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EDITORIAL

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COVID-19 vaccines: the importance of transparency and fact-based education

When one or more of the 160+[1] vaccines for the SARS-CoV-2 virus currently under development are shown to be sufficiently safe and effective, the largest vaccination campaign ever will hopefully contribute to extract the world from its current crisis. This will take place in the midst of rising vaccine hesitancy sentiments in many parts of the world, and will, in addition, engraft its own challenges due to what has been called vaccine development at pandemic speed.[2] If transparency was key for public trust in the 'old normality', it becomes more relevant when confronted with this unprecedented paradigm in vaccine development.

Vaccine development is always the establishment of a link between *working* (a neutralizing antibody response or specific T cell development) and *helping* (the prevention of a disease in a population base with an acceptable safety profile). Although the standards for benefit and risks are the same as for all medicines, the routes for development and assessment will however be stretched to the limit in view of the public health emergency we are facing. SARS-CoV-2 has already killed more humans than HIV and measles together this year[3,4] and produced economic and societal damage that will cause negative effects for years to come, also for worldwide public health.

The enormity of the crisis has also led to an extraordinary effort to find treatments, ranging from immunomodulators, antivirals and hyperimmune serums. These include success to date with dexamethasone[5] and remdesivir,[6] which are now widely used in clinical practice in COVID-19 patients 6 months after discovery of the disease.

Preventing disease and community spread via mass vaccination is generally assumed to be the best way out of the crisis and this realization has led to more than 160[1] vaccines being developed in parallel. Several published papers report that some of these vaccines have now been shown to work in preclinical and early phase clinical trials[7–9] with regard to neutralizing antibody formation and protection against induced disease in animals. If confirmed by regulatory assessment, this would, in itself, be a major accomplishment especially as this rapid development process has to be in line with guidelines for vaccine development.[10–12] Trials to evaluate vaccines' safety and efficacy are ongoing, performed under a level of public scrutiny that is understandably beyond the usual public interest for drug development. This puts severe stress on a system that previously proceeded at a much steadier rate.

There have been many voices underlining the importance of only releasing vaccines when they are proven to be effective and safe. However, an important nuance is what is meant by 'safe' and how this is perceived by the public, who often assume that 'safe' implies no side effects at all. The difficulty in conveying messages around vaccines' benefits and risks is a fact, and general statements without qualification or proper explanation do not help. Thus, it is particularly important to increase the public understanding that risks are inherent to all medicines, and that no vaccine is 100% effective in preventing a disease or 100% safe in all vaccinated people; despite that, we need to build public understanding and consensus that the benefits of vaccines are unquestionable when one considers, for example, that they made the eradication of smallpox possible, and have almost completely achieved this for polio.

Trials (in about 30–50,000 volunteers) are unable to detect certain vaccine-related adverse drug reactions (ADR) that are very rare but serious. The common adverse reactions to vaccines (occurring in about 1 in 100 people) are mostly local, well known and short-lived. Side effects should not be regarded as synonymous with adverse event or adverse reaction, an event which occurs after treatment and which may be an intercurrent event/illness, related to a pre-existing condition or an adverse drug reaction. Adverse events are rare post vaccination and the causal relationship to vaccination can be difficult, if not impossible, to determine. These events can all occur spontaneously also in unvaccinated people and can therefore be coincidental and the only way this can be determined in clinical trials is by a statistically reliable assessment of the number of events following vaccination versus the number of events in a similar non-vaccinated population. This is unlikely at the expected incidences of the events and the size of the Phase III trials.

The first news of a relevant adverse effect during a COVID-19 vaccine trial occurred in early September 2020, when all global trials with a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19 or AZD 1222)[13] were temporarily paused because of a neurological adverse effect that was disclosed by the media as transverse myelitis. This produced headlines all over the globe, after which trials in some countries were restarted without a clear explanation from the sponsors on why. Communications were sparse and left the scientific community and the general public behind, uninformed and confused about the nature of the event and why this caused the trial to be first stopped and then rapidly resumed.

Transverse myelitis and immune-mediated polyneuropathies (Guillain-Barré syndrome) have been associated to vaccination. Both are rare diseases, with respective incidences in the general population of around 1–5 and 11–18 per million per year. With such low incidences, hundreds of thousands of observations would be required to

detect modestly increased risks after vaccination. There are examples where Guillain Barre is listed in the EU prescribing information as adverse events detected post-marketing, but frequency cannot be estimated from the available post-marketing data.[14] Post-vaccination auto-immune events are plausible as they also occur after infections and Guillain-Barré syndrome has been described after the COVID-19 outbreak in Italy.[15] In addition, demonstration of causality can be a prolonged investigation for extended periods as has been shown for the possible association between the vaccine for H1N1 influenza and narcolepsy in Scandinavian countries in 2009.[16]

