published online, 29 June 2021) <https://jamanetwork.com/journals/jamacardiology/fullarticle/2781600>.

[93] AM Navar et al, 'Temporal Associations Between Immunization With the COVID-19 mRNA Vaccines and Myocarditis The Vaccine Safety Surveillance System is Working' JAMA Cardiology (published online 29 June 2021) <https://jamanetwork.com/journals/jamacardiology/fullarticle/2781599>.

[94] CJ Bowman et al, 'Lack of Effects on Female Fertility and Prenatal and Postnatal Offspring Development in Rats with BNT162b2, a mRNA-based COVID-19 Vaccine' (2021) 103 Reproductive Toxicology 28-35 (published on line, 28 May 2021) <https://doi.org/10.1016/j.reprotox.2021.05.007>.

[95] A Phase 1/2/3 study to Evaluate the Safety, Tolerability, Immunogenicity and Efficacy of SARS-CoV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals. Study Intervention Number PF-07302048. US IND Number 19736. <https://cdn.pfizer.com/pfizercom/2020-11/C4591001_Clinical_Protocol_Nov2020.pdf>

[96] Investigator's Brochure BNT162/PF-07302048. 12 August 2020. <https://www.tga.gov.au/sites/default/files/foi-2183-09.pdf> Response to FOI 2183.

[97] Australian Government, Department of Health, Therapeutic Goods Administration (n 33).

[98] TT Shimabukuro (n 78).

pregnant persons who received mRNA Covid-19 vaccines. However, more longitudinal follow-up, including follow-up of large numbers of women vaccinated earlier in pregnancy, is necessary to inform maternal, pregnancy, and infant outcomes.'

TGA labels Pfizer vaccine category B1. Nonetheless, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) did not recommend use in pregnancy prior to June 9, 2021.[99] A joint ATAGI/ RANZCOG statement released June 9, 2021 stated:

> RANZCOG and ATAGI recommend that pregnant women are routinely offered Pfizer mRNA vaccine (Cominarty) at any stage of pregnancy. This is because the risk of severe outcomes from COVID-19 is significantly higher for pregnant women and their unborn baby. Global surveillance data from large numbers of pregnant women have not identified any significant safety concerns with mRNA COVID-19 vaccines given at any stage of pregnancy. Furthermore, there is also evidence of antibody in cord blood and breastmilk, which may offer protection to infants through passive immunity. Pregnant women are encouraged to discuss the decision in relation to timing of vaccination with their health professional.[100]

Further to this, on August 6th 2021 RANZCOG states pregnant women are a priority group for COVID-19 vaccination, and should be routinely offered the Pfizer vaccine (Comirnaty) and advised to receive it at any stage of pregnancy.[101] Reasons given for the altered policy concern the increased COVID-19 morbidity during pregnancy as discussed in section 3.j(i). Pregnant women's eligibility for Pfizer vaccine has been increased.

Neither genotoxicity nor carcinogenicity studies were performed. The components of the Pfizer vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Research is needed regarding the effects of biodistribution of mRNA vaccines. Pre-clinical evaluation of distribution of vaccine lipid nanoparticles in the rat following administration of a single 50 ucg dose show: 'The concentration of radioactive lipid marker reached the peak level in plasma (8.9 µg lipid eqv/mL) between 1–4 h post-dose and distribution mainly into liver, adrenal glands, spleen and ovaries over 48h.'[102]

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[99] COVID-19 Vaccination in Pregnant and Breastfeeding Women', Royal Australian and New Zealand College of Obstetricians and Gynaecologists (Web Page, 2021) <https://mailchi.mp/ranzcog.edu.au/covid-19-vaccination-in-pregnant-and-breastfeeding-women?e=9674ffe0a4>.

[100] 'Joint Statement between RANZCOG and ATAGI about COVID-19 Vaccination for Pregnant Women', Australian Government, Department of Health <https://www.health.gov.au/news/joint-statement-between-ranzcog-and-atagi-about-covid-19-vaccination-for-pregnant-women>.

[101] Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 'Covid-19 Vaccination in Pregnant and Breastfeeding Women' Statements and Guidelines (Web Page, 6 August 2021) <https://ranzcog.edu.au/statements-guidelines/covid-19-statement/covid-19-vaccination-information>

[102] Australian Government, Department of Health, Therapeutic Goods Administration, 'Non-clinical Evaluation Report BNT162b2 [mRNA] COVID-19 Vaccine (ComirnatyTM) Jan 2021' FOI 2389 Document 6, Submission PM-2020-05461-1-2.

Accumulation in rat ovaries at 48 hours post dose is more than ten times the concentration exceeding that in most other organs, with the exception of liver, spleen and adrenals. It is not known if a similar biodistribution phenomenon occurs in the ovaries of human vaccinees, or if this could affect human ovarian function or possibly be related to the menstrual irregularities observed post vaccination.[103]

Regarding assessment of possible COVID-19 disease effects on fertility:

A prospective observational study[104] was performed on the semen of 30 men with SARS-CoV-2 infection, due to the known high ACE2 expression in the male genital system. Total sperm numbers in 83% (25/30) were below the 25th percentile 11 to 64 days after a positive PCR test. Semen parameters can expect to be impacted by acute illness with fever, and 29 subjects were symptomatic at the time of sample collection. While baseline sperm counts pre-infection were not known, five participants had progress assessment 3 months later which showed similar sperm counts to that during symptoms. The authors concluded long term follow up is necessary to evaluate the effect of SARS-CoV-2 infection on spermatogenesis.

Ovarian function was also investigated after COVID-19 disease.[105]In a matched control group study of 78 women in Wuhan with COVID-19 disease, and a median age of 43 years, results indicate that although no obvious menstrual cycle change was observed, women affected by COVID-19 have a significantly lower serum anti-Mullerian hormone level and higher testosterone/prolactin level, suggesting a poor ovarian reserve and abnormal reproductive hormones compared to the age-matched healthy unaffected women. Authors concluded that COVID-19 disease may have a potential deleterious effect on ovarian reserve and endocrine function, but advised that more samples from younger women and long-term prospective cohorts are needed to further determine the effects of COVID-19 diseases on ovarian function. Dosages of most excipients are omitted from the Product Information.

Anaphylaxis, a severe allergic reaction, is very rare. For most vaccines the rate is less than one per million doses. According to the world allergy organization, the Pfizer vaccine has a rate approaching 1 per 200,000 doses.[106] A more recent report from the USA General Brigham Hospital Network found 2.7 anaphylaxes per 10,000

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[103] H. Merchant (n 66).

