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Review Article

A systemic review and recommendation for an autopsy approach to death followed the COVID-19 vaccination

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Abstract

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in December 2019. An immediate prevention approach for the outbreak is the development of a vaccination program. Despite a growing number of publications showing the effectiveness of vaccination in preventing SARS-CoV-2 outbreak and reducing the mortality rate, substantial fatal adverse effects were reported after vaccination. Confirmation of the causal relationship of death is required to reimburse under the national vaccination program and could provide a reference for the selection of vaccination. However, a lack of guidelines in the laboratory study and autopsy approach hampered the investigation of post-vaccination death. In this paper, we performed a systematic electronic search on scientific articles related to severe Covid-19 vaccination adverse effects and approaches in identifying the severe side effects using PubMed and Cochrane libraries. A summary on the onset, biochemistry changes and histopathological analyses of major lethally side effects post-vaccination were discussed. Ultimately, a checklist is suggested to improve the quality of investigation.

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Keywords: COVID19 Vaccine Myocarditis Thrombosis Anaphylaxis Adverse effects

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https://doi.org/10.1016/j.forsciint.2022.111469
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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was firstly reported in China and declared as a pandemic by World Health Organization (WHO) in the year 2020. Generation of vaccines and the establishment of vaccination programs immediately took place to mitigate the infection and mortality rate. Upon the starting of vaccination programs, severity on vaccine adverse effect and the causal relationship between vaccination and death brings up the attention of publicity. An average of 0.0018% SARS-CoV-2 vaccine-related death cases were reported by Vaccine Adverse Event Reporting System (VAERS) before July 2021. [1] Unfortunately, due to the limitation of time, guideline and procedure in the postmortem investigation during the pandemic, bias in the justification of the causal association between vaccination and death remained unsolved [2]. Therefore, compensations for vaccine-related death were hardly determined.

The vaccine-related injury or death compensation was initially covered under National Vaccine Injury Compensation Program (NVICP or VICP). In the case of recently developed SARS-CoV-2 vaccines, two medico-legal compensation guidelines, which are no-fault vaccine injury regimens and constructing a third regimen under COVAX's authority, were applied for the compensation of SARS-CoV-2 vaccine injuries [3]. The no-fault vaccine injury regimens are generally applied to wealthier countries, such as Canada [4]. However, Nepal and Vietnam also took this guideline to compensate SARS-CoV-2 vaccine-related injury. The constructing a third regimen under COVAX's authority compensates WHO, donors, manufacturers, and health care workers who helps in performing vaccination. Though the two systems are currently useful to covered part of the vaccine-related injury or death compensation, a lack of guideline and procedure in biochemistry investigation, pathology analysis and autopsy procedure prohibited the judgement of successful claims. Of note, the judgement on limited time for investigation should not be considered in any of the compensation scheme.

To develop a procedure for identification on the cause of death after vaccination, massive studies should be revisited and compiled. Firstly, a biological understanding on the serious adverse effect caused after SARS-CoV-2 vaccination should be included and a specific downstream specimen collection could be proposed in postmortem investigation. Generally, severe adverse effects which might lead to fatality are classified into anaphylaxis, thrombotic event, and myocarditis [5]. Anaphylaxis is a fatal allergy reaction, which could be observed in the first few hours and rarely up to days of vaccination, causing shock or asphyxia. Generally, mRNA vaccines utilized lipid nanoparticle (LNP) delivery system to improve the efficacy of mRNA delivery. However, the cationic/ionizable lipid in LNP delivery system activates innate inflammation and therefore initiates subsequent immune responses. Though the use of viral vector vaccine excludes the necessity of a LNP delivery system, polyethylene glycol (PEG) is commonly added to increase the half-life and effective concentration of the viral vectors [6]. Polysorbate is another chemical that works similarly as PEG to improve the efficacy of viral vector vaccines. Both molecules could potentially induce immune responses, which lead to different degrees of allergic reaction [7].

