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Submission to the Department of Industry, Transport, Science and Resources

Understanding our RNA potential: Response to discussion paper

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Part 1: Into a new era?

Multiple sources attest to the notion of new era in vaccinology, consequent to novel mRNA therapeutics and the world wide roll-out of modified-RNA-based vaccines for COVID-19 disease. The brief selection in Box 1 is a minuscule selection of that optimistic sentiment. If humanity seems set sail into a new therapeutic epoch, should Australia simply just book its ticket? Or should we be more circumspect with regard to the decision to embrace this new industry? As industry comes knocking, should we simply open the door? Or can Australia expect real and impartial scrutiny of this platform, including an independent reckoning of the safety of novel COVID-19 modified-RNA-based vaccines?

We believe that evidence of the potential risks associated with RNA technology on the health and safety has accumulated in Australia and abroad. We present here an assessment of concerns regarding the possible future development of RNA therapeutic technology in Australia to be considered by the Australian Government. We here argue that a very thorough and circumspect retrospective look at every aspect of mRNA therapeutics is appropriate before embarking on partnerships with an industry which may yet be shown to have already causes great harm – and may well yet for that reason fail conspicuously. In the current environment, with the precedent of haste being set by recent pandemic responses and the unpopularity of heterodox voices in the such a time, it is in our view that a highly critical approach is needed by the Public Service and Elected Representatives: one that is free from undue influence and willing to consider any and all questions, especially from independence and non-aligned bodies such as ourselves.

The Australian Medical Professionals' Society (AMPS) comprises a collective of medical and allied health experts, supported by independent analysts and subject matter experts, united by a core mission: safeguarding and advancing the interests of our members and their patients, while advocating optimal health outcomes across Australia. We deeply cherish the tenets of medical ethics, prioritising patient well-being and community welfare above every other commitment and consideration. As staunch proponents of these values, AMPS embraces the chance to offer input to the Submission to the Department of Industry, Transport, Science and Resources, Understanding our RNA potential: Response to discussion paper.

The COVID-19 pandemic presented an unprecedented threat to world health and required an immediate response. That response came in the form of mRNA gene-based COVID-19 vaccines. These therapeutics were developed in record time (10 months under Operation Warp Speed under the direction of the US Government) and in doing so, many quality, safety and efficacy standards were compromised in order to make these vaccines available. *Unfortunately, initial assurances of quality, safety and efficacy were not met.* The COVID-19 vaccines do not prevent infection or transmission of infection and have been associated with the highest incidence of vaccine related death, serious adverse events and permanent injury than any drug in the history of the pharmaceutical industry.

Claims that the COVID-19 vaccines have saved up to 20 million lives are not credible. Such claims are typically backed by flawed modeling studies and we invite readers to consider a recent analysis of this problem by Canadian, Denis G. Rancourt[1]. We further invite readers to consider how powerfully modelling can be used to manipulate perceptions of success or failure of various policies within the context of the pandemic. The abstract of that paper begins,

> *Fantastic statements that the Nobel-Prize-winning COVID-19 vaccines saved millions (and tens of millions) of lives are based on the theoretical scenarios of Watson et al. (2022), published in The Lancet Infectious Diseases. Watson et al. (2022) theoretically inferred massive mortality reductions distributed globally, occurring solely during 2 vaccine rollouts.*

We argue that claims of very high estimates of population saved are untenable *in the presence of an acknowledged excess of mortality,* with a demonstrable reversal of trends occurring from the first half of 2021. Such a trend is of course of great relevance to those considering the impact of novel COVID-19 vaccines: the determination of causative factors warrants careful attention, but equally, on its face, is largely incompatible with a claim of lives saved in any significant quantity. In this regard, the reader should also be aware that AMPS, motivated by scientific enquiry and the public interest, is holding a symposium in Canberra on this very issue of excess mortality in Australia and around the world. AMPS considers that, given the gravity of the issue and the unique timing of the event, the sum of what has been done to date via official channels to investigate this problem in Australia falls well short of what is required for the people of Australia. We hope that the beginning of our independent efforts, including a 470-page book with 18 authors, will be well received by our intended audience, elected representatives, relevant public servants and other members of the public health establishment.

