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The Safety of COVID-19 Vaccinations — Should We Rethink the Policy?

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Abstract

Background: COVID-19 vaccines have had expedited reviews without sufficient safety data. We wanted to compare risks and benefits.

Methods: We calculated the Number Needed to Vaccinate (NNTV) to prevent one death from a large Israeli field study. We accessed the Adverse Drug Reactions database of the Dutch National Register (Lareb) to extract the number of cases reporting severe side-effects and the number of cases reporting fatal side-effects.

Results: The NNTV is between 200 and 700 to prevent one case of COVID-19 for the mRNA vaccine marketed by Pfizer. NNTV to prevent one death is between 9,000 and 100,000 (95% confidence interval), with 16,000 as a point estimate. We observed strong variability in the number of Individual Case Safety Reports (ICSRs) per 100,000 vaccine doses across all EU member states. The estimate for the number of ICSRs per 100,000 vaccinations derived from the Lareb database was approximately 700. Among those, there were 16 serious ICSRs, and the number of ICSRs reporting fatal side-effects was at 4.11/100,000 vaccinations. Thus, for 6 (95% CI 2–11) deaths prevented by vaccination, there were approximately 4 deaths reported to Dutch Lareb that occurred after vaccination, yielding a potential risk/benefit ratio of 2:3.

Conclusion: Although causality between ICSRs and vaccination has not been established, these data indicate a lack of clear benefit, which should cause governments to rethink their vaccination policy.

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Keywords
SARS-CoV2; COVID-19; vaccination; mRNA-vaccine; Number Needed to Vaccinate; safety; side-effects; adverse event; adverse drug reaction; fatal side-effects; European Medicines Agency; EMA

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1 Introduction

During the SARS-CoV-2 pandemic, new regulatory frameworks were put into place that allowed for expedited review of data and admission of new vaccines without adequate and sufficient safety data.[1–3] The European Medicines Agency website[4] lists all four COVID-19 vaccines that have market authorization in the EU (Comirnaty [BioNTech-Pfizer], Spikevax [Moderna], Vaxzevria [AstraZeneca], and the Janssen COVID-19 vaccine [Johnson & Johnson]) as having received conditional market approval, awaiting the outcome of long-term trials. The same is true for the US (see, for instance, the Emergency Use Authorization for the Pfizer-BioNTech vaccine [4]).

Many of the new vaccines use completely new technologies that have never been used in humans on a large scale outside of trials so far.[5] The rationale for this action was that the pandemic was such a ubiquitous and dangerous threat, and that there was no efficacious treatment for it, that this exceptional situation warranted exceptional measures. Thus, the vaccination campaign against SARS-CoV-2 has started, beginning in January 2021, after Comirnaty was the first substance to receive conditional market authorization on December 21st, 2020, followed by Spikevax (Moderna) on January 21st, 2021, and Vaxzevria (AstraZeneca) on February 18th, 2021.[5]

To date (July 22nd, 2021), roughly 435.3 million doses have been administered in the EU,[6] primarily the vector vaccination product developed by the Oxford vaccination group and marketed by AstraZeneca, Vaxzevria [6] (about 25% coverage in the EU); the RNA vaccination product of BioNTech, marketed by Pfizer, Comirnaty [7, 8] (about 60%); and the mRNA vaccination product developed by Moderna [9] (about 10%). Other products account for only about 5% of all vaccinations.

The safety of these vaccines has been tested only in comparatively short and small phase 3 trials, and long-term trials are ongoing and not foreseen to end before 2022 and 2023.[2] Post-marketing surveillance studies are not underway, as far as we know. A search of the trial register clinicaltrials.gov on July 18th, 2021, revealed some 500 phase 2 or phase 3 licensing trials with long-term observational periods of up to two years, but no single post-marketing surveillance study was registered. The ongoing long-term trials are being unblinded at a fast rate, thus obfuscating potential comparisons between treatment and controls.[2] We therefore wanted to establish a way to determine the effectiveness of the vaccines and compare them with the costs in terms of side-effects.

2 Methods

We used a large Israeli field study testing the BioNTech vaccine,[10] which involved approximately 1 million persons, and the data reported therein to calculate the Number Needed to Vaccinate (NNTV) to prevent one case of SARS-

4 https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines; accessed July 22nd, 2021.
5 https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty; accessed July 22nd, 2021.
6 https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab; accessed July 22nd, 2021.

