Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Vaccine 39 (2021) 3025–3027

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

Developing standard safety outcomes for COVID-19 vaccines

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ARTICLE INFO

Article history:
Received 21 February 2021
Received in revised form 1 March 2021
Accepted 2 March 2021
Available online 12 March 2021

Keywords:
Vaccine safety
COVID-19 vaccines
Surveillance
Standards
Pharmacovigilance

The rapid development of COVID-19 vaccines has resulted in the implementation of multiple vaccines with different approaches. The unprecedented pace of development and implementation is broadly considered the best hope in reducing the human, social and economic devastation of COVID-19. However, this welcome speed brings its own challenges. In an era where vaccine hesitancy is a major threat to public health, and confidence in vaccines is linked to perception of vaccine safety, we are trialling and introducing different vaccine designs and regimens, in a myriad of settings [1–3]. This is in conjunction with reduced times for trial follow-up post-immunisation and the use of post-implementation safety surveillance programs to monitor real-world safety.

Never has it been so important to know that potential adverse events following immunisation (AEFI) are being consistently described and defined between different trials, nations, and levels of health care delivery. Achieving this consistency allows an "apples with apples" comparison, providing confidence AEFIs mean the same in all settings [4–6].

This issue contains papers that propose international consensus case definitions for three important adverse events of special interest (AESI) for COVID-19 vaccines. These are Vaccine Associated Enhanced Disease (VAED), Adult Respiratory Distress Syndrome (ARDS), and Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A) [7–9]. All remain potential AEFI that may be observed following COVID-19 vaccination, despite no reported cases to date in clinical trials. All revolve around the theoretical possibility that COVID-19 vaccination may predispose some individuals to a more severe manifestation of SARS-CoV-2 infection than if they had never been vaccinated. These concerns are based upon historical lessons, and experience from early non-SARS-CoV-2 coronavirus vaccines in animal models [10]. Lessons learned were incorporated into the design and safety testing of current COVID-19 vaccine candidates.

VAED was first observed following randomised trials of an inactivated respiratory syncytial virus (RSV) vaccine more than 5 decades ago [10–13]. These sobering human trials resulted in pediatric RSV vaccine recipients who were seronegative prior to vaccination developing more severe disease when they subsequently experienced natural RSV infection. Two children died from RSV disease. Since then, clinical evidence of VAED has been observed in some recipients following an inactivated measles vaccine, a live-recombinant tetravalent dengue vaccine, and histologic evidence in animal models following SARS-CoV-1 and Middle Eastern Respiratory Syndrome (MERS) coronavirus vaccines [10]. An additional, poorly understood example of enhanced acquisition of infection was also observed with an adenovirus 5 vectored HIV vaccine, with infected recipients also appearing to progress to disease faster [14].

Factors associated with VAED have been: non-neutralising antibodies; a T-helper 2 (T_H2) biased immune response; and, post-fusion target protein conformation. Mechanisms include poorly neutralising antibody increasing viral entry into cells, immune

DOI of original article: https://doi.org/10.1016/j.vaccine.2021.01.054https://doi.org/10.1016/j.vaccine.2021.01.053https://doi.org/10.1016/j.vaccine.2021.01.055
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https://doi.org/10.1016/j.vaccine.2021.03.004

complex formation with complement activation, and T_H2 cytokines with allergic inflammation [7,10]. In response newly developed COVID-19 vaccines aim to induce high levels of neutralising antibodies, and cellular immune responses that demonstrate a T_H1 bias [15–18].

The other case definitions, Adult Respiratory Distress Syndrome (ARDS) and Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A) have been observed with COVID-19 disease and represent severe endpoints of enhanced disease. Both involve complex interplays between immune responses and inflammatory responses. ARDS may be a presentation of vaccine associated enhanced respiratory disease (VAERD) while MIS-C/A typically occurs weeks after primary infection with SARS-CoV-2 [19,20]. ARDS has traditionally been described as having two phenotypes, based upon the systemic inflammation observed (hyperinflammatory and hypoinflammatory), while MIS-C/A present following an initial febrile illness with mucosal symptoms (especially gastrointestinal) and a hyperinflammatory state [19,21].