[1] https://correlation-canada.org/wp-content/uploads/2023/10/2023-10-08-Correlation-Whether-Nobel-vaccine-saved-millions-of-lives.pdf

Box 1: a new era, and paradigm shift?

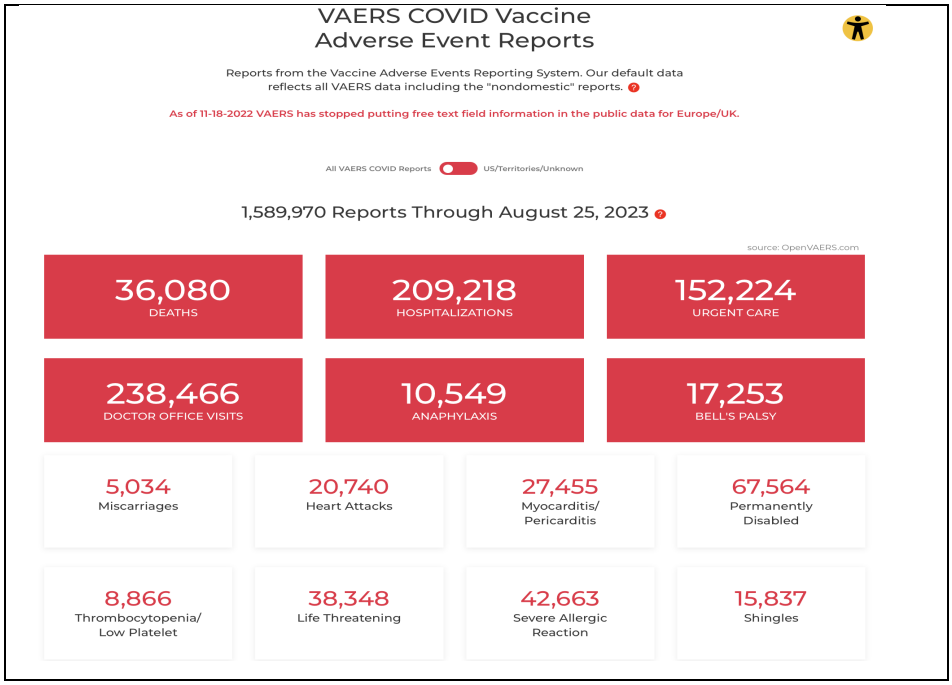
Thus, it is eminently arguable that the COVID-19 vaccines have NOT resulted in the nett saving of any lives. **This should also have been evident from pharmacovigilance signals quite early in the roll-out, if one considers the number of worldwide reported vaccine associated deaths (which need to be multiplied by the underreporting factor of about 50x according to a recent UK Parliamentary Report). We contend that a thoroughgoing independent and critical appraisal mRNA vaccines for COVID, with harm to benefit ratios, remains outstanding. Again, this falls well short of what the Australian people require.**

We believe we are on very solid ground in suggesting the Therapeutic Goods Administration (TGA) Adverse Drug Event Notification (DAEN) system grossly under-reports the true incidence of death and serious adverse events in relation to the COVID-19 vaccines.

In support of this proposition we supply the following information.