[104] JC Best et al, 'Evaluation of SARS-CoV-2 in Human Semen and Effect on Total Sperm Number: A Prospective Observational Study' (2021) 39(3) World Journal of Men's Health 489-495 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8255403/>.

[105] T Ding et al, 'Analysis of Ovarian Injury Associated with COVID-19 Disease in Reproductive-Aged Women in Wuhan, China, in an Observational Study' Frontiers in Medicine, 19 March 2021 <https://www.frontiersin.org/articles/10.3389/fmed.2021.635255/full>.

[106] PJ Turner et al, 'COVID-19 Vaccine-associated Anaphylaxis: A Statement of the World Allergy Organization Anaphylaxis Committee' (2021) 2 (14) World Allergy Organization Journal <http://doi.org/10.1016/j.waojou.2021.100517>. See also, COVID-19 Vaccine Safety Update, 27 January 2021.

doses, approximately 25 times higher than that reported by the Centers for Disease Control and Prevention.[107] Vaccination is a suggested contraindication in persons with a known (diagnosed) allergy to polyethylene glycol (PEG), or to other mRNA vaccine components.[108] Australian guidelines for COVID-19 vaccine providers limit this contraindication to a history of anaphylaxis to the vaccine or to its components, with special precautions to be taken for those with other allergy-related conditions as per administration guidelines in the Australian Immunization Handbook.[109] Facial paralysis (Bell's palsy) is listed as a possible side effect due to four cases occurring in vaccinated trial participants and none in placebo recipients.[110]

The safety, efficacy and immunogenicity of the Pfizer vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The effects of immunosuppressive medication, especially methotrexate and rituximab, on a COVID-19 vaccine response are yet to be determined and will need evaluation, especially given their effects on decreasing serological responses to other vaccines. Efficacy may be lower in immunosuppressed individuals.[111]

The Unknown Risks of COVID-19 Vaccination

The completion of safety analysis and ongoing safety observation is problematic due to vaccination of the placebo arms of COVID-19 vaccine trials.[112] For full license approval, two years of follow-up vaccine data are needed. The data will be contaminated as trials are being un-blinded.[113]

Nonetheless, the requirement for safety in modern prophylactic vaccines needs to be extremely stringent since vaccines are administered to healthy individuals.[114] The Brighton Collaboration publish regular 3-monthly lists of possible vaccine Adverse

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[107] Anthony Scholefield, 'Anaphylaxis after Pfizer COVID-19 Vaccine '25 Times Higher' Than Previously Reported' Australian Doctor, 9 March 2021 <https://www.ausdoc.com.au/news/anaphylaxis-after-pfizer-covid19-vaccine-25-times-higher-previously-reported?mkt_tok=MjE5LVNHSi02NTkAAAF7tDkbwGsH3Lgb92jpvlRqFrSL1zhtGe-fmpWV_WVfoWxljqOH_JwC4dExvHMo6BIjm39Nov9SKyZYO8STGdzyMpWxrjXHS2JhS5B2ot1RPJV26g>.

[108] 'Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States' Center for Diseases and Prevention Control (Web Page, page last reviewed 5 March 2021) <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fcovid-19%2Finfo-by-product%2Fpfizer%2Fclinical-considerations.html>.

[109] See, 'Clinical guidance on use of COVID-19 Vaccine in Australia in 2021 (v3.0)' Australian Technical Advisory Group on Immunization('ATAGI') (Web Page, 5 May 2021) <https://www.health.gov.au/sites/default/files/documents/2021/05/covid-19-vaccination-atagi-clinical-guidance-on-covid-19-vaccine-in-australia-in-2021_0.pdf>.

[110] Fernando P. Polack (n 1). See also, Food and Drug Administration, 'Vaccine and Related Biologic Products Advisory Committee Meeting December' Briefing Paper on Pfizer BioNTech COVID 19 Vaccine, 10 December 2020 <https:// www.fda.gov/media/144245/download>.

[111] B Sohani et al, 'Letter to the Editor' (2021) 40 Clinical Rheumatology 797.

[112] (2021) 27 Nature Medicine 569.

[113] J Lenzer, 'Should Vaccine Trials be Unblinded? (2020) BMJ 371 m4956, doi: <https://doi.org/10/1136/bmj.m4956>.

[114] Norbert Pardi et al, 'mRNA vaccines—A New Era in Vaccinology' (2018) 17 Nature Reviews Drug Discovery 261.

Events of Special Interest (AESI) to be alert to in the community, and case definitions, and requests their occurrences to be notified. The relevance of events is then assessed after cumulative analysis of clinical information. Brighton Collaboration updates are published quarterly. Recent items added to AESI are rhabdomyolysis, pancreatitis and subacute thyroiditis.[115] A draft case definition for thrombosis with thrombocytopoenia syndrome has been developed[116] and, more recently, for myocarditis.[117] Australian vaccine providers have been alerted to be aware of and report such cases of myocarditis and pericarditis.[118]

Post marketing, adverse event data gathering usually relies on a voluntary system which normally captures less than 10% of adverse pharmaceutical events. It is therefore imperative, and is indeed mandatory upon Australian vaccination providers, that all adverse events occurring after investigational COVID-19 vaccination be formally notified e.g. to the Database of Adverse Event Notifications.[119]

Unknown Risks Which Require Further Research Are:

1) Vaccine-Associated Enhanced Disease (VAED) sometimes called Antibody Dependent Enhancement, is a modified presentation of a clinical infection affecting individuals exposed to a wild-type virus after having received a prior vaccination for the same pathogen.[120] Past examples are atypical measles and enhanced respiratory syncytial virus (RSV) occurring after administration of inactivated vaccine for these pathogens. In this situation, severe disease has been documented resulting from infection in individuals primed with non-protective immune responses against the respective wild-type viruses. This was well documented in previous trials of corona vaccines and is acknowledged as a possible side effect for COVID-19 vaccines.[121] The risk of VAED cannot be calculated and assessed until further data is collected over time,[122] which will be more difficult by standard means after vaccination of the placebo arms of the safety trials.[123]

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[115] Barbara Law, 'SO2-D2.1.2 Priority List of COVID-19 Adverse events of special interest: Quarterly Update December 2020' 1(2) Safety Platform For Emergency Vaccines <https://brightoncollaboration.us/wp-content/uploads/2021/01/SO2_D2.1.2_V1.2_COVID-19_AESI-update-23Dec2020-review_final.pdf>.