With this knowledge, the occurrence of a very rare adverse event at this stage, such as of transverse myelitis is not entirely unexpected and cannot be attributed with any confidence to the vaccine; the question is when an adverse event is enough reason to stop enrollment. Interrupting a trial would be warranted if the event could change the risk–benefit balance of the trial for other participants, should it be found to be related to the vaccination. In such a case, it may be necessary to (temporarily) interrupt the trial to analyze the event further, to obtain more certainty about the causality or to introduce additional measures to examine or deal with this possibility, or mitigate its risks in future trial participants. Most adverse events are rapidly understood to be in line with the drug's mechanism of action or to be more likely attributable to chance or to underlying disease or other associated conditions. Incidental cases of adverse events that can also occur spontaneously will rarely lead to unexpected interruptions, because their causality to the vaccination can only be resolved by comparison of the incidence in the control group and the treated group. Like in any trial, the number of cases must be sufficiently high to take a decision. For such situations, independent data safety monitoring committees are in place, which have frequent access to unblinded data, and can make decisions *in camera* to avoid unblinding the study to researchers and others and to prevent uncoordinated communication.

There are however compelling reasons to be transparent about the adverse effects of new vaccines. Several COVID-19 vaccines that are currently in development also make use of an adenoviral vector, and serious unexpected reactions that occur with one vaccine could also be relevant for other agents in the same class. Moreover, an analysis of the aggregate of side effects in the adenoviral vector population versus the RNA vaccines could be of scientific interest. Such information is currently considered proprietary by the different companies and unlikely to be shared. We conclude that timely and effective communication and transparent handling of cases like this single event, is essential to reinforce the level of trust in the system.

At the current development speed, it is expected that first mass vaccination can start in the coming months, in some parts of the world. The success of this vaccination campaign in ultimately billions of people across the globe will be fully dependent on trust. Transparency and clear information from regulatory authorities and pharmaceutical companies on COVID-19 vaccine development, approval and safety monitoring will be pivotal in enabling such trust.

Whatever happens, the medical and scientific community will also be required to inform patients and the general public, and the message must be consistent and informed. Good information materials and educational programs for the general public should start as soon as possible. In parallel the scientific community will need to be well informed to be able to maintain the trust that is an essential component of a vaccine that helps by strongly reducing the incidence of disease without serious safety issues rather than **works** by producing an immune response. Even if a vaccine works **and** helps it can only be of value when the uptake of the vaccine in the general population is sufficiently high. Many younger people will have a low risk of dying from a COVID-19 infection, of about 1:10,000 to about 1: 100,000[17] and therefore clear, truthful and proactive representation of the possibility of serious complications that may or not be causally related or coincidental is essential.

In this context EU regulators are taking a step further in increasing the level of transparency for COVID-19 medicines. In particular for all COVID-19 medicines, the European Medicines Agency (EMA) will publish the full product information with details of the conditions of use once the scientific opinion is adopted, even before the formal marketing authorisation is granted. In addition, the publication of the full EPAR (European Public Assessment Report) will be made available within 3 days of authorisation by the European Commission. Furthermore, all clinical data submitted to EMA in support of applications for COVID-19 medicines, as well as the full risk management plan after assessment by the EMA's scientific committees and the subsequent Commission Decision will be published. However, such scientific and regulatory transparency does not automatically translate to public confidence and a much broader educational effort is necessary.

It is with this intention of enhancing transparency around COVID-19 vaccines and on safety on particular, that academics and regulators in Europe call for the following actions to be taken urgently in line with other recent calls for action.[18] We therefore reiterate to all parties, including private companies, regulators and other governmental and non-governmental organizations the importance of voluntarily complying with the actions below. Although two companies (Moderna and Pfizer) have released their Phase III protocols as of September 18th many others still have to follow, and this should, in our opinion, be routine.

1. Full public release of non-clinical data and protocols for trials with COVID-19 vaccine trials at the start of these trials.
2. Proactive public explanation of serious adverse events that lead to temporary halt and after review where appropriate resumption of studies, or explanation for early termination of the studies.
3. Establishment of data safety monitoring committees for all Phase III trials operating under identical charters and with the requirement to have confidential access to unblinded data when required. The data safety monitoring committees should have standardized protocols about what to share with regulators and the public.
4. Urgently establishing a comprehensive program for education of the general public about how vaccines work, risks in relation to benefits for the individual and society, the possibility of coincident adverse events, and the *a priori* limitations of establishing causality. This program must be established by a task force of regulatory and

social scientists, media and educational experts and make use of all modern and traditional communication channels and should be established as a matter of the utmost urgency. Listening to people's concerns will be fundamental to any successful approach,[19] including thorough engagement with the general public, intended recipients of the vaccine, consumers and healthcare professionals in discussions on COVID-19 vaccines.

Increased transparency by all parties (academic institutions, regulators, commercial participants and governments) will support and make global research more efficient and allow public scrutiny and independent review by academics, medical and public health authorities. Ultimately every effort to open up data to public scrutiny will attract people to the right sources of information and help increase vaccine science literacy, rather than leaving a void where obscure theories can propagate.