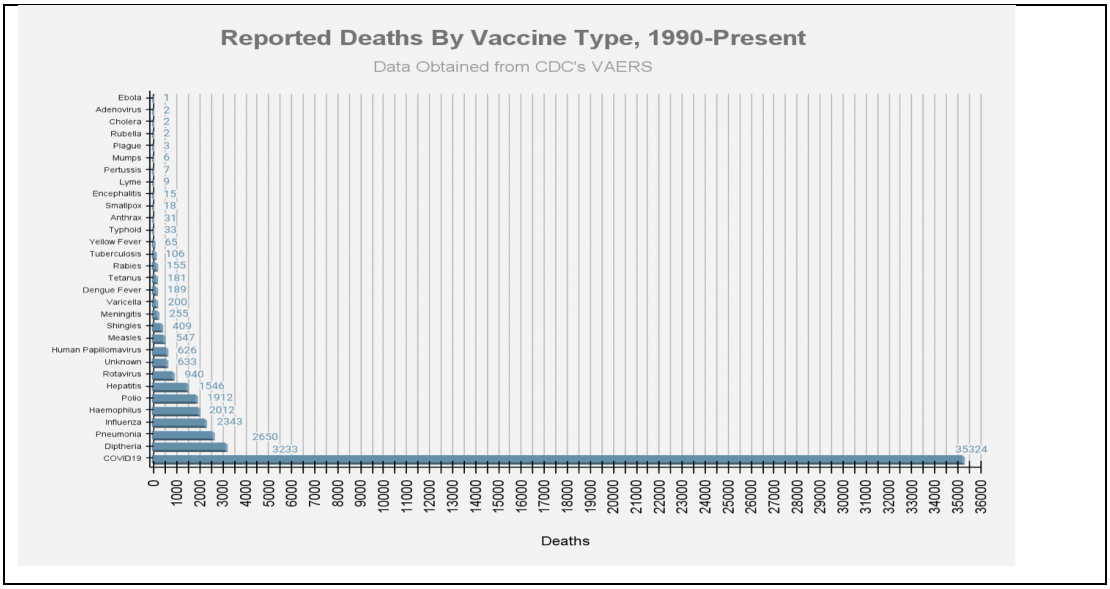
A. The latest US Center for Disease Control (CDC) Vaccine Adverse Event Reporting System (VAERS) report concerning COVID vaccines is shown below:

Box 2



B. Below is a comparison of the deaths reported for the COVID vaccines vs other vaccines in the VAERS database showing the rate of death of the COVID-19 vaccines is substantially higher than any other vaccine in history.

Box 3: VAERS Summary for COVID-19 vaccines through 5/5/2023



https://vaersanalysis.info/2023/05/12/vaers-summary-for-covid-19-vaccines-through-5-5-2023/

C. We also attach below an extract from the West Australian Vaccine Safety Surveillance – Annual Report 2021 which shows dramatically how the introduction of the COVID vaccines resulted in a remarkable spike in vaccine adverse events far in excess of the rate reported for all other vaccines.

Box 4: WA Vaccine Safety Surveillance

The number of AEFI reported to WAVSS was significantly higher in 2021 than in previous years (10,726 compared with an average of 276 per year for the 2017-2020 period) due to the introduction of the COVID-19 vaccination program. To allow comparison of AEFI numbers to previous years, Figure 2 presents all AEFI reported to WAVSS for persons vaccinated in 2021, and Figure 3 excludes adverse events following COVID-19 vaccination. The high number of reports in 2021 following COVID-19 vaccination reflects higher uptake of COVID-19 vaccination, and high engagement from the public and health care providers with the monitoring of vaccine safety.