[116] Ibid.

[117] 'Draft Myocarditis Case Definition (Version_1.4.2_30.May.2021)' Brighton Collaboration (Webpage, 30 May 2021) <https://brightoncollaboration.us/myocarditis-case-definition-update/>.

[118] 'Covid Vaccine Weekly Safety Report 27-05-21', Australian Government, Department of Health, Therapeutic Goods Administration (Web Page) <https://tga.gov.au/periodic/covid-19-vaccine-weekly-safety-report-27-05-2021>.

[119] 'Report a Problem or Side Effect', Australian Government, Department of Health, Therapeutic Goods Administration (Web Page) <www.tga.gov.au/reporting-problems>.

[120] FM Munoz et el, 'Vaccine -associated Enhanced Disease: Case Definition and Guidelines for Data Collection Analysis and Presentation of Immunization Safety Data (2021) 39 Vaccine 3053-3056 (published on line, 23 February 2021) <https://doi.org/10.1016/j.vaccine.2021.01.055>.

[121] Fernando Polack et al (n 2).

[122] SB Halstead and L Katzelnick, 'COVID-19 Vaccines: Should We Fear ADE?'(2020) 222(12) Journal of Infectious Diseases 1946. <https://pubmed.ncbi.nlm.nih.gov/32785649/>.

[123] D Follman et al, 'A Deffered-Vaccination Design to Assess Durability of COVID-19 Vaccine Effect After the Placebo Group is Vaccinated' (2021) Annals of Internal Medicine M20-8149 (published on linem 13 April 2021) doi:10.7326/M20-8149 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8099035/>.

Pathogenic Priming[124] is another phenomenon, which has been described as immune priming that could involve an autoimmune reaction due to previous exposure to the spike protein, and occur via exposure, infection or injection.

2) Serious adverse events.

The occurrence of life threatening arrythmia following vaccination requires further research (See Pfizer section 3.e). The phase 3 trial of the Pfizer vaccine reported 'paroxysmal ventricular arrythmia' and another vaccine recipient's death due to 'cardiac arrest' of unknown cause, following vaccination in the observation period.[125] This requires further research. Older age group trial participants and vaccine recipients in the general population will have co-morbidities such as obesity and arteriosclerosis. In the absence of a causative diagnosis for these serious adverse events (e.g. 'myocardial infarct'), a link to the vaccine cannot be excluded. It could be misleading, in the absence of a causative diagnosis, to directly attribute life threatening arrythmia and cardiac arrest to obesity and arteriosclerosis common in these age groups.

While deaths in the placebo group were due to diagnosed myocardial infarct and cerebrovascular accident, these diagnoses were not present in the vaccine group's arrhythmic/dysrhythmic events. The risk is likely to be very small but requires researched clarification as to those who may be rendered more vulnerable to such events via pre-existing co-morbidities or drug interactions.

3) Deaths following vaccination.

In the U.K., whose vaccination programme since December 8th 2020 is ahead of Australia's, 24 million persons had been fully vaccinated by May 6th 2021. From January 4th to May 26th 2021, 1,253 post vaccination deaths had been notified to the Yellow Card adverse event reporting system and U.K. Medicines and Healthcare Products Regulatory Agency (MHRA).[126] Interpretation of this mortality data is not possible until the end of thorough investigation, and does not mean the vaccine caused these deaths. This is a limitation of pharmacovigilance upon which investigational vaccines rely heavily.

The pathophysiology of death in the elderly may require post-mortem evaluation since all elderly patients will likely have 'significant co-morbidities' to which death may be attributed.

4) Interactions with other medications are unknown.

5) Interactions with other vaccines are unknown.

Given the lack of safety and efficacy data for mRNA COVID-19 vaccines administered with other vaccines, the vaccine series should routinely be administered alone, with a minimum interval of 14 days before or after receiving any other vaccine.[127]

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[124] J Lyons-Weiler, 'Pathogenic Priming Likely Contributes to Serious and Critical Illness and Mortality in COVID-19 via Autoimmunity (2020) 3 (100051) Journal of Translational Autoimmunity doi: 10.1016/j.jtauto.2020.100051 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7142689/>.

[125] Fernando Polack et al (n 2).

[126] Letter to Dr. J Raine, the Chief Executive of the Medicines and Healthcare Products Regulatory Agency from Dr Tess Lawrie,Director, Evidence-based Medicine Consultancy Ltd. and EbMC Squared CiC, dated 9 June 2021 < https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/>.

[127] Centers for Disease Control and Prevention (n 72). See also, 'Covid-19 Vaccination Decision Guide for Women Who Are Pregnant, Breastfeeding of Planning Pregnancy' Australian Government,

6) Genotoxicity.

Since the possibility of incorporation of vaccine DNA and mRNA into host DNA is considered either negligible or non-existent, genotoxicity studies on vaccines currently available in Australia have not been performed. However, less certainty has been suggested regarding non-integration resulting from the adenovirus vector-based vaccine and mRNA vaccines.[128,129] Therefore, it would seem applicable to have genotoxicity studies on these novel gene vaccines to ensure safety and public confidence.

3.f) Whether the Intervention is Investigational (Experimental) or Conventional;

The TGA has provisionally approved COVID-19 vaccines for 2 years, subject to strict conditions, such as monitoring longer term efficacy and safety.[130]

As the vaccines are still under investigation, they are experimental or investigational. This is not mentioned in the Australian Government consent form for COVID-19 vaccination.[131] However, this knowledge underscores the importance of reporting adverse events post vaccinations. Notifications of adverse events that occur at these times can be made by health personnel, patients or their advocates. As such, they cannot themselves establish causality. Reports are used to assess possible safety signals which may generate an alert or a subsequent hypothesis for further research. Hence the need for vigorous case reporting and follow-up.

It is imperative that all post-vaccination adverse events are notified to the TGA Database of Adverse Events notifications to enable investigation, follow-up and analysis.

3. g) Other Options for Management;

These include exploring concerns about an individual's reluctance and obtaining specialist advice when a patient has a medical condition which may make COVID-19 vaccination more complex. An alternative should be offerable when there is a conscientious objection to vaccines developed or produced using cell lines derived from aborted babies. The NVX-CoV2373 'Novavax' vaccine, awaiting introduction to Australia (with a finalized purchase agreement of 51 million doses), utilized aborted fetal cell lines

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Department of Health (Web Page, 29 March 2021) <https://www.health.gov.au/resources/publications/covid-19-vaccination-covid-19-vaccination-decision-guide-for-women-who-are-pregnant-breastfeeding-or-planning-pregnancy>.