CoV-2 infection and to prevent one death due to COVID-19. In addition, we used the most prominent trial data from regulatory phase 3 trials to assess NNTV.[8, 9, 11] NNTV is the reciprocal of the absolute risk difference between the control group and the test group. For example: an absolute risk of 0.8 in the control group and an absolute risk of 0.3 in the test group would result in an absolute risk difference of 0.5; thus, the NNTV would be 1/0.5 = 2. This is the clinical effectiveness of the vaccine. Usually, vaccine efficacy is used as a measure of vaccination success. This is a measure derived from a ratio of effectiveness between the groups. This veils the fact that, when incidence of an infection and infectivity is relatively low, many people have to be vaccinated to see an effect, clinically speaking. Because we were interested in the clinical effect and its relationship to side-effects which might occur in all those vaccinated, we used NNTV as a measure of clinical effect size.

We checked the Adverse Drug Reaction (ADR) database of the European Medicine Agency (EMA).[6] Looking up the number of single cases with side-effects reported for the three most widely used vaccines (Comirnaty [BioNTech/Pfizer]; vector vaccination product Vaxzevria [AstraZeneca]; mRNA vaccine Spikevax [Moderna]) by country, we discovered that the reporting of side-effects varies widely between European countries (Figure 1). On the European average, we see 127 Individual Case Safety Reports (ICSRs; cases with side-effect reports) per 100,000 vaccinations. The Dutch authorities register 701 reports per 100,000 vaccinations, while Poland registers only 15 ISCRs per 100,000 vaccinations. We know that reporting standards of ADR databases are generally weak.[12] To use data that are as realistic as possible, we decided to use the ADR database according to high reporting number. We deemed it unlikely that in a country such as the Netherlands, the ADR reporting would produce overestimates. Rather, we assumed that the reporting standards are higher. We therefore decided to use the data of the Dutch national register[7] to gauge the number of reported severe and fatal side-effects per 100,000 vaccinations. We compared these quantities to the NNTV to prevent one clinical case and one fatality by COVID-19.

3 Results

Table 1 shows the data from the Israeli field study testing Comirnaty (BioNtech/Pfizer). This was based on matched pairs, using propensity score matching with a large number of baseline variables, in which both the vaccinated and unvaccinated persons were still at risk at the beginning of a specified period.[10] We use the estimates from Table 1 because they are likely closer to real life and are derived from the largest field study to date. But we also report the data from the phase 3 trials conducted for obtaining regulatory approval in Table 2 and use them for a sensitivity analysis.

It should be noted that the cumulative incidence of the infection, visible in the control group after seven days, is low (Kaplan-Meier estimate <0,5%, Figure 2 in Dagan et al. [10]) and remains below 3% after six weeks. In the other studies, incidence figures after three to six weeks in the placebo groups are similarly low, between 0.86% and 1.8%. The absolute infection risk reductions given by Dagan et al. translate into a NNTV of 486 (95% CI 417–589) two to three weeks after the first dose, or 117 (90–161) after the second dose until the end of follow-up to prevent one documented case (Table 1). Estimates of NNTV to prevent SARS-CoV-2 infection from the phase 3 trials of the most widely used vaccination products 1–4 are between 61 (Moderna) and 123 (Table 2) and were estimated to be 256 by Cunningham.[14] However, it should

6 http://www.adrreports.eu/en/search_subst.html#; accessed May 28th, 2021. The COVID-19 vaccines are accessible under "C" in the index.
7 https://www.lareb.nl/coronameldingen; accessed May 29th, 2021.

Table 1: Risk differences and Number Needed to Vaccinate (NNTV)[7] to prevent one infection, one case of symptomatic illness and one death from COVID-19; Data from Dagan et al.,[10] N=596,618 in each group[8]

	Documented Infection		Symptomatic Illness		Death from COVID-19	
Period	Risk difference [no./1000 persons] (95% CI)	NNTV (95% CI)	Risk difference [no./1000 persons] (95% CI)	NNTV (95% CI)	Risk difference [no./1000 persons] (95% CI)	NNTV (95% CI)
14–20 days after first dose	2.06 (1.70–2.40)	486 (417–589)	1.54 (1.28–1.80)	650 (556–782)	0.03 (0.01–0.07)	33,334 (14,286–100,000)
21–27 days after first dose	2.31 (1.96–2.69)	43 (372–511)	1.34 (1.09–1.62)	747 (618–918)	0.06 (0.02–0.11)	16,667 (9,091–50,000)
7 days after second dose to end of follow-up	8.58 (6.22–11.18)	117 (90–161)	4.61 (3.29–6.53)	217 (154–304)	NA	NA

7 NNTV = 1/risk difference.

8 Data taken from Table 2 in Dagan et al.

Table 2: Number Needed to Vaccinate (NNTV) calculated from pivotal phase 3 regulatory trials of the SARS-CoV2 mRNA vaccines of Moderna, BioNTech/Pfizer und Sputnik.[9]