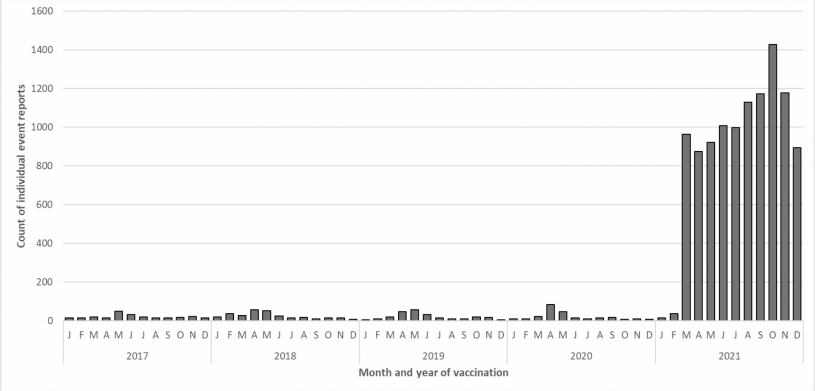
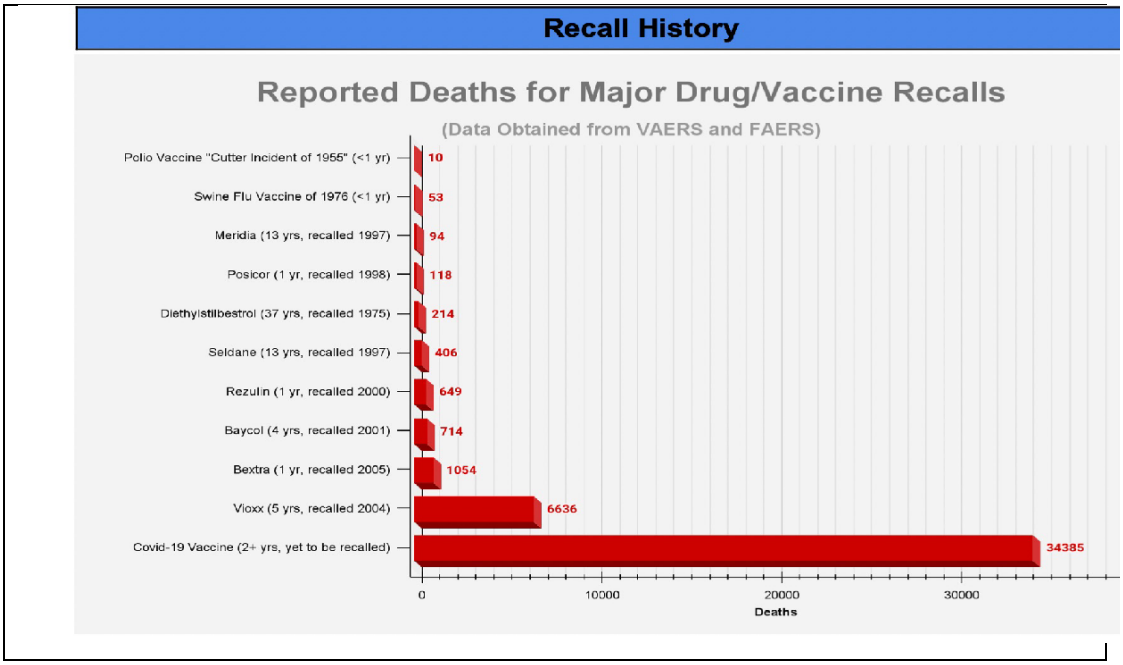


Figure 2: Adverse events following immunisation reported to WAVSS by month, 2017-2021, excluding active surveillance reports for routine vaccination adverse events.

D. It can easily be seen that the COVID vaccines are reported to cause an alarming number of reported vaccine related deaths. The number of reported COVID vaccine associated deaths far exceed reported associated deaths due to many drugs which have been recalled (see below Recall History). History has recorded many instances of safety issues with vaccines which had to be withdrawn due to safety issues. However, the safety issues regarding the largely experimental mRNA vaccines, and other mRNA based therapeutics, rise to a new level of concern.

Box 5: VAERS Recall History



Part 2: Specific considerations and recommendations?

The mRNA COVID vaccine technology which has sparked current government interest for potential future therapeutics, was made possible using a lipid nanoparticle platform as a delivery system. However, pursuit of this technology presents many special concerns of high interest including the following:

1. The lipid nanoparticles used currently in pharmaceutical formulations to protect the RNA from the natural degradation processes of the body have a toxicity of their own and disseminate distribute RNA throughout the body with preferential accumulation to certain tissues and organs. There is special concern, for example, regarding the penetration of the blood-brain-barrier or distribution to organs responsible for reproduction (ovaries and testes). In the opinion of our organization, this has been inadequately addressed by Australian authorities, evidencing at times an incomplete or incorrect understanding of the vital biodistribution issue. Especially in the light of the proposed onshore expansion of the mRNA industry, we are ready, willing and able to provide an independent briefing on this critical issue. **Our position is of course that mRNA therapeutics should never disseminate: sponsors of new therapeutics should be able to demonstrate highly targeted or localized biodistribution, as well as the absence of dissemination and recirculation.**

2. Natural RNA is short-lived in the body and would be expected to pose no prolonged safety issue but the RNA used in the COVID-19 vaccines (and other RNA based therapeutics) is different to natural RNA. As the reader may be aware, it is a synthetic RNA with modified nucleotide (N1-methylpseudouridine) components to extend its biological activity and protect the molecule from degradation. On the one hand, this work is quite ingenious and has been the subject of a recent Nobel Prize nomination; on the other hand, it raises the increasingly well recognised issue of unnatural durability and unwanted persistence of the RNA and its product, the Spike Protein. Table 1 is a selection of studies showing such persistence; it is duly noted that the CDC had to remove the following words from its website last year: *"The mRNA and the spike protein do not last long in the body. Our cells break down mRNA from these vaccines and get rid of it within a few days after vaccination. Scientists estimate that the spike protein, like other proteins our bodies create, may stay in the body up to a few weeks"*.