[128] W Doerfler. Adenoviral Vector DNA- and SARS-CoV-2 mRNA-Based Covid-19 Vaccines: Possible Integration into the Human Genome—Are Adenoviral Genes Expressed in Vector-based Vaccines? Virus Research Vol 302:198466. doi: 10.1016/j.virusres.2021.198466. Published online 1 June 2021. <https://pubmed.ncbi.nlm.nih.gov/34087261/>.

[129] N Cimolai, 'Do RNA Vaccines Obviate the Need for Genotoxicity Studies?' (2020) 35 Mutagenesis 509-510 (published 20 November 2020) doi: 10.1093/mutage/geaa028 <https://pubmed.ncbi.nlm.nih.gov/33216145/>.

[130] 'TGA provisionally approves Pfizer COVID-19 Vaccine', Australian Government, Department of Health, Therapeutic Goods Administration (Web Page, 25 January 2021) <https://www.tga.gov.au/media-release/tga-provisionally-approves-pfizer-covid-19-vaccine>.

[131] 'Consent Form for Covid Vaccination', Australian Government, Department of Health (Web Page) <https://www.health.gov.au/sites/default/files/documents/2021/02/covid-19-vaccination-consent-form-for-covid-19-vaccination_2.pdf>.

during testing, but not during development and production. In this regard, the Pfizer vaccine is equivalent.

As a protein-based vaccine, Novavax may be more acceptable to those who prefer not to have a genetically modified organism in the vaccine or who prefer not to use a gene-based vaccine. It has demonstrated suitable effectiveness.[132] There are both societal and medical reasons for vaccine choice. Dr Paul Griffin, the Infectious Disease physician and microbiologist who oversaw the Australian arm of phase 1/2 'Novavax' trials, reports of medical reasons:

> Even within our country, we're going to need a range of different vaccines that cater potentially for different populations or different comorbidities, for example, and different environments…another benefit for Australia in particular, is the fact that Novavax's candidate relies on a different mechanism to generate immunity than the Pfizer/BioNtech mRNA vaccine and AstraZeneca's viral vector candidate, AZD1222.[133]

Other viable ways of significantly reducing the risk of COVID-19 transmission such as physical distancing, cleaning, use of personal protective equipment, and minimising contact with others (working from home, shopping on-line etc.) should be explained.

There is significant clinical dissention in medical ranks and divergent models of research-based care which is consistent with a disease about which knowledge is accruing. It is therefore important to provide current, evidence-based research pertaining to the prevention and treatment of COVID-19 infection as patients may enquire about these alternatives to vaccinations. Government Treatment Guidelines are accessible and continuously updated eg the use of monoclonal antibodies in the outpatient setting.[134] Examples of treatments which have shown some benefit to treat early COVID-19 infection include Vitamin D[135] and Vitamin C.[136] Zinc has some evidence for recommendation since zinc deficiency is associated with poorer outcomes.[137] Further research is needed.

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[132] Elisabeth Mahase, 'Covid-19: Novavax Vaccine Efficacy is 86% Against UK Variant and 60% Against South African Variant' (2021) 372 British Medical Journal doi: <https://doi.org/10.1136/bmj.n296 <https://www.bmj.com/content/372/bmj.n296>.

[133] RACGP newsGP, 14 January 2021 interview Matt Woodley <https://www1.racgp.org.au/newsgp/clinical/novavax-candidate-may-prove-best-long-term-solution>.

[134] See 'Covid Treatment Guidelines' NIH (Web Page) <https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults—therapeutic-management/>.

[135] See, Petre Cristian Ilie, 'The Role of Vitamin D in the Prevention of Coronavirus Disease 2019 Infection and Mortality' Researchsqaure <https://www.researchsquare.com/article/rs-21211/v1>; Adrian R Martineau et al, 'Vitamin D Supplementation to Prevent Acute Respiratory Tract Infections: Systemic Review and Meta-Analysis of Individual Participant Data'(2017) 356 BMJ i6583 <https://www.bmj.com/content/356/bmj.i6583 https://doi.org/10.1136/bmj.i6583>.

[136] See, Luis Chiscano-Camon et al, 'Vitamin C Levels in Patients with SARS-Co-V-2 Associated Acute Respiratory Distress Syndrome' (2020) 24 BMC 522.

[137] Y Yasui et al, 'Analysis of the Predictive Factors for a Critical Illness of COVID-19 During Treatment—Relationship Between Serum Zinc Level and critical Illness of COVID-19 (2020) 100 International Journal of Infectious Diseases 230. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7476566/>.

However, Australian Guidelines for the Clinical Care of People with COVID-19 recommend no disease modifying treatments for mild cases having routine outpatient management.[138] They also have no outpatient management guidance to address intercurrent deficiencies in Vitamin D, Vitamin C and Zinc. All such treatments, if used, should be under medical supervision of dosage and contraindications (eg zinc may cause pancytopenia in those with a copper deficiency such as can occur following gastric bypass surgery) and to prevent toxicities. Coronavirus Disease 2019 Communicable Diseases Network Australia National Guidelines for Public Health Units (version 4.5, 25th May) also state:

> …readers should not rely solely on the information contained within these guidelines. Guideline information is not intended to be a substitute for advice from other relevant sources including, but not limited to, the advice from a public health specialist or other health professional. Clinical judgment and discretion may be required in the interpretation and application of these guidelines.[139]

Ivermectin, included in the WHO Essential Medicines list, is a common drug used to treat scabies and worms, and has been investigated with fourteen clinical trials of variable strength for treatment of COVID-19. These have been mostly clinician led, as opposed to having pharmaceutical sponsoring, and many are pre-print. Some trials have suggested Ivermectin as an adjunct reduced the rate of mortality, low O2 duration, and duration of hospitalisation in adult COVID-19 patients. The improvement of other clinical parameters suggested that Ivermectin, with a wide margin of safety, had a high therapeutic effect on COVID-19.[140] However, one systematic review of randomized controlled trials[141] (at this stage accepted for publication) evaluating ten RCTs of Ivermectin treatment for their risk of bias and quality of evidence, found three RCTs showing a significant reduction in all cause mortality were at high risk of bias. The authors recommended additional RCTs be completed to update their analysis, and that Ivermectin use should be confined to these trials. The following studies were referred to as having a high risk of bias with small numbers of participants, and their authors had called for more research:

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[138] Australian Guidelines for Clinical Care of Persons with COVID-19 Disease, 'Australian National COVID-19 Clinical Evidence Taskforce, section 6, version 40.1, 6/10/21' (Web Page) <https://files.magicapp.org/guideline/8b6f065b-814f-41f0-a1a5-70279b722e19/published_guideline_4346-12_0.pdf>.