Vaccine	N participants Vaccine group	N participants Placebo group	SARS-CoV-2 -positive at end-of-trial: vaccine group	SARS-CoV-2 - positive at end-of-trial placebo group	Absolute Risk Difference (ARD)	Number Needed to Vaccinate 1/ARR
Moderna [9][10]	15,181 (14,550)[12]	15,170 (14,598)[12]	19 (0.13%)[14]	269 (1.77%)[14]	0.0165	61
Comirnaty (BioNTech/ Pfizer) [8][10]	18,860	18,846	8 (0.042%)[15]	162 (0.86%)[15]	0.00817	123
Sputnik V [11][11]	14,964	4,902	13 (0.087%)[13,16]	47 (1%)[13,16]	0.0087	115

9 The vector vaccine of AstraZeneca is not contained here, as the study [13] was active-controlled and not placebo-controlled.

10 Outcome is a symptomatic COVID-19 case.

11 Outcome is confirmed infection by PCR test.

12 Modified intention to treat; population basis for calculation.

13 Taken from the publication because of slightly different case numbers.

14 After 6 weeks.

15 After 4 weeks.

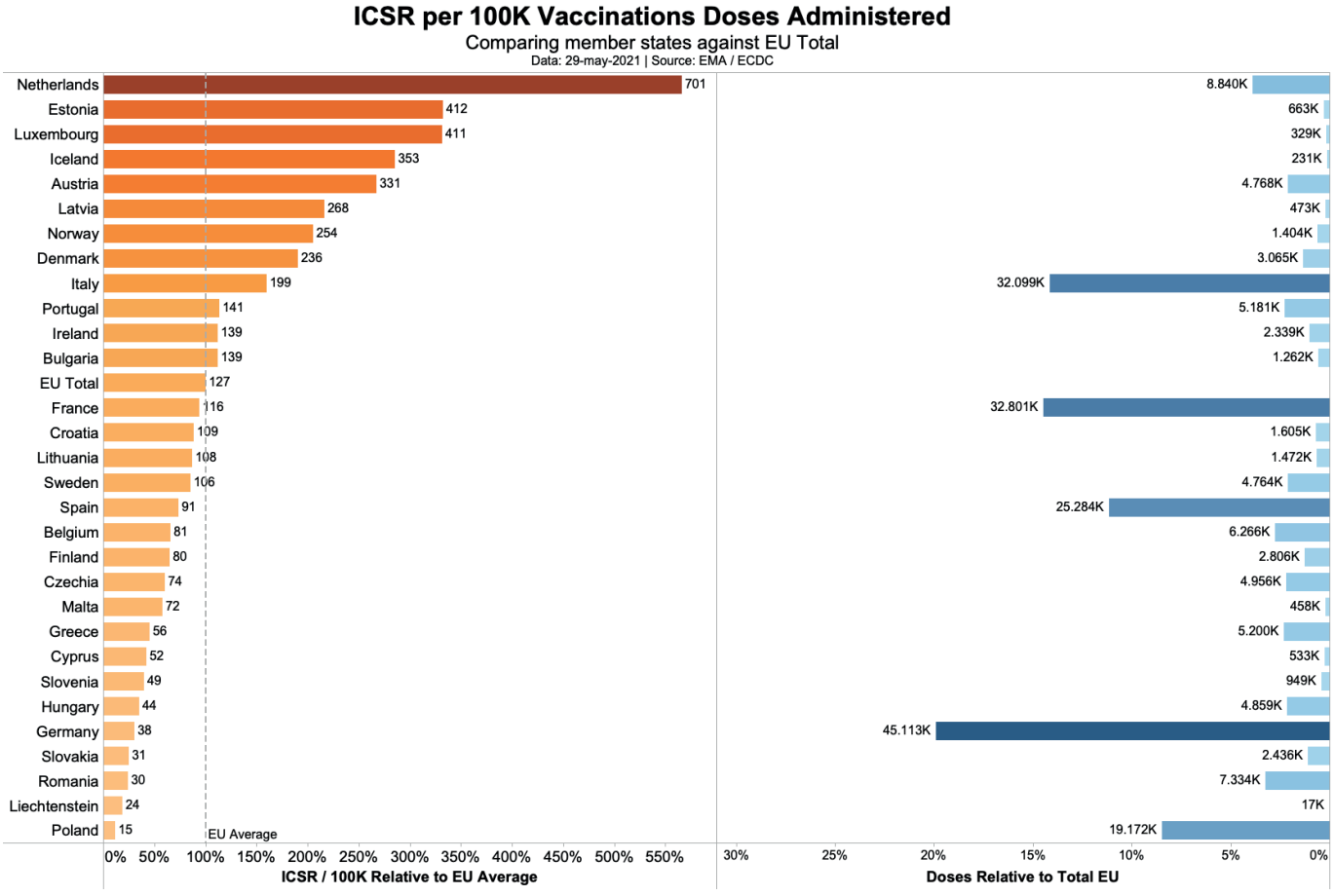
16 After 3 weeks.