Vaccine induced thrombotic thrombocytopenia (VITT), similar to heparin-induced thrombocytopenia, results in formation of anti-platelet factor 4 (PF4) leading to thrombocytopenia and thrombosis. Pomara et al., 2021 suggested the causality of VITT after AstraZeneca vaccination through activation of platelet-activating antibodies against platelet factor 4 (PF4) [8]. The most frequently reported fatal adverse reaction with VITT is cerebral venous sinus thrombosis (CVST). Myocarditis is another key severe adverse effect described after vaccination. Myocarditis is an inflammatory event which leads to the damage of heart muscle. It was reported that mRNA vaccines, particularly Pfizer vaccine, induced a higher occurrence of myocarditis [9]. The mechanism of vaccine-induced myocarditis is largely unknown.

In this systematic review, the three major fatal adverse effects are discussed, including anaphylaxis, myocarditis, and thrombosis. An autopsy approach is suggested to improve the efficiency of sample collection for subsequent investigation on the causality of post-vaccination death.

2. Methods

This study was conducted according to Cochrane collaboration recommendations [10]. The objectives of our systemic review are to summarize the reported pathomorphological adverse reactions post COVID-19 vaccination, followed by recommendations in autopsy approach in those suspected fatal adverse reaction following vaccination.

2.1. Search strategy

Systemic searches were conducted in PubMed and Cochrane library. The search strategy included the following descriptors: “adverse”, “vaccine”, “covid-19”, “sars-cov-2”, “anaphylaxis”, “allergy”, “thrombosis”, “myocarditis” with Boolean operators “AND” and “OR”. All searches were limited to articles written in English. Reference lists of included articles were hand-searched to ensure that relevant publications were not missed.

2.2. Eligibility criteria

The studies were included in this systemic review if they met all the following eligibility criteria: (i) Original articles published in peer reviewed journal, including research papers reviews articles, case reports and case series (ii) serious adverse reaction including anaphylaxis, myocarditis and thrombosis, (iii) the type of vaccine is specified. The date of last searches is February 28th, 2022, hence any articles published after this date are excluded. We will exclude articles that are not published in peer-reviewed journal, incomplete full test records, preliminary communications, conference and commentaries papers.

2.3. Data extraction and bias assessment

Three authors (TLJ, KCP, LSK) critically reviewed all the studies retrieved and selected relevant articles. The title and abstracts were independently screened for eligibility by the authors. Search results were exported into Atlas.ti (Scientific Software Development,
Technical University, Berlin) [11] and duplicate articles deleted. Relevant articles were read in full and those that met the inclusion criteria had their data extracted by 4 reviewers (LSK, MSO, HH, KCP) independently: authors, type of vaccine, country of the reported event, total vaccinated population, age group, vaccine dose and types of adverse reaction. Two reviewers (TLJ, KCP) evaluated independently the risk of bias in each study using Diagnostic Precision Study Quality Assessment Tool (QUADAS-2) recommended by the Cochrane Collaboration.

3. Results

3.1. Study selection

A total of 1025 articles were yielded after initial searching (Fig. 1). Of these, 980 articles were identified after duplicates removal, with 319 articles being fully reviewed and 140 articles meeting the inclusion criteria. Finally, 47 articles were unintelligible and unable to be included, leaving a total of 96 articles. (Fig. 2).

3.2. Study characteristics

Studies included in this review were tabulated according to the three major types of fatal adverse effects: anaphylaxis (Table 1), myocarditis (Table 2) and thrombotic events (Table 3). All included studies were cohort designs and case report, and most of the studies are conducted based on registry databases.

3.3. Severe allergic effect related to anaphylaxis

Studies included in this review were 25 cohort studies and 8 case report or case series. Among the studies, the incidence of anaphylaxis was reported varies from 8 in 100,000 up to 5 in 1000 doses in Pfizer (1151 cases), 2 in 100,000 up to 1 in 100 doses in Moderna (544 cases), 1 in 10,000 up to 3 in 1000 doses in AstraZeneca (875 cases) and 2 in 1000 doses in Janssen vaccine (59 cases). Anaphylaxis is more frequently reported with the mRNA vaccine (Table 1). In three of the mRNA vaccination studies, hypersensitive and/or allergy source of Pfizer vaccine is linked to the presence of PEG [12–14]. Perivascular lymphocytic infiltration with or without mentioning eosinophils were found in biopsy of allergy skin reaction [15–18]. Other studies reported local skin reaction to the injection site, facial edema, throat swelling and bronchospasm.