[139] Coronavirus Disease 2019 Communicable Diseases Network Australia, National Guidelines for Public Health Units (version 4.5, 25th May) (Web Page) <https://www1.health.gov.au/internet/main/publishing.nsf/Content/7A8654A8CB144F5FCA2584F8001F91E2/$File/COVID-19-SoNG-v4.5.pdf>.

[140] S Ahmed et al, 'A Five Day Treatment with Ivermectin for the Treatment of Covid-19 May Reduce the Duration of Illness' (2021) 103 International Journal of Infectious Diseases 214: doi: 10.1016/j.ijid.2020.11.191.

[141] YM Roman et al, 'Ivermectin for the Treatment of COVID-19: A Systematic Review and Meta-analysis of Randomized Controlled Trials (Accepted manuscript), *Clinical Infectious Diseases*, ciab591, <https://doi.org/10.1093/cid/ciab591 Published by Oxford University Press for the Infectious Diseases Society of America <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab591/6310839>.

1) Iranian double-blind RCT hospital research, in pre-print and not peer reviewed, claimed reduced mortality, reduced duration of hypoxia and reduced duration of hospitalization, in a small study of 180 mild to severe COVID-19 hospitalized patients,[142] with confirmed PCR in 71% and confirmatory chest imaging.

2) A double-blind RCT in 72 persons claims evidence of the potential benefit of early intervention with Ivermectin for the treatment of adult patients diagnosed with mild COVID-19. Early intervention promoted faster viral clearance during disease onset, which authors suggest might have prevented significant immune system involvement and hastened recovery.[143]

Australian Guidelines for the Clinical Care of People with COVID-19 have not recommended Ivermectin due to the rate of side effects and perceived weakness of the evidence citing improvements across various parameters of reducing Intensive Care admissions, mortality, and the requirement for artificial ventilation.[144] Given the politicization and controversy around Ivermectin, and evidence of anti-SARS-CoV-2 infection in vivo benefit demonstrated by a most recent Pasteur Institute hamster study[145] which 'supports the use of immunomodulatory drugs such as Ivermectin to improve the clinical condition of SARS-CoV-2 -infected persons', its exclusion from the WHO Solidarity Trial for re-purposed drugs for COVID-19 is unfortunate.

Another controversial option, currently under use by some physicians for very early treatment of COVID-19, is the Zelenko protocol. This protocol was associated with reduced hospitalizations in a retrospective case series[146] study of COVID-19 outpatients. Controversy should not affect presentation and discussion of peer-reviewed, evidence-based medicine,[147] particularly around early outpatient care, where so little has been published. However, the need for close medical supervision including screening for contraindications is emphasized by the authors. For example, screening for QT intervals, retinopathy and glucose-6-phosphate dehydrogenase deficiency is required.

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[142] Morteza Shakhsi Niaee et al, 'Ivermectin as an Adjunct Treatment for Hospitalised Adult COVID-19 Patients: A Randomized Multi-Center Clinical Trial' doi: 10.21203/rs.3.rs-109670/v1 (pre-print).

[143] S Ahmed, MM Karim, AG Ross et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. International Journal of Infectious Diseases. 103 (2021) 214-216. 26th November 2020. <https://doi.org/10.1016/jijid.2020.11.191>.

[144] Australian Guidelines for Clinical Care of Persons with COVID-19 Disease (n 138).

[145] GD de Melo et al, 'Attenuation of Clinical and Immunological Outcomes During SARS-CoV-2 Infection by Ivermectin' EMBO Molecular Medicine, June e14122 <https://research.pasteur.fr/en/publication/attenuation-of-clinical-and-immunological-outcomes-during-sars-cov-2-infection-by-ivermectin/>.

[146] R Derwand, M Scholz and V Zelenko, 'COVID-19 Outpatients: Early Risk-stratified Treatment with Zinc Plus Low-dose Hydroxychloroquine and Azithromycin: A Retrospective Case Series Study, (2020) 56 International Journal of Antimicrobial Agents <https://doi.org/10.1016/j.ijantimicag.2020.106214>.

[147] R Bhopal and A Munro, 'Scholarly Communications Harmed by Covid-19 (2021) BMJ 372, doi: <https://doi.org/10.1136/bmj.n742>; I Torjesen, 'Covid-19: Sweden Vows Greater Protection for Academic as Researcher Quite After Aggressive Social Media Attack' (2021) BMJ 372, doi: <https/doi.org.10.1135.bmj.n489>.

A meta-analysis of RCTs[148] and of other studies of chloroquine and hydroxychloroquine has presented reports of COVID-19 treatments with significant dose variations of differing formulations of chloroquine and hydroxychloroquine, with differing initiation protocols at different stages of illness and target groups. These authors found inconsistent efficacy and concluded no improvement in clinical outcomes. In subsequent discussion, the same authors cite the retracted Lancet Surgisphere hydroxychloroquine data study,[149] which presented false Australian and other data and claimed increased hydroxychloroquine mortality. Its accompanying Lancet editorial was also removed and replaced. The meta-analysis authors wrongly claim the retraction was chiefly due to 'lack access to data [sic]..held by a private company'. These authors do conclude, however, that 'well designed randomized trials are required for assessing the efficacy and safety of hydroxychloroquine and chloroquine for COVID-19'.

Prophylaxis:

There is published evidence of some prophylactic benefit from use of Ivermectin,[150] which would also benefit from more research. Meta-analysis of three trials involving 738 participants evaluating Ivermectin for COVID-19 prophylaxis among health care workers and COVID-19 contacts found that 'Ivermectin prophylaxis among health care workers and COVID-19 contacts probably reduces the risk of COVID-19 infection' by an average of 86% (95% confidence interval, range 79%–91%). Five percent vs. 29.6% contracted COVID-19, respectively. This was assessed as low-certainty evidence and downgraded due to study design limitations and few included trials. No severe adverse events were recorded in two of the three trials involving a total of 538 participants.