also be noted that the outcome "Documented infection" in Table 1 is SARS-CoV-2-infection as defined by a positive PCR test; i.e. without considering false positive results.[15] This means that the outcome "symptomatic illness" may better reflect vaccine effectiveness. If clinically symptomatic COVID-19 until the end of follow-up is used as an outcome, the NNTV is estimated as 217 (95% CI 154–304). A comparison between the most important pivotal phase 3 regulatory trials and the Israeli field study by Dagan concluded that the Dagan study gives a robust estimate of the clinical effect.[16]

In the Israeli field study, 4,460 persons in the vaccination group became infected, as determined by PCR test and clinical symptomatology, during the study period. Nine persons died, translating into an infection fatality rate (IFR) of 0.2% in the vaccination group. In the control group, 6,100 became infected and 32 died, resulting in an IFR of 0.5%, which is within the range found by a review. [17, 18]

Using the data from Table 1, we can calculate that the absolute risk difference is 0.00006 (ARD for preventing one death after 3–4 weeks), which translates to a NNTV of 16,667. The 95% confidence interval spans the range from roughly 9,000 to 50,000. Thus, we need to vaccinate between 9,000 and 50,000 people, with a point-estimate of roughly 16,000, to prevent one COVID-19 related death within the following 3–4 weeks.

Figure 1: Individual Safety Case Reports in Association with COVID-19 Vaccines in Europe



For the other studies listed in Table 2, in the case that positive infection (i.e. infection determined by a PCR test) was the outcome,[11] we can calculate the NNTV to prevent one death using the IFR estimate of 0.2%.[18] In the case that clinically positive COVID-19 was the outcome,[8, 9] we can use the Case Fatality Rate of 2% estimated as the number of worldwide COVID-19 cases/COVID-19 related deaths estimated from one of the prominent COVID-19 statistical dashboards,[17] which is likely an over-estimate and thus a conservative choice, as fatalities were much higher in the elderly and in comorbid patients,[18–20] while the vaccine trials recruited mainly middle-aged and comparatively healthy individuals. In the case of the Sputnik vaccine, one would thus have to vaccinate 5,750 to 57,500 people to prevent one death. In the case of the Moderna vaccine, one would have to vaccinate 3,050 to 30,500 people to prevent one death. In the case of Comirnaty, the Pfizer vaccine, 6,150 to 61,500 vaccinated people would prevent one death, and using the figure by Cunningham,[14] it would be 12,300 to 120,300 vaccinations to prevent one death.

The side-effect data reported in the Dutch register[18] are shown in Table 3. Thus, there were 16 reports of severe adverse reactions and 4 reports of deaths per 100,000 COVID-19 vaccinations delivered. According to the point estimate of NNTV = 16,000 (95% CI 9,000-50,000), to prevent one COVID-19 related death, for every 6 (95% CI 2-11) deaths prevented by vaccination in the following 3–4 weeks there are approximately 4 deaths

Table 3: Individual Case Safety Reports for the most widely distributed COVID-19 vaccines according to the Dutch side-effects register,[18] absolute numbers per vaccine, and standardized per 100,000 vaccinations

	General Number of Reports[18]	Serious Side-Effects Reported[18]	Deaths Reported[19]	Number of Vaccinations (Dutch data)[20]	Number of Vaccinations (ECDC)[21]
Comirnaty (Pfizer)	21,321	864	280	5,946,031	6,004,808
Moderna	6,390	114	35	531,449	540,862
Vaxzevria (AstraZeneca)	29,865	411	31	1,837,407	1,852,996
Janssen	2,569	7	-	142,069	143,525
Unknown	129	15	5	-	540
Total	60,301	1,411	351	8,456,956	8,542,731
Per 100,000 vaccinations (Dutch data)	713.03	16.68	4.15		
Per 100,000 vaccinations (ECDC)	705.87	16.52	4.11		

17 https://www.worldometers.info/coronavirus/; accessed May 29th, 2021.
18 https://www.lareb.nl/coronameldingen; accessed May 27th, 2021.
19 https://www.lareb.nl/pages/update-van-bijwerkingen; accessed on May 27th, 2021.
20 https://coronadashboard.rijksoverheid.nl/landelijk/vaccinaties. The Dutch Government reports two numbers; we took the calculated amounts.
21 ECDC: European Center for Disease Prevention and Control. https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea; accessed on May 27th, 2021.

reported to Lareb that occurred after COVID-19 vaccination. Therefore, we would have to accept that 2 people might die to save 3 people.