3.4. Cardiovascular adverse events

This review included 8 cohort studies and 24 case report or case series. Cardiovascular adverse events, including myocarditis and myopericarditis were reported after the vaccination. There are 1059 reports (ranging from 4 in 100,000 up to 3 in 1000 doses) of myocarditis after the Pfizer, 249 reports (ranging from 2 in 10,000 up to 1 in 1000) after Moderna, 178 reports (4 in 100,000) after AstraZeneca and 8 cases (2 in 10,000) after Janssen vaccine. Similar with anaphylaxis, myocarditis is more frequently reported with mRNA vaccine (Table 2). Overall, most cases occurred after the second dose of vaccine, mainly affecting the adolescent age groups and male gender is predominant. Seven cases of death were reported [17,19], only one study stated the exact cause of death as intracranial bleeding with hypertensive crisis after vaccination [19].
| Vaccine Brand | Country | Age group | Vaccine dose | Total vaccine administered/Reported case | Total cases | Incidence | Reference | Risk of Bias | Applicability Concerns |
|---------------|---------|-----------|--------------|-----------------------------------------|-------------|-----------|-----------|-------------|-----------------------|
| Pfizer        | US      | NS        | 1st          | 25,929 persons                          | 7 cases     | $2 \times 10^4$ | Blumenthal et al. [20] | ○ | ○ | ○ | ○ | ○ | ○ |
| Pfizer        | US      | > 16      | 1st, 2nd     | 51,205 persons                          | 297 cases   | 0.005     | Singh et al. [21] | ○ | ○ | ○ | ○ | ○ | ○ |
| Pfizer        | US      | > 16      | 1st, 2nd     | 6994 doses                              | 46 cases    | 0.006     | Gee et al. [22] | ○ | ○ | ○ | ○ | ○ | ○ |
| Pfizer        | US      | 27–60     | 1st          | 1,893,360 persons                       | 21 cases    | $1 \times 10^{-5}$ | CDC covid19 response team [23] | ○ | ○ | ○ | ○ | ○ | ○ |
| Pfizer        | US      | 18–80     | 1st, 2nd     | 1,271 persons                           | 1 case      | $7 \times 10^4$ | Kadali et al. [24] | ○ | ○ | ○ | ○ | ○ | ○ |
| Pfizer        | US      | 19–89     | 1st, 2nd     | 62 cases                               | 62 cases    | –         | Kaplan et al. [25] | ○ | ○ | ○ | ○ | ○ | ○ |
| Pfizer        | US      | > 16      | 2nd          | 18,801                                  | 1 case      | $1 \times 10^{-5}$ | Clinical Trial data by FDA [26] | ○ | ○ | ○ | ○ | ○ | ○ |
| Pfizer        | US      | 18–80     | 2nd          | 1,889 persons                           | 1 case      | –         | Frank et al. [27] | NA | NA | NA | NA | NA | NA |
| Pfizer        | US      | 19–89     | 1st, 2nd     | 6994 doses                              | 6 cases     | –         | Park et al. [28] | NA | NA | NA | NA | NA | NA |
| Pfizer        | Canada  | > 25      | NS           | 737,728 doses                           | 28 cases    | $4 \times 10^{-5}$ | Ontario public health agency [29] | ○ | ○ | ○ | ○ | ○ | ○ |
| Pfizer        | US      | 39.3 mean age | 1st, 2nd     | 1,291 persons                           | 2 cases     | 0.001     | Vanegas et al. [30] | ○ | ○ | ○ | ○ | ○ | ○ |
| Pfizer        | UK      | NS        | 1st, 2nd, 3rd| 71,645,000 doses                        | 2 cases     | $8 \times 10^{-6}$ | MHRA [17] | ○ | ○ | ○ | ○ | ○ | ○ |