3. h) The Degree of Uncertainty of the Outcome;

In relation to vaccine efficacy see discussion in previous section 3. d) above. The duration of vaccine effectiveness (immunity) is unknown.[151] The recent drive to vaccinate children who are themselves at low risk of severe COVID-19 disease, to reduce onward transmission in the community and achieve a level of herd immunity from an overall vaccination rate approaching 80%, exposes children to the known and un-

[148] A Elavarasi et al, 'Chloroquine and Hydroxychloroquine for the Treatment of COVID-19: a Systematic Review and Meta-analysis' (2020) 35(11) Journal of General Internal Medicine 3308-14 <https://link.springer.com/article/10.1007/s11606-020-06146-w>.

[149] RETRACTED MR Mehra et al, 'Hydroxychloroquine or Chloroquine with or without a Macrolide for Treatment of COVID-19: A Multinational Registry Analysis, (2020) Lancet doi: <https://doi.org/10.1016/S0140-6736(20)3118-6> <https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31180-6/fulltext>.

[150] A Bryant et al, 'Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines' (2021) 28(4) American Journal of Therapeutics, e434-e460 doi:10.1097/mjt.0000000000001402 <https://journals.lww.com/americantherapeutics/fulltext/2021/08000/ivermectin_for_prevention_and_treatment_of.7.aspx>.

[151] 'Coronavirus disease (COVID-19): Vaccines', World Health Organization (Web Page, 19 February 2021) <https://www.who.int/news-room/q-a-detail/coronavirus-disease-(covid-19)-vaccines>.

known risks of gene based vaccines[152] with novel platforms for little gain to themselves, to protect vulnerable adults.[153] Health outcomes in children following mass childhood vaccination are uncertain.

3. i) The Likely Consequences of Not Choosing the Proposed Procedure, or of Not Having Any Procedure at All;

The consequences depend on the reason(s) for declining or deferring vaccination, the level of COVID-19 alert, the alternative anti-COVID measures adopted (as in point 3.g above), and the patient's risk of developing severe complications or death as a result of COVID-19 infection (see section 3.a). Declining or deferring vaccination avoids vaccine-related side effects at the expense of possibly suffering severe COVID-19 disease and its attendant risks (COVID-19 symptoms, hospitalisation, ventilation and death) during a subsequent community outbreak.

Other consequences may include Occupational Health and Safety considerations for health or aged care workers, and travel restrictions, should the Australian Government or other state/territory governments introduce border entry/re-entry requirements conditional on proof of vaccination or previous documented infection.[154]

There is also the potential social stigma of being inappropriately labelled an "antivaxxer."

3. j) Any Significant Long Term Physical, Emotional, Mental, Social, Sexual or Other Outcome That May Be Associated With the Proposed Procedure;

Because the development of these vaccines has been hastened, only short-term safety data is available and the long term safety of these vaccines is not established.

1) Vaccination of pregnant or breastfeeding women:

Observational data demonstrate that, while the absolute risk is low, pregnant women with COVID-19 have an increased risk of severe illness, hospitalization, intensive care admission and ventilation.[155] There is also increased risk of stillbirth. There is a possibility of vertical transmission of the COVID-19 virus and an increased incidence of third trimester premature birth due to medical intervention.[156] Pregnant women are

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[152] A Dionne et al, 'Association of Myocarditis with BNT162b2 Messenger RNA COVID-19 Vaccine in a case Series of Children' (2021) JAMA Cardiology Doi:10.1001/jamacardio.2021.3471 (published online, 10 August 2021) <https://jamanetwork.com/journals/jamacardiology/fullarticle/2783052>.

[153] E Abi-Jaoude, P Doshi and C Michal-Teitelbaum, 'Covid-19 Vaccines for Children: Hypothetical Benefits to Adults Do Not Outweigh Risks to Children, BMJ Opinion (Blog Post, 13 July 2021) <https://blogs.bmj.com/bmj/2021/07/13/covid-19-vaccines-for-children-hypothetical-benefits-to-adults-do-not-outweigh-risks-to-children/>.

[154] Australian Government, Australian Covid Vaccination Policy, 6 <https://www.health.gov.au/sites/default/files/documents/2020/12/covid-19-vaccination-australian-covid-19-vaccination-policy.pdf>.

[155] COVID-19 Vaccination in Pregnant and Breastfeeding Women. RANZCOG. Update August 6th. <https://ranzcog.edu.au/statements-guidelines/covid-19-statement/covid-19-vaccination-information>.

[156] Royal Australian and New Zealand College of Obstetricians and Gynaecologists (n 99).

now known to be at increased risk of other adverse pregnancy outcomes, such as pre-eclampsia, coagulopathy, and preterm birth that is not due to medical intervention.[157]

There are no phase III trial data on the safety of COVID-19 vaccines in pregnant or breastfeeding women.[158] Long term effects of gene-based COVID-19 vaccines on the fetus, breastfed infant or milk production/excretion are not known.[159] There is limited data on vaccine effectiveness during pregnancy and on subsequent pregnancy outcomes after vaccinations, and no long term outcome data. USA research into mRNA vaccine safety in pregnancy[160] is underway. A first dose of mRNA vaccine in the third trimester of pregnancy thus far reveals no short term safety signals of concern and the authors note transplacental transfer of antibodies after maternal vaccination may help protect the neonate. The authors mistakenly assess the spontaneous abortion rate as a fraction of total completed pregnancies rather than as a proportion of total vaccinated pregnancies per gestational trimester. AstraZeneca safety in pregnancy has not been researched.

The recently published reproductive toxicology research[161] on the Pfizer vaccine examined pre-implantation fetal loss, fetal abnormalities and other parameters. The study concluded vaccination caused no effects on embryo-fetal or postnatal survival, growth, or development in the offspring through to the end of lactation. Higher percentage pre-implantation loss in the vaccinated group compared with the control group ($p < 0.5$) was within the historical control data range and the authors attributed it due to a higher rate of ovulation in the vaccinated rat cohort. Of the rat pups examined from the maternally vaccinated cohort, there were 3 malformations (defined as 'structural defects rare in the control population and thought to be life-threatening or of major physiological consequence') compared with no malformations in the control group. These malformations were gastroschisis, agnathia with short and fused mandibles and a small mouth, and malformation of the right-sided aortic arch, in separate pups. These malformations, as well as minor abnormalities, were deemed within background historical control incidence.

RANZCOG's position changed from strongly considering, in June 2021 to 'routinely offering' mRNA COVID-19 vaccination to all pregnant women.[162] Women who

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[157] See, Vaccines and Immunizations, Centers for Disease Control and Prevention (Web Page, last updated 14 May 2021) <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html?CDC_AA_refVal+https%3A%2F%2Fwww.cdc.gov%Fvaccines%2Fcovid-10%2Finfo-by-product%2Fpfizer%2Fclinical-considerations.html>.