The risk-benefit ratio looks better if the stronger effect sizes from the phase 3 trials are used for calculation. Using Cunningham's estimate of NNTV = 12,300, which stems from a non-peer-reviewed comment, 8 deaths are prevented per 100,000 vaccinations, and in the best case, 33 deaths are prevented by 100,000 vaccinations. Thus, in the optimum case, 4 deaths are risked to prevent 33 deaths, a risk-benefit ratio of 1:8. The risk-benefit ratio in terms of deaths prevented and possible deaths associated with vaccines thus ranges from 2:3 to 1:8. It is obvious that the time period of the Dagan study was much too short, as vaccinations might develop their clinical effect over time, thus potentially changing the risk-benefit ratio to the better. Unfortunately, we do not have the data to argue this point.

4 Discussion

The COVID-19 vaccines are immunologically effective and can prevent infections, morbidity and mortality associated with SARS-CoV-2, according to the data reported in regulatory trials.[(8, 9, 13, 21] Relative risk reduction (RRR), defined as:

$$\text{RRR} = 1 - \left(\frac{\text{Attack Rate } \textit{vaccinated}}{\text{Attack Rate } \textit{unvaccinated}}\right)$$

ranges between 67% and 95%.[16] In a non-peer-reviewed opinion blog article, Dr. Helen Petousis-Harris pointed out that RRR would be the correct parameter for assessing vaccine effectiveness and criticized the usage of NNTV, stating that "[v]accine effectiveness is never calculated by using a NNT/NNV."[22]

However, as pointed out by Olliaro et al.,[16] "RRR considers only participants who could benefit from the vaccine, [while] the absolute risk reduction (ARR), which is the difference between attack rates with and without a vaccine, considers the whole population". Thus, clearly, ARR is the more robust estimate to assess the clinical, not the theoretical, benefit of a vaccine (and any intervention). The ARR is expressed as Number Needed to Vaccinate (NNTV), which is simply its reciprocal. For the aim of our study, which was the comparison between risks and benefits in the whole population, we had to use NNTV, although this measure is typically ignored in vaccine effectiveness studies, because ARRs "give a much less impressive effect size than RRRs".[16] Cunningham was the first to point out the high NNTV in a non-peer-reviewed comment: around 256 persons to prevent one case with the Pfizer vaccine.[14] Olliaro and colleagues [16] remind us that NNTV ranges between 78 and 119 for the regulatory trials and 217 for a naturalistic study like the one by Dagan and colleagues outside a trial, thus confirming indirectly our choice of the main database. This absolute effectiveness must be compared to the costs of an intervention. Apart from the economic costs, there is a comparatively high rate of reported side-effects and a comparatively high rate of reported fatalities, as our analysis shows. The current figure is around 4 fatalities reported per 100,000 vaccinations, as documented by the Dutch side-effects register Lareb. This is in agreement with a recently conducted analysis of the US Vaccine Adverse Reactions Reporting System, which found 3.4 fatalities reported per 100,000 vaccinations, mostly with Comirnaty (Pfizer) and Moderna vaccines.[22]

Is this few or many? The answer to this question is dependent on one's view of how severe the pandemic is and whether it is true that there is hardly any innate immunological defense or cross-reactional immunity. Some argue that we can

22 https://sciblogs.co.nz/diplomaticimmunity/2021/07/03/fundamentally-flawed-study-on-covid-19-vaccine-safety-is-rapidly-retracted/; accessed July 30th, 2021.

assume cross-reactivity of antibodies to conventional coronaviruses in 30% to 81% of the population.[23–27] An innate immune reaction is difficult to gauge. Thus, low sero-prevalence figures [18, 28, 29] may not only reflect a lack of herd immunity but also a mix of undetected cross-reactivity of antibodies or T-cell immunity to other coronaviruses, as well as clearing of infection by innate immunity. Thus, since natural immunity is present, the necessity to induce sub-optimal immunity via vaccination becomes less urgent. It might be worthwhile to study the prevalence of cross-immunity mediated by T-cells more widely.

The study which we used to gauge the NNTV is a single field study with too short an observation time, even though it is the largest to date. The other data stem from regulatory trials that are not designed to detect maximum effects. The field study is somewhat specific to the situation in Israel, and studies in other countries and other populations or other post-marketing surveillance studies might reveal more beneficial clinical effect sizes, when the prevalence of the infection is higher. Some of the cases from the field study were omitted, presumably due to a loss to follow-up. However, the regulatory studies compensate for some of the weaknesses and thereby generate a somewhat more beneficial risk-benefit ratio.