   The persistence of mRNA and Protein, by may drastically alter the correct frame to be studying off-target effects and AEFIs. We recommend that Pharmacovigilance systems allow for a longer lead time between the onset of any notified condition or death and the date of vaccine administration, since to limit surveillance to a restricted timeframe in N1-methylpseudouridine-based mRNA therapeutics is counterfactual and may curtail the appreciation of serious AEFIs and long-term safety considerations.

3. The use of RNA therapeutics introduces special concerns regarding considerations of dose-response. This is because this RNA technology relies on the individual's own biochemistry to manufacture the active entity with pharmacological activity following RNA administration. Some individuals will produce small amounts of the intended product of the RNA and some individuals will produce larger amounts. In the case of the COVID-19 vaccines the pharmacological entity which was produced was the Spike Protein. Individuals will vary in their innate ability or capacity to produce a protein so there is likely to be large differences in efficacy and in safety by comparison to conventional small molecule drugs where a definite amount of active pharmacological substance is administered.

Table 1. **Studies demonstrating persistence of vector-based vaccine constituents and/or derivative spike protein. Abbreviations: MoH – Ministry of Health;** Table adapted from Parry, et al. (2023)

Author	Constituents / tissue type / assay technique	Duration measured
Experimental Animals		
Pfizer (Japanese MoH) (2020)	**Radiolabeled unloaded LNP in plasma and tissues**	**140 hours – 14 days**
Human Subjects		
Ogata et al. (2021)	**Spike protein and S1 subunit (assay)**	**3 days**
Bansal et al. (2021)	**Spike Protein**	**4 months**
Fertig et al. (2022)	**LNPs and mRNA**	**15 days**
Krauson, et al. (2023)	**Vaccine-specific mRNA**	**30 days**
Röltgen et al. (2022)	**mRNA and Spike Protein in ipsilateral lymph nodes; 2-7 days post dose in blood**	**60 days**
Yamamoto et al. 2022)	**Spike Protein in skin**	**3 months**
Yonker et al. (2023)	**Spike Protein in blood**	**1-19 days in cases of myocarditis**
Castruita et al. (2023) [43]	**mRNA in plasma**	**28 days**

4. **Considerations for nucleotide-based therapies.** We are strongly of the view that the legal definitions for gene technology were clearly met by the 'new biologic entities', as they were approved at the time, the mRNA vaccines from Pfizer and Moderna. We take note that this is in a view in a matter presently before the Federal Court, with potential criminal implications. As a society, we have found the replies of the Health Department to be scientifically lightweight and unsatisfying with regard to potential DNA-integration, with no acknowledgment of the obvious burden of proof jointly on the Regulator and Sponsor. With any gene-based therapeutic there is the chance of genotoxicity, either via reverse transcription of synthetic RNA, or integration of contaminant DNA. In this regard that the Department cannot be unaware of the demonstration in 2023 of plasmid DNA contamination in very significant amounts. Certainly the public is increasingly aware, witness a recent report by Australian Journalist, Rebekah Barnett, which quickly gathered over 34 million hits/shares[2].

   These are well-known phenomena and potentially this could have serious consequences including intergenerational effects. Without specialized long-term safety studies this is an obvious risk. It would be unconscionable to consider using RNA therapeutics on health individuals, children, infants or pregnant women unless assurances can be guaranteed of safety. **We strongly advise that the Department monitor the issues to which we alert them here and recommend against Sponsors of any future mRNA therapeutics dealing in their products without submitting to a thoroughgoing assessment by the Office of Gene Technology Regulator. We recommend the Gene Technology Regulation Act 2000 should be revised in the light of recent technological developments.**

5. **Concerns relating to manufacture and contamination.** As we have learned in relation to the COVID-19 vaccines, mRNA products are difficult to manufacture and rely on Process 2, as has now become well appreciated. Given that this large scale production method requires E. coli and DNA plasmids, it also introduces the specter endotoxin contamination. There appears to have been considerable batch to batch variation, which carries safety concerns. In addition, there have been numerous credible reports of dangerous DNA contamination and endotoxin contamination which can have fatal consequences. These concerns have been recognized by overseas drug regulators. Before the reader may be tempted to dismiss the concerns of