These case definitions have been developed by the international Brighton Collaboration network, established in 2000 to help standardise assessment of vaccine safety [4]. This was in recognition that multiple varying definitions of the same AEFI were being used across different trials of similar vaccines, making comparison difficult. They have become the standard choice for vaccine development clinical trials globally. The fundamental strength of the approach is to allocate levels of confidence that the AEFI the patient has experienced is truly the condition diagnosed (akin to categorising by definite/probable/possible etc). Increased clinical and investigational detail increases the probability that confidence can be allocated to the highest level, level 1, a designation of the degree of confidence the episode represents the AEFI of interest. However, for many case definitions, this causes challenges for clinical trials conducted in resource poor settings, and in post-marketing surveillance, where access to detailed information is less frequently available [22]. The groups convened by the Coalition for Epidemic Preparedness Innovations (CEPI) for these three case definitions include pharmacovigilance, immunological, and epidemiological experts, and clinicians experienced in developed and developing settings. This approach maximises the potential applicability of the case definitions.

The COVID-19 vaccines currently being implemented presented clinical trial data up to 2 months following the final dose. Well conducted phase 3 trials such as the Pfizer BioNTech and Moderna mRNA COVID-19 vaccines, and the Janssen adenovirus-vectored vaccine have statistical power to detect adverse events occurring more frequently than 1 in 5000 doses [23]. Due to the global need to rapidly implement successful vaccine candidates, less frequent AEFI such as anaphylaxis will primarily be detected by post-licensure surveillance, as has already been the case with episodes reported to the US Vaccine Adverse Event Reporting System (VAERS), utilising the pre-existing Brighton Collaboration case definition [5,24,25]. Similarly, the safety profile in populations not involved in the clinical trials, such as frail elderly with multiple comorbidities, pregnant and lactating women, and immunosuppressed patients, is likely to be first elicited from post-implementation studies.

These new case definitions are integral in ensuring ongoing confidence in COVID-19 immunisation programs globally. Vaccine confidence in health care workers and communities is consistently linked to perceptions of safety of vaccines [1,2]. The VAED case definition will be critical to ensure that potentially severe episodes observed in varying settings can be potentially combined to maximise the chance of detecting or refuting VAED as a real concern for multitude of COVID-19 vaccines of differing designs. These include novel designs for human vaccinology, such as the mRNA vaccines already implemented [18].

ARDS, the most common serious complication of COVID-19 disease, will also continue to occur due to non-SARS-CoV-2 causes, including in vaccinated individuals [8]. This new case definition utilises existing internationally accepted definitions in adults (the Berlin Definition 2012) and children (PALICC Definition 2015), but introduces alternative criteria to allow incorporation of lower levels of confidence [26–28]. VAED may share clinical features with ARDS, especially vaccine associated enhanced respiratory disease (VAERD), however, unlike the VAED case definition, the ARDS definition does not require evidence of SARS-CoV-2 infection [7,8].

Similarly, acute inflammatory conditions of children and adults, including Kawasaki disease, will occur in some who have been vaccinated. Unlike VAED and ARDS, MISC-C/A appears to be a novel syndrome [9]. First described in April 2020 in the UK, MISC-C has since been described globally wherever SARS-CoV-2 has been circulating. MISC-C is an uncommon but serious post-infectious complication, with reports typically 4–6 weeks after peaks of COVID-19 infections in the same population, and most patients having detectable IgG against SARS-CoV-2 [19,20]. Clinically, some features are shared with Kawasaki disease, a childhood syndrome characterised by a febrile illness, clinical inflammatory manifestations involving skin, eye and mouth mucosae, cervical lymph nodes and the periphery [29]. The systemic vasculitis of Kawasaki disease may also affect cardiac vessels, with coronary artery aneurysms a principal complication [30]. The etiology of Kawasaki disease remains elusive despite nearly 5 decades of investigation, with coronaviruses among the many organisms proposed as precipitants, but without consistent evidence to support this association [31]. MISC-C/A shares clinical and laboratory features with Kawasaki disease, especially the more severe subset Kawasaki shock syndrome, but also has some distinct manifestations, including abdominal symptoms being predominant in comparison with Kawasaki disease. MISC-C/A requires a separate case definition, not least to avoid Kawasaki cases being labelled as MISC-C/A. Neither condition has a specific diagnostic test, and both share the possibility of coronary artery aneurysms as a manifestation of their systemic inflammatory processes [9]. MISC-C/A has yet to be reported in the overwhelmingly adult clinical trial or post-implementation COVID-19 vaccine recipients.

Although widely utilised case definitions exist already for ARDS and MISC-C, the need to capture and categorise as many potential AEFI cases as possible renders the Brighton Collaboration approach incorporating levels of confidence necessary. This will maximise the chance, across geographic settings where COVID-19 vaccines are being utilized, to ascertain and report these potential AEFI. This is vitally important, both to protect populations where vaccines are being implemented, and to maximise confidence that despite offering overwhelming benefit, risks are being looked for comprehensively.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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