| Pfizer        | UK      | 52        | NS           | 1 case                                 | Anaphylaxis, positive skin prick test to PEG [31] | – | Sellaturay et al. [13] | NA | NA | NA | NA | NA | NA |
| Pfizer        | Italy   | > 19      | 1st, 2nd     | 2,030 persons                           | 1 case      | 0.0004    | Osasto et al. [31] | ○ | ○ | ○ | ○ | ○ | ○ |
| Pfizer        | Italy   | 30        | 1st          | 1 case                                 | Anaphylaxis | –         | Restivo et al. [32] | NA | NA | NA | NA | NA | NA |
| Pfizer        | Israel  | 52 mean age| 1st, 2nd     | 429 persons                            | 3 cases     | 0.007     | Shavit et al. [33] | ○ | ○ | ○ | ○ | ○ | ○ |
| Pfizer        | Lebanon | 30        | 1st          | 1 case                                 | Biphasic Anaphylaxis | – | Ali Zeid Dau et al. [34] | NA | NA | NA | NA | NA | NA |
| Pfizer        | Korea   | > 19      | NS           | 288 persons                            | 1 case      | 0.003     | Song et al. [35] | ○ | ○ | ○ | ○ | ○ | ○ |
| Pfizer        | Japan   | 22–56     | 1st, 2nd     | 578,835 doses                          | 47 cases    | $6 \times 10^{-5}$ | Iuchi et al. [36] | ○ | ○ | ○ | ○ | ○ | ○ |
| Pfizer        | Japan   | 23–58     | 1st, 2nd     | 181,184 persons                        | 37 cases    | 0.0002    | Hashimoto et al. [37] | ○ | ○ | ○ | ○ | ○ | ○ |
| Moderna       | US      | > 16      | 1st, 2nd     | 61,258 persons                         | 392 cases   | 0.006     | A Singh et al. [21] | ○ | ○ | ○ | ○ | ○ | ○ |
| Moderna       | US      | 31–63     | 1st          | 4,042,396 persons                       | 10 cases    | $2 \times 10^{-6}$ | CDC covid19 response team [23] | ○ | ○ | ○ | ○ | ○ | ○ |
| Moderna       | US      | NS        | 1st          | 38,971 persons                          | 9 cases     | 0.0002    | Blumenthal et al. [20] | ○ | ○ | ○ | ○ | ○ | ○ |
| Moderna       | US      | 18–80     | 1st, 2nd     | 1,116 persons                          | 16 cases    | 0.0009    | Kadali et al. [24] | ○ | ○ | ○ | ○ | ○ | ○ |
| Moderna       | US      | 31–63/F  | 1st          | 4,041,396 doses                        | 10 cases    | $2 \times 10^{-6}$ | Shimabukuro [38] | ○ | ○ | ○ | ○ | ○ | ○ |
| Moderna       | US      | > 16      | 1st          | 1,373 doses                            | 16 cases    | 0.01     | Gee et al. [22] | ○ | ○ | ○ | ○ | ○ | ○ |
| Moderna       | US      | 19–89     | 1st, 2nd     | 50 cases                               | 50 cases    | –         | Kaplan et al. [25] | NA | NA | NA | NA | NA | NA |
| Moderna       | Canada  | > 25      | NS           | 152,876 doses                          | 5 cases     | $3 \times 10^{-5}$ | Ontario public health agency [29] | ○ | ○ | ○ | ○ | ○ | ○ |
| Moderna       | UK      | NS        | 1st, 2nd     | 2.3 million doses                      | Anaphylaxis | 61 cases | MHRA [17] | ○ | ○ | ○ | ○ | ○ | ○ |
| Moderna       | UK      | NS        | 1st, 2nd     | 49 million doses                       | Anaphylaxis | 61 cases | NA [17] | ○ | ○ | ○ | ○ | ○ | ○ |
| Janssen       | US      | > 16      | 1st          | 28,745 persons                         | 58 cases    | 0.002     | Song et al. [35] | ○ | ○ | ○ | ○ | ○ | ○ |
| Janssen       | US      | 19–89     | 1st, 2nd     | 28,745 persons                         | 58 cases    | 0.002     | A Singh et al. [21] | ○ | ○ | ○ | ○ | ○ | ○ |