The time-frame of this study, as well as that of regulatory phase 3 trials, is short. One could argue that this study did not provide data for death as an outcome after the second vaccination but only after the first. However, if we use the outcome data after the second vaccination as a proxy, which is hospitalization, there we see no difference between the absolute risk difference after the first and the second vaccination (data only in the original Table of Dagan et al. [10]).) Obvious side-effects captured by ADR reporting systems occur relatively quickly after a vaccination in most cases. The analysis of the US VAERS database found that 70% of all individuals reported had an onset of the ADR 48 hours after the first dose.[22] As Seneff & Nigh [30] show, potential late toxicities are also important but won't be captured by the reporting systems. Hence, what we refer to are short-term negative effects reported after COVID-19 vaccinations. Supporters of such vaccinations would argue that such vaccinations would only show their benefit over time. Hence, ideally, a long-term study with large numbers and an observation period of 6 months or longer to gauge clinical effectiveness would be needed and should have been initiated. The data we used, limited as they are, are what is currently available.

The ADR database of the EMA collects reports made by doctors, patients and authorities. We have seen (Figure 1) that the reporting standards vary hugely across countries. It might be necessary for the EMA and for national governments to install better monitoring procedures to generate more reliable data. Some countries have tight reporting schemes; some report in a rather loose fashion. As we must assume that the average number of side-effects is roughly similar across countries, we would expect similar reporting quota. However, upon inspection of the reports according to country, we see a large variance. Our decision to use the Dutch data as proxy for Europe was derived from that discovery. One might want to challenge this decision. But we do not see that data from other countries are more valid in terms of more diligent monitoring and confirmation than the ones we use here. Apart from this, our findings correspond to previously published findings,[22] which indirectly provides validation of our method.

We emphasize that we are dealing with associations that, ideally, would have to be investigated carefully for causal links using established methodologies such as the Bradford-Hill Criteria.[31, 32] However, the Dutch data are checked by investigators. All reports received are checked for completeness and possible ambiguities. If necessary, additional information is requested

from the reporting party and/or the treating doctor. The report is entered into the database with all the necessary information. Side-effects are coded according to the applicable (international) standards. Subsequently, an individual assessment of the report is made. The reports are forwarded to the European database (Eudravigilance) and the database of the WHO Collaborating Centre for International Drug Monitoring in Uppsala. The registration holders are informed about the reports concerning their product.[23] The head of pharmacovigilance of Lareb also stated that 58% of the reports in the Dutch register stem from market authorization holders; i.e. from companies which are required by law to forward suspicions of product-related side-effects and fatalities.[24] Thus, although direct causality cannot be inferred from these databases, strong associations are possible. It is important to note: The burden of proof is not on those who doubt the safety of the vaccine but on those who proclaim its safety. Our data cast doubt on that claim. Although this doubt is far from incontrovertible, considering the short time-frame of the data we used, it is strong enough, we contend, to be taken seriously.

In addition, there is mechanistic evidence supporting a causal link between vaccinations and reported side-effects. A recent experimental study showed that the SARS-CoV-2 spike protein is sufficient to produce endothelial damage.[33] This provides a potential causal rationale for the most serious and most frequent side-effects, namely vascular problems such as thrombotic events. The vector-based COVID-19 vaccines can produce soluble spike proteins, which multiply the potential damage sites.[34] The spike protein also contains domains that may bind to cholinergic receptors, thereby compromising the cholinergic anti-inflammatory pathways, enhancing inflammatory processes.[35] Lyons-Weiler demonstrated that most SARS-CoV-2 proteins, including the spike protein, showed more or less homology to human proteins, potentially leading to immunological priming and autoimmune reactions against self-antigens after vaccination.[36] Finally, a recent review lists several other potential side-effects of COVID-19 mRNA vaccines that may also emerge later than in the observation periods covered here.[30]

In the Israeli field study, the observation period was six weeks, and in the US regulatory studies, four to six weeks. Such periods are commonly assumed to be sufficient to see a clinical effect of a vaccine, because it would also be the time-frame within which someone who was infected initially would also fall ill and perhaps die. Had the observation period been longer, the clinical effect size could have increased; i.e. the NNTV would have become lower and consequently the ratio of benefit to harm would have increased in favor of the vaccines. However, as noted above, there is also the possibility of side-effects developing with some delay and influencing the risk-benefit ratio in the opposite direction.[30] This should be studied more systematically in a long-term observational study.

Another point to consider is that initially mainly older persons and those at risk were entered into the national vaccination programs. It is to be hoped that the tally of reported fatalities associated with the vaccinations becomes lower as the age of those vaccinated decreases.