[2] https://www.spectator.com.au/2023/09/scientists-shocked-and-alarmed-at-whats-in-the-mrna-shots/

endotoxin in vaccine batches as negligible, we counsel caution and investigation: very small quantities may amount to serious biological effects, especially given the novelty of the LNP delivery platform, which will deliver both mRNA and contaminants. It is obvious – and highly relevant to this submission regarding a proposed new industry – that the pharmaceutical industry has some way to go to improve the quality control of these RNA products. However, while the world-wide public is increasingly appraised of these issues, it is unclear to us how communicative the industry has been with Regulators.

We recommend that Good Manufacturing Practice adherence be given a whole new level of priority in any forthcoming industrial partnerships, with thoroughgoing demonstration of *decontamination* of plasmid DNA, DNA fragments and endotoxin (where manufacture entails bacterial processes). We strongly recommend that the public-facing Pharmacovigilance System, the DAEN by upgraded to allow public scrutiny of Batch numbers, instead of withholding or failing to collect these, as was done during the COVID vaccine roll-out and which we believe to be out of keeping with international standards.

6. It must be recognized that RNA based therapeutics are in their infancy: there is much to learn. So far, when used on a population wide basis as the COVID-19 vaccines, these products have been associated with unprecedented numbers of death and serious adverse events. The long-term consequences are unknown. It must be asked: "If we do not know the long-term consequences, why commit to this class of therapeutic until the problems of quality, safety and efficacy have been resolved?" Any new mRNA therapeutics should be accompanying by refreshed efforts to enhance engagement with Pharmacovigilance in Australia, among physicians, pharmacists, other health care workers and the public. We are of the view that Pharmacovigilance should not be left to the domain of Industry and Government Departments, but should be reformed to allow maximum transparency and a focus of open-source collaboration and reporting, so as to maintain accountability.

It is anticipated that any Public-Private-Partnership with the pharmaceutical industry to research, develop and produce RNA based therapeutics would involve government to agree to industry indemnity from litigation due to the history of safety issues with the COVID-19 vaccines. **If this were to be the case, there would be no incentive for the pharmaceutical industry to ensure as far as possible the safety of the RNA products. This should not be permitted under any circumstances.**

Conclusions

We thank the Department for the opportunity to make this presentation and submission of the reasonable concerns of our membership. Whether we perceive it as a paradigm shift, new era in therapeutics, or an enterprise opportunity, the Australian Government must precede with a maximum of caution into any future on-shoring of the mRNA therapeutics industry. The Department of Industry, Science and Resources, must exercise due diligence and appraise the concerns raised in this submission, especially those emerging with regard to DNA contamination and those intersecting with the paramount concern of the safety of Australians. Especially with regard to the issue of DNA contamination and potential integration, that the gravity of the situation is not lost upon the reader.

The Department must take note that the Industry is one possessed of unparalleled marketing dominance and one with an established ability to influence perceptions among experts and peak bodies. Anyone abreast of the last 20 years or so will confirm that cover-ups are a part of a normative part of the 'corporate playbook' of Big Pharma. The profit advantage of big pharmaceutical companies in transferring novel therapeutics onto the basis of mRNA or similar biologics, is fairly obvious: drastic reduction of development timelines. Nevertheless, as stated, given the industry's relative infancy, it remains a fact that the there are many issues which could curtail or derail its progress.

Hence, the concerns raised here should not be dismissed lightly, in a rush to take hold of a new era. What is currently unknown or uncertain, given the right circumstances, could prove fatal for the hopes of mRNA apologists. The platform could end almost as quick as it sprung up.

In conclusion, we believe that the issues raised above represent significant safety risks in relation to the development of future RNA therapeutics. For and on behalf of the health and wellbeing of all Australians, we urge the Australian Government to reconsider its direct commercial involvement and support for this experimental class of therapeutics until basic quality, safety and efficacy issues can be satisfactorily addressed. We would be more than happy to be approached to consult further and develop any of the points raised in this submission.