Abbreviation: AZ, AstraZeneca; CDC, Center of Disease Control and Prevention; F, female; FDA, Food and Drug Administration; M, male; MHRA, Medicine and Healthcare Products Regulatory Agency; NS, not specified; PEG, Polyethylene Glycol; ○, low risk; Ⓛ, high risk; NA, not applicable.
| Vaccine brand | Country | Age group | Vaccine dose | Total vaccine administered/Reported cases | Total cases | Incidence | References | Risk of Bias | Applicability Concerns |
|---------------|---------|-----------|--------------|------------------------------------------|-------------|-----------|------------|-------------|------------------------|
| Pfizer        | US      | > 18      | 1st,2nd     | 51,205 persons                           | Myocarditis(108) | 0.002     | A Singh et al.[21] | Ⓛ Ⓛ Ⓛ | ? ? ? |
| Pfizer        | US      | 12–17     | 1st,2nd     | 9246 persons                             | Myocarditis(247) | 0.03      | Hause et al.[39] | Ⓛ Ⓛ ? | ? ? ? |
| Pfizer & Moderna | US | 19–94     | 1st,2nd     | 296 million dose                         | Myocarditis(1226) | 4 × 10^-6 | Gargano et al.[40] | Ⓛ Ⓛ ? | ? ? ? |
| Pfizer        | UK      | NS        | 1st, 2nd    | 46.4 million doses                       | Myocarditis(543), pericarditis(378), eosinophilic myocarditis (1), death(4) | 1 × 10^-5 (Myo) 8 × 10^-6 (Per) | MHRA[17] | Ⓛ ? ? | ? ? ? |
| Pfizer        | US      | 12–18/M   | 2nd         | 15 cases                                 | Myocarditis(15) | –         | Dionne et al.[41] | NA NA NA | NA NA NA |
| Pfizer        | US      | 14–19/M   | 2nd         | 7 cases                                  | Myocarditis, myopericarditis(7) | –         | Marshall et al.[42] | NA NA NA | NA NA NA |
| Pfizer        | US      | 20–51/M   | 1st(1), 2nd(6) | 7 cases                                 | Myocarditis(7) | –         | Montgomery et al.[43] | NA NA NA | NA NA NA |
| Pfizer        | US      | 19–39/M   | 1st(1), 2nd(4) | 5 cases                                 | Myocarditis(5) | –         | Rosner et al.[44] | NA NA NA | NA NA NA |
| Pfizer        | US      | 23, 24/M  | 2nd         | 2 cases                                 | Myopericarditis(2) | –         | Kim et al.[45] | NA NA NA | NA NA NA |
| Pfizer        | US      | 46/M      | 2nd         | 1 case                                  | Myopericarditis(1) | –         | Bartlett et al.[46] | NA NA NA | NA NA NA |
| Pfizer        | US      | 16/M      | 2nd         | 1 case                                  | Myopericarditis(1) | –         | McLean et al.[47] | NA NA NA | NA NA NA |
| Pfizer        | Israel  | 18–24/M   | 2nd         | 7 cases                                 | Myocarditis(7) | –         | Levin et al.[48] | NA NA NA | NA NA NA |
| Pfizer        | Israel  | 16–45/M   | 1st(1), 2nd(5) | 6 cases                                 | Myocarditis(6) | –         | Abu Mouch et al.[49] | NA NA NA | NA NA NA |
| Pfizer        | Italy   | 21–56/M   | 1st(1), 2nd(4) | 5 cases                                 | Myocarditis(5) | –         | Larson et al.[50] | NA NA NA | NA NA NA |
| Pfizer        | Italy   | 56/M      | 2nd         | 1 case                                  | Myocarditis(1) | –         | Ammirati et al.[51] | NA NA NA | NA NA NA |
| Pfizer        | Italy   | 20/M      | 2nd         | 1 case                                  | Myopericarditis(1) | –         | Facetti et al.[52] | NA NA NA | NA NA NA |
| Pfizer        | Korea   | 29/M      | 2nd         | 1 case                                  | Myopericarditis(1) | –         | Kim et al.[53] | NA NA NA | NA NA NA |
| Pfizer        | Spain   | 39/M      | 2nd         | 1 case                                  | Myocarditis(1) | –         | Bautista Garcia et al.[54] | NA NA NA | NA NA NA |
| Pfizer        | France  | 19/M      | NS          | 1 case                                  | Myocarditis(1) | –         | Schmitt et al.[55] | NA NA NA | NA NA NA |
| Moderna       | US      | > 17      | 1st,2nd     | 61,258 persons                           | Myocarditis(101) | 0.001     | A Singh et al.[21] | Ⓛ Ⓛ Ⓛ | ? ? ? |
| Moderna       | UK      | NS        | 1st, 2nd    | 2.8 million doses                        | Myocarditis(122), pericarditis(69), hypersensitivity myocarditis(1), death(1) | 4 × 10^-5 (Myo) 2 × 10^-5 (Per) | MHRA[17] | Ⓛ ? ? | ? ? ? |
| Moderna       | US      | 20–51/M   | 1st(2), 2nd(14) | 16 cases                                 | Myocarditis(16) | –         | Montgomery et al.[43] | NA NA NA | NA NA NA |
| Moderna       | US      | 36/M, 70/F | 2nd         | 2 cases                                 | Myocarditis(2) | –         | Kim et al.[45] | NA NA NA | NA NA NA |
| Moderna       | US      | 39/M      | 2nd         | 1 case                                  | Myocarditis(1) | –         | Rosner et al.[44] | NA NA NA | NA NA NA |
| Moderna       | US      | 24/M      | 2nd         | 1 case                                  | Myocarditis(1) | –         | Albert et al.[56] | NA NA NA | NA NA NA |
| Moderna       | US      | 52/M      | 2nd         | 1 case                                  | Myocarditis(1) | –         | Muthukumar et al.[57] | NA NA NA | NA NA NA |
| Moderna       | Italy   | 22–31/M   | 2nd         | 3 cases                                 | Myocarditis(3) | –         | Larson et al.[50] | NA NA NA | NA NA NA |
| Moderna       | Italy   | 30/M      | 2nd         | 1 case                                  | Myocarditis(1) | –         | D’Angelo et al.[58] | NA NA NA | NA NA NA |
| Moderna       | Greece  | 71/F      | 1st         | 1 case                                  | ICE, hypertensive crisis, death(1) | –         | Athyros & Doumas[19] | NA NA NA | NA NA NA |