Given the data, we should act now and use the data available to study who might be at risk of suffering side-effects from COVID-19 vaccinations. Careful safety monitoring needs to be put in place, together with a dedicated large-scale cohort study in which vaccinated individuals are followed up by medical specialists for a longer period, all complaints about side-effects are carefully

23 https://www.lareb.nl/media/eacjg2eq/beleidsplan-2015-2019.pdf, p. 13; accessed June 22nd, 2021.
24 https://www.regulatoryscience.nl/editions/2021/12/prof.-dr.-eugene-van-puijenbroek-on-the-nature-of-signals; accessed 29th June 2021.

investigated, and all fatalities undergo autopsy to verify causes of side-effects and deaths.

Finally, we note that experience with side-effects reporting from other drugs has shown that only a small fraction of side-effects is reported to adverse events databases.[37, 38] The median underreporting can be as high as 95%.[12]

5 Conclusion

The present assessment raises the question of whether it could be necessary to rethink vaccination policies. Given the high number of serious side-effects already reported, the current political trend of vaccinating children who are at very low risk of suffering from COVID-19 in the first place must be reconsidered. It is also vital that these products be made accessible only to those who are willing to use them and to accept potential risks that come with the products. In our view, the EMA and national authorities should begin a review into the safety database of COVID-19 vaccines, and governments should carefully re-consider their policies in the light of these data. Ideally, independent scientists should be permitted to carry out thorough case reviews of the very severe cases, so that there can be evidence-based recommendations on who is likely to benefit from a SARS-CoV-2 vaccination and who is in danger of suffering from side effects. In addition, because SARS-CoV-2 is a BSL2 pathogen, autopsies should be carried out on every body. Currently, our estimates show that we must accept 4 reports of fatal and 16 reports of serious side effect per 100,000 vaccinations in order to save the lives of 8 to 33 people. Bluntly, we would have to accept that 2 people might die to save the lives of three to 15 people. This ratio might improve as more time after vaccination passes, but this needs to be studied diligently.

6 References

1 Arvay CG. Genetische Impfstoffe gegen COVID-19: Hoffnung oder Risiko. *Schweizerische Ärztezeitung*. 2020;101(2728):862–4.

2 Doshi P. Covid-19 vaccines: In the rush for regulatory approval, do we need more data? *BMJ*. 2021;373:n1244.

3 Lamb YN. BNT162b2 mRNA COVID-19 Vaccine: First approval. *Drugs*. 2021;81(4): 495–501.

4 Food and Drug Administration. Fact Sheet for Healthcare Providers Administering Vaccine: Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19). Washington: Food and Drug Administration; 2021.

5 Pilkington EH, Suys EJA, Trevaskis NL, Wheatley AK, Zukancic D, Algarni A, et al. From influenza to COVID-19: Lipid nanoparticle mRNA vaccines at the frontiers of infectious diseases. *Acta Biomaterialia*. 2021; in print.

6 Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): A single-blind, randomised, controlled, phase 2/3 trial. *Lancet*. 2020;396(10267):1979–93.

7 Walsh EE, Frenck RW, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and Immunogenicity of two RNA-Based Covid-19 vaccine candidates. *New England Journal of Medicine*. 2020;383:2493–50.

8 Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *New England Journal of Medicine*. 2020;383(27):2603–15.

9 Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *New England Journal of Medicine*. 2020;384(5): 403–16.

10 Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *New England Journal of Medicine*. 2021;384:1412–23.

11 Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: An interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet*. 2021;397(10275):671–81.

12 Hazell L, Shakri SAW. Under-reporting of adverse drug reactions: A systematic review. *Drug Safety*. 2006;29(5):385–96.

13 Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: A preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet*. 2020;396(10249):467–78.

14 Cunningham AS. Rapid response: Covid-19 vaccine candidate is unimpressive: NNTV is around 256. *BMJ*. 2020;371:m4347. Non-peer-reviewed comment.

15 Klement RJ, Bandyopadhyay PS. The Epistemology of a Positive SARS-CoV-2 Test. *Acta Biotheoretica*. 2020(Sept 4):1–17.

16 Olliaro P, Torreele E, Vaillant M. COVID-19 vaccine efficacy and effectiveness – the elephant (not) in the room. *Lancet Microbe*. 2021;2(7):e279–e80.

17 Ioannidis JPA, Axfors C, Contopoulos-Ioannidis DG. Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters. *Environmental Research*. 2020;188:109890.

18 Ioannidis J. The infection fatality rate of COVID-19 inferred from seroprevalence data. *Bulletin of the World Health Organization*. 2021;99:19–33F.

19 Ioannidis JPA. Reconciling estimates of global spread and infection fatality rates of COVID-19: An overview of systematic evaluations. *European Journal of Clinical Investigation*. 2021;51:e13554.