[158] 'Information and Decision Aid' Royal College of Obstetricians and Gynecologists (Web Page, updated 14 May 2021) <https://rcog.org.uk/globalassets/documents/guidelines/2021-02-24-combined-info-sheet-and-decison-aid.pdf>.

[159] Centers for Disease Control and Prevention (n 108).

[160] TT Shimabukuro et al, 'Preliminary findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons' (2021) 384 New England Journal of Medicine 2273-2282 <https://www.nejm.org/doi/full/10.1056/nejmoa2104983>.

[161] CJ Bowman et al (n 94).

[162] Joint Statement ATAGI and Royal Australian and New Zealand College of Obstetricians and Gynaecologists (n 100).

are classified as being extremely vulnerable to severe complications of COVID-19, it is advised, would especially benefit from vaccination.[163]

Significant inflammation on the maternal side of the placenta was observed at microscopy in a well-documented case of mid trimester foetal demise in COVID-19 disease in pregnancy.[164] This phenomenon has been seen in 40% of maternal infections with Middle East Respiratory Syndrome[165] and Severe Acute Respiratory Syndrome.[166] It has been speculated that the similarity between coronavirus spike protein antigens, either in the wild or in the vaccine, with a placental protein Syncytin-1 could theoretically establish an immune reaction to the placenta.[167] In the case of the vaccine, this would not be limited to the duration of a wild virus infection but could be permanent i.e. there is a theoretical possibility that the vaccine may, by a similar molecular mechanism, establish an immune reaction to the placenta which could endure. Pfizer state it is 'very unlikely our vaccine could harm the placenta.'[168] To date, this has not been fully investigated although it is considered that the section of the similar protein sequence in syncitin-1 does not share sufficient similarities and is covered under the surface of the protein, preventing binding by anti-spike antibodies. COVID-19 infected mothers' antibodies to the spike protein might also attack Syncitin-1 and have a similar risk of miscarriages. Ongoing pregnancy studies of entire pregnancies and subsequent pregnancies will clarify these issues.

Providing some level of reassurance, preliminary research of a single dose only of mRNA vaccine received from 30 weeks of gestation onwards in 75 women (plus 9 with unknown gestation) was not associated with placental inflammation.[169] However, the corresponding author stated 'we want to look at patients who are vaccinated in the pre-conception period as well, partially to look at if we see evidence of placental injury at delivery from women vaccinated at that point.'[170] Further research is still needed. The

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[163] Ibid.

[164] D Baud et al, 'Second Trimester Miscarriage in a Pregnant Woman with Sars-CoV-2 Infection' (2020) 323 (21) Journal of American Medical Association doi:10.1001/jama.2020.7233.

[165] G Favre et al, '2019-nCoV Epidemic: What about Pregnancies?'(2020)395(10224) E40 Lancet doi: 10.1016/S0140-6736(20)30311-1.

[166] SF Wong et al, 'Pregnancy and Perinatal Outcomes for Women with Severe Acute Respiratory Syndrome (2004) 19 (1) American Journal of Obstetrics and Gynecology 292, doi: 10.1016/j.ajog.2003.11.019.

[167] Giverse Vernon, 'Of HERVS and COVID-19: Questions for the Future' British Journal of General Practice (Post, 21 May 2020) <https://bjgplife.com/2020/05/21/of-hervs-and-covid-19-questions-for-the-future/>.

[168] 'The Facts about Pfizer and BioNTech's COVID-19 Vaccine', Pfizer, (Web Page, 6 January 2021) <https://www.pfizer.com/news/hot-topics/the_facts_about_pfizer_and_biontech_s_covid_19_vaccine>.

[169] E. Shanes et al, 'Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccination in Pregnancy Measures of Immunity and Placental Histopathology' Research Letter, Obstetrics and Gynaecology (11 May 2021) doi: 10.1097/AOG.0000000000004457.

[170] JA Goldstein quoted in 'Clearing up a misconception: COVID-19 Vaccines and Infertility/Pregnancy Loss May 14th 2021. <https://www.biospace.com/article/no-known-link-between-covid-19-vaccines-and-infertility-pregnancy-loss-/>.

authors referenced observations made in mice in 2007 that changes at the feto-maternal interface, following similar immune processes as occur in the functioning of COVID-19 vaccines, included impaired spiral artery modification with increased fetal losses in the mid-gestation period.[171]

Concerns have been expressed about gaps in our knowledge of the effects of altered proportions of immune cells in pregnancy after COVID-19 vaccination.[172] Successful pregnancy outcomes are heavily dependent on heightened helper T cell type 2 (Th2) and regulatory T cell activity, with reduced helper T cell type 1 (Th1) responses. Disruption of the balance of T cell responses during pregnancy is associated with adverse perinatal outcomes including foetal loss and pre-term birth.[173] Data on two mRNA vaccine candidates indicate an altered balance of these cells in a broad immune response following vaccination.[174]

An accepted limitation of rat and mouse species for pre-clinical studies is their different placentation from humans. They are also less sensitive than humans to fertility perturbations.[175]

2) Conscientious objection

Deeply held convictions regarding vaccine derivation may be a source of tension personally and interpersonally. In relation to a patient considering vaccination but having a conscientious objection to vaccines which have used aborted foetal cell lines in their development, production or testing, such vaccines should be identified to patients where the doctor knows or suspects this information would affect the patient's decision to undergo vaccination, and an ethical alternative offered i.e. a vaccine which has been produced avoiding or, at the very least, minimising the use of cell lines derived from aborted babies.

For such patients, the Pfizer vaccine, which utilised aborted foetal cell lines only in its testing, is more likely to be acceptable than the AstraZeneca product, which used such cell lines in both its development and production. The Moderna vaccine is equivalent to AstraZeneca vaccine in this regard. Pending availability, the NVX-CoV2373

[171] Jianhong Zhang et al, 'Toll-like Receptor 3 Agonist Induces Impairment of Uterine Vascular Remodeling and Fetal Losses in CBAxDBA/2 Mice' (2007) June (1-2) Journal of Reproductive Immunology 2007 61. Doi:10.1016/j.jri.2006.10.005.

[172] SL Klein, P Creisher and I Burd, 'COVID-19 Vaccine Testing in Pregnant Females is Necessary' (2021) Journal of Clinical Investigation doi.org/10.1172/JCI147553.