(continued on next page)
### 3.5. Thrombosis, thrombocytopenia related adverse event

Studies included in this review included 10 cohort studies and 57 case report or case series. A total of over 24,000 thrombotic events have been reported, the majority of which have been associated with adenoviral vector-based vaccine, particularly AstraZeneca (5 in 100,000 up to 6 in 1000), followed by Janssen (8–30 in 1,000,000 doses), Pfizer (6 in 1,000,000 up to 1 in 1000 doses) and Moderna (4 in 10,000,000). Antibodies against platelet factor 4 (PF 4) were positive in 67 cases in AstraZeneca and 17 cases in Janssen, and it was not tested or mentioned in cases of mRNA-based vaccine. Overall, the thrombotic event is more frequently occurred after 1st dose of AstraZeneca vaccine (Table 3). Death related with thrombotic event was registered 238 cases in Pfizer, 186 cases in AstraZeneca, 54 cases in Moderna and 17 cases in Janssen. The incidence of thrombosis is more commonly observed in female gender (103) than male (24). Vaccine-induced immune thrombotic thrombocytopenia (VITT) has heterogeneous presentation, however, the main cause of death is related to complication of cerebral venous sinus thrombosis.

### 4. Discussion

Deaths that occurred within short intervals post-vaccination are exceptionally driven the public concern about the safety of vaccination programs. Except for the concern on vaccination programs, compensation schemes related to vaccine-related injury or death are of high interest in public. As a consequence, a guideline on postmortem investigation is important to evaluate the cause of death and determine the causality for the claim of compensation. Here, we comprehensively discussed the onset, autopsy approach, histopathology, and biochemistry analysis of the three most common post-vaccination lethally adverse effects: anaphylaxis, VITT, and myocarditis.