20 Ioannidis JPA. Coronavirus disease 2019: the harms of exaggerated information and non-evidence-based measures. *European Journal of Clinical Investigation*. 2020;50(4):e13222.

21 van Doremalen N, Lambe T, Spencer A, Belij-Rammerstorfer S, Purushotham JN, Port JR, et al. ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. *bioRxiv*. 2020:2020.05.13.093195.

22 Rose J. A report on the U.S. Vaccine Adverse Events Reporting System (VAERS) on the Covid-19 messenger ribonucleic acid (mRNA) biologicals. *Science, Public Health Policy, and the Law*. 2021;2:59–80.

23 Edridge AW, Kaczorowska JM, Hoste AC, Bakker M, Klein M, Jebbink MF, et al. Human coronavirus reinfection dynamics: Lessons for SARS-CoV-2. *medRxiv*. 2020:2020.05.11. 20086439. Non-peer-reviewed preprint.

24 Havers FP, Reed C, Lim T, Montgomery JM, Klena JD, Hall AJ, et al. Seroprevalence of antibodies to SARS-CoV-2 in 10 sites in the United States, March 23–May 12, 2020. *JAMA Internal Medicine*. 2020;180(12):1576–86.

25 Mateus J, Grifoni A, Tarke A, Sidney J, Ramirez SI, Dan JM, et al. Selective and cross-reactive SARS-CoV-2 T cell epitopes in

unexposed humans. *Science*. 2020;370(6512): 89–94.

26 Doshi P. Covid-19: Do many people have pre-existing immunity? *BMJ*. 2020;370:m3563.

27 Nelde A, Bilich T, Heitmann JS, Maringer Y, Salih HR, Roerden M, et al. SARS-CoV-2-derived peptides define heterologous and COVID-19-induced T cell recognition. *Nature immunology*. 2021;22(1):74–85.

28 Lorent D, Nowak R, Roxo C, Lenartowicz E, Makarewicz A, Zaremba B, et al. Prevalence of anti-SARS-CoV-2 antibodies in Poznań, Poland, after the first wave of the COVID-19 pandemic. *Vaccines*. 2021;9(6):541.

29 Bendavid E, Mulaney B, Sood N, Shah S, Ling E, Bromley-Dulfano R, et al. COVID-19 antibody seroprevalence in Santa Clara County, California. *International Journal of Epidemiology*. 2021;50(2):410–9.

30 Seneff S, Nigh G. Worse than the disease? Reviewing some possible unintended consequences of the mRNA vaccines against COVID-19. *International Journal of Vaccine Theory, Practice, and Research*. 2021;2(1):38–79.

31 Rawlins M. What constitutes credible evidence? London: Office of Health Economics; 2013.

32 Glasziou P. When are randomised trials unnecessary? Picking signal from noise. *BMJ*. 2007;334:349–51.

33 Lei Y, Zhang J, Schiavon Cara R, He M, Chen L, Shen H, et al. SARS-CoV-2 spike protein impairs endothelial function via downregulation of ACE 2. *Circulation Research*. 2021;128(9): 1323–6.

34 Kowarz E, Krutzke L, Reis J, Bracharz S, Kochanek S, Marschalek R. "Vaccine-Induced Covid-19 Mimicry" Syndrome: Splice reactions within the SARS-CoV-2 Spike open reading frame result in Spike protein variants that may cause thromboembolic events in patients immunized with vector-based vaccines. *Research Square*. 2021. Non-peer-reviewed preprint.

35 Farsalinos K, Eliopoulos E, Leonidas DD, Papadopoulos GE, Tzartos S, Poulas K. Nicotinic cholinergic system and COVID-19: In silico identification of an interaction between SARS-CoV-2 and nicotinic receptors with potential therapeutic targeting implications. *International Journal of Molecular Sciences*. 2020;21(16):5807.

36 Lyons-Weiler J. Pathogenic priming likely contributes to serious and critical illness and mortality in COVID-19 via autoimmunity. *Journal of Translational Autoimmunity*. 2020; 3:100051.

37 Alatawi YM, Hansen RA. Empirical estimation of under-reporting in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS). *Expert Opinion on Drug Safety*. 2017;16(7):761–7.

38 Moore TJ, Bennett CL. Underreporting of hemorrhagic and thrombotic complications of pharmaceuticals to the U.S. Food and Drug Administration: Empirical findings for Warfarin, Clopidogrel, Ticlopidine, and Thalidomide from the Southern Network on Adverse Reactions (SONAR). *Semin Thromb Hemost*. 2012;38(08):905–7.

7 Author statements

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Rainer J Klement, PhD, checked analysis for correctness and contributed to the writing.

Wouter Aukema analyzed COVID-19 vaccination volumes reported by ECDC and the ICSR reports from EMA and produced graphs.

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