[173] S Saito et al. 'Th1/Th2/Th17 and Regulatory T-cell Paradigm in pregnancy' (2010) 63(6) American Journal of Reproductive Immunology 601.

[174] EE Walsh et al, 'Safety and Immunogenicity of Two RNA-Based Vaccine Candidates' (2020) 383 (25) New England Journal of Medicine 2439; U Sahin et al, 'BNT162b2 induces SARS-Co-V-2-neutralizing Antibodies and T Cells in Humans' (2020) medRxiv <https://www.medrxiv.org/content/10.1101/2020.12.09.20245175v1>.

[175] 17 February 2020 EMA/CHMP/ICH/544278/1998 Committee for Medicinal Products for Human Use ICH S5 (R3) guideline on reproductive toxicology: Detection of Toxicity to Reproduction for Human Pharmaceuticals.

'Novavax' vaccine is an alternative to the Pfizer vaccine, as it also utilised aborted foetal cell lines only in the testing process.[176]

3.k) The Time Involved;

Eligible patients at each phase can book directly with a delivery hub, or accredited GP. There is no requirement for a referral for COVID-19 vaccination. There is no restriction on seeing only existing patients or patients in a particular area.

3. l) The Cost Involved, Including Out of Pocket Costs;

Cost varies from country to country. While vaccines for Australian citizens are government funded, those not eligible for this (some migrant workers and student visa holders) should be referred to a General Practitioner respiratory clinic or to state/territory immunisation centres.

Discussion

The COVID-19 pandemic is of great concern across the globe. COVID-19 morbidity, mortality and the transmissibility of the new Delta variant require effective management tools. Safe and effective vaccination is one such tool.

COVID-19 vaccination is a rapidly changing field with many emerging findings in different stages of publication and demonstration. There is much speculation in existing sources of literature which raise reasonable concerns about vaccination. However, given the rapid flux of new findings, both negative and positive, at the present time it is almost impossible to state this Guidance is complete.

This Guidance aims to address the important concern of ethical informed consent in an area of care delivery where there are many drivers, some unethical, for obtaining consent and use. Such drivers include the pressure for those obtaining consent to not exercise their duty to the consentee, but rather alter the consent process to achieve other laudable, but conflicting goals, such as herd immunity, public safety targets and protections, political mandates, etc.

We have provided an evidenced platform to deal with knowns and unknowns not covered in standard consent forms, from which to select issues to present to a greater or lesser extent, as relevant to the patient. The main challenges to address in our duty of care to the vaccinee are:

1) Ensuring the informed consent process for COVID-19 vaccination captures satisfactorily all the components deemed necessary for ethical informed consent without adding unnecessary obstacles to the vaccination process.
2) Informing consentees about a medical product when there are reasonable concerns about the product but no information yet to satisfactorily confirm or deny those concerns, and there is genuine concern about time to act on the reception of that product.

[176] T McGovern 'Vaccinated or Not: Answering Common Questions for Catholics' Federation Internationale des Associations de Medecins Catholiques (post 29 Dec 2020). <https://www.fiamc.org/covid-19/to-be-vaccinated-or-not-answering-common-questions-for-catholics/>.

3) Clarifying, in a timely manner, what constitutes substantive information to tell the proposed vaccine recipient, in the midst of a potentially life-threatening disease epidemic.
4) Defining any individuals/groups who may not benefit from vaccination or indeed may be harmed by it.
5) Advising a consentee with concerns on how long to wait for the data to collect when an epidemic is spreading.
6) Discussing alternative risk-reduction measures to vaccination and whether they can be used to assist in vaccine effectiveness.

Pertinent examples of concerns in informed consent include fetal safety following maternal vaccination, long term reproductive and gonadal safety for younger men and women, and groups who are low risk for morbidity and mortality from COVID-19 infection and yet are being included in vaccination campaigns. The latter are primarily minors of different ages, who are at low risk for death and injury from COVID-19 disease as best we know, but are at risk for known[177] and unknown vaccine side effects and complications. However, vaccinating them may contribute to protecting older groups more at risk for death and morbidity, including those already vaccinated, due to incomplete vaccine protection. Thus, the very young are being asked to shoulder risks that may outweigh the benefit for themselves. If protection of at-risk groups is the main benefit then such should be stated in the informed consent document.

Conclusion

On the basis of the data presented, if a patient considering vaccination with Pfizer and AstraZeneca vaccines were to ask about the chance of their protection against severe COVID-19 disease improving, one could answer confidently that protection against the original strain is very high in the short term, and against emerging strains relies on evolving information but appears reduced.

Obtaining informed consent for COVID-19 vaccination, however, goes well beyond this important question, and we therefore encourage vaccinators to raise the 12 guidance points in a patient-specific manner for everyone considering vaccination. The key point is that all considerations, including personal, family and societal ones, need to be counterbalanced against an individual's risk of developing severe disease when exposure to the SARS-CoV-2 virus occurs.

Nothing is known about the long term effects of the disease or of any COVID-19 vaccine. Absence of evidence of long term vaccine side effects is not evidence of safety, and further vaccine safety assessment will be more difficult to achieve without an unvaccinated comparator cohort to complete safety trials, due to vaccination of the control arms. There will be crucial reliance on recognition and notifications of post-vaccination adverse events by patients as well as practitioners. Some of these will require heightened public awareness for reporting, such as occurrences of new onset menstrual abnormalities which could be relevant to gonadal health. Failure to alert vaccinees to significant

[177] E Abi-Jaoude (n 153).

cluster reports associated with COVID-19 vaccination jeopardizes awareness and recognition of adverse event reporting, thereby reducing pharmacovigilance effectiveness.

Therefore, the combination of significant unknowns makes it difficult to assess, but necessary to discuss, the risk-benefit issues for any individual getting the infection and recovering or, possibly suffering long term COVID-19 sequelae, versus receiving an investigational vaccine and developing its side effects and complications. Each vaccine recipient will need to make their own judgement and the informed consent process will include concerns with no concrete science to deny or support the concerns as yet.

As should be apparent from this Guidance document, obtaining consent for vaccines still under investigation in the midst of a global pandemic, is a more complex task than obtaining consent for conventional vaccines. Doctors have an obligation to act in the best interests of their patients. This involves being aware of information on the risks, benefits and alternatives to the COVID-19 vaccines available in Australia, tailoring the advice and information they give to their patients to ensure that fully informed consent is achieved, and enquiring about adverse events and reporting them. It is hoped that this Guidance will provide Australian doctors with more comprehensive information to achieve these ends.