In a 2019 paper, describing adverse events after the influenza H1N1 pandemic vaccination, Edwards et al conclude.[16]

> *"..one of the lessons learned from the 2009 pandemic was that there is a need for an internationally coordinated vaccine safety infrastructure so that the safety of pandemic vaccines, which are rapidly deployed in large numbers, can be rapidly evaluated. We know another pandemic is coming, but we do not know when."*

The challenge of dealing with the medical complications of the current pandemic are not over, but as (academic) clinicians, regulators and scientists we have a duty to inform and teach in addition to care and hopefully prevent as well as cure.

COMPETING INTERESTS

There are no competing interests to declare.

Adam F. Cohen[1]
Joop van Gerven[2,3]
Juan Garcia Burgos[4]
Anthonius de Boer[5]
Ron A. M. Foucher[6]
H. Flore[7]
Zvi Teitelbaum[8]
Willem van Eden[9,10]
Andrew Webb[11]
Serge Cremers[12]

[1]*Centre for Human Drug Research (CHDR), Leiden, The Netherlands*
[2]*Central Committee for Human Research (CCMO) and Competent Trial Authority of The Netherlands, The Hague, The Netherlands*
[3]*Faculty of Medicine, Division of Neurology, Leiden University, Leiden, The Netherlands*
[4]*Stakeholders and Public Engagement Department, European Medicines Agency, Amsterdam, The Netherlands*
[5]*Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands*
[6]*Department of Viroscience, Erasmus Medical Center, Rotterdam, The Netherlands*
[7]*HAL Allergy Group, Leiden, The Netherlands*
[8]*Section of Clinical Pharmacology and Toxicology, Rambam Health Care Campus, Haifa, Israel*
[9]*Faculty of Veterinary Medicine, Department of Biomolecular Health Sciences - Infectious Diseases & Immunology, Utrecht University, Utrecht, The Netherlands*
[10]*CSO Trajectum Pharma, Utrecht, The Netherlands*
[11]*Faculty of Life Sciences & Medicine, Department of Vascular Risk & Surgery, King's College London, London, UK*
[12]*Department of Pathology & Cell Biology, Division of Laboratory Medicine, Columbia University, New York*

Correspondence
Adam F. Cohen, Centre for Human Drug Research (CHDR), Leiden, The Netherlands.
Email: ac@chdr.nl

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REFERENCES

1. WHO. The push for a COVID-19 vaccine. 2020.
2. Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 vaccines at pandemic speed. *N Engl J Med*. 2020;382(21):1969-1973.
3. WHO. Fact sheet HIV/AIDS. 2020.
4. WHO. Measles Fact Sheet. 2020.
5. Eurpean Medicines Agency. EMA endorses use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation. Web page. 2020.
6. European Medicines Agency. Veklury. EPAR. 2020.
7. Mercado NB, Zahn R, Wegmann F, et al. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. *Nature*. 2020. http://www.nature.com/articles/s41586-020-2607-z
8. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2 — preliminary report. *N Engl J Med*. 2020. https://doi.org/10.1056/nejmoa2022483
9. Zhu F-C, Li Y-H, Guan X-H, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. *Lancet*. 2020;6736(20):1-10. https://linkinghub.elsevier.com/retrieve/pii/S0140673620312083
10. FDA, U.S. Department of Health and Human Services., Food and Drug Administration. Development and Licensure of Vaccines to Prevent COVID-19 Guidance for Industry - FDA Guidance for Industry. 2020;24. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19
11. European Medicines Agency. Guideline on clinical evaluation of vaccines. EMA Guidelines. 2018 Oct.

12. WHO Technical Report, Series No. 924 2004. Annex 1 Guidelines on clinical evaluation of vaccines: 2004;(924):35–102.
13. Folegatti PM, Ewer KJ, Aley PK, 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):467-478.
14. European Medicines Agency. Product information Gardasil [Internet]. EPAR Gardasil. https://www.ema.europa.eu/en/documents/product-information/gardasil-epar-product-information_en.pdf
15. Toscano G, Palmerini F, Ravaglia S, et al. Guillain-Barré syndrome associated with SARS-CoV-2. *N Engl J Med*. 2020;382(26):2574-2577.
16. Edwards K, Lambert PH, Black S. Narcolepsy and pandemic influenza vaccination: what we need to know to be ready for the next pandemic. *Pediatr Infect Dis J*. 2019;38(8):873-876.
17. Levin AT, Cochran KB, Walsh SP. Assessing the Age Specificity of Infection Fatality Rates for COVID-19: Meta-Analysis & Public Policy Implications. medRxiv. 2020;2020.07.23.20160895. https://www.medrxiv.org/content/10.1101/2020.07.23.20160895v1%0Ahttps://www.medrxiv.org/content/10.1101/2020.07.23.20160895v1.abstract
18. Bloom BR, Nowak GJ, Orenstein W. "When will we have a vaccine?" — understanding questions and answers about Covid-19 vaccination. *N Engl J Med*. 2020;1969–73. https://www.nejm.org/doi/full/10.1056/NEJMp2025331
19. Larson HJ. The biggest pandemic risk? Viral misinformation. *Nature*. 2018;562(7727):309. https://doi.org/10.1038/d41586-018-07034-4