During the pandemic, COVID-19 screening is generally required prior any postmortem examination. Positive virus detection could be an alternative explanation for the cause of adverse reactions following vaccination. A multi-site viral detection study in mildly infected patient found higher nasopharyngeal viral loads in the early course of disease, despite finding Viral RNA in sputum for longer periods of time [117]. When compared to deep respiratory samples, nasopharyngeal swabs were relatively insensitive for detecting virus in critically ill patient [118]. The viral genome could be found in lung tissues for months after death, indicating the virus’s stability [119,120]. Grassi et al. examined 29 autopsy cases and discovered that the mean viral load of SARS-CoV-2 death is higher in those who died without hospitalization than in those who died while hospitalized. The relationship between the presence of replicative mRNA and death without hospitalization and that between minimum cycle threshold value of SARS-CoV-2 RNA and the cycle threshold value of replicative SARS-CoV-2 mRNA were found to be statistically significant. As a result, autopsies of untreated SARS-CoV-2 patients may pose a higher risk of infection; therefore, strict adherence to biological safety guidelines in the autopsy room is required [121].

#### 4.1. Anaphylaxis

In the clinical setting, the acute symptoms of anaphylaxis include allergic skin changes, respiratory, cardiovascular and/or severe gastrointestinal symptoms [122,123]. Adverse Events of Special Interest (AESI) for anaphylaxis case definition, required an event time course that includes “sudden onset” - the event occurred unexpectedly and without warning, resulting in marked changes in a subject's previously stable condition and rapid progression [123]. Of note, the pathological changes in vaccine-related anaphylaxis and allergy reactions to other medications or foods are similar.

Diagnosis of anaphylaxis in autopsy is challenging as there is no pathognomonic change. Gross findings included local or generalized

| Table 2 (continued) |
|---------------------|
| **Vaccine** |
| **Country** |
| **Age group** |
| **Total vaccine administered/Reported cases** |
| **Total vaccine dose** |
| **Incidence** |
| **Risk of Bias** |
| **Applicability Concerns** |
| **References** |

- **Vaccine brand**: AZ, AstraZeneca; CDC, center of disease control and prevention; MHRA, Medicine and healthcare products regulatory agency; NS, not specified; PF 4, platelet factor 4; VITT, vaccine-induced immune thrombotic thrombocytopenia.

- **Incidence**: 3×10^6 (Myocarditis), 4×10^6 (Pericarditis), 1×10^6 (Autoimmune myocardiitis), 2×10^6 (Death), 0.0002 (Peritonitis), 1 case (Myocarditis).

- **Risk of Bias**: Low risk, high risk, not applicable.

- **Applicability Concerns**: Not specified.

- **References**: A Singhal et al. [144].
| Vaccine brand | Country | Age group | Vaccine dose | Total vaccine administered/Reported cases | Total cases | Incidence of thrombosis | PF-4 | Study | Risk of bias | Applicability concerns | Methodological quality of the included studies | Patient selection | Index test | Reference standard | Flow & timing |
|---------------|---------|-----------|--------------|------------------------------------------|-------------|------------------------|------|-------|-------------|------------------------|---------------------------------------------|------------------|------------|----------------|----------------|
| 1 AZ          | England | > 16      | 1st          | 196 008 008 persons                      | CVST(23), thrombocytopenia(1 480), venous(3 077), arterial(1 161), thrombosis, stroke(3 976) | 8 × 10^-6 | NS   | Hippisley-Cox et al.[59] | ( ) | ? | ? | ? | ? | ? |
| 2 AZ          | UK      | NS        | 1st, 2nd     | 49 million doses                         | CVST(1 56), thrombotic thrombocytopenia(429), death(75) | 8 × 10^-6 | NS   | MHRA[17] | ( ) | ? | ? | ? | ? | ? |
| 3 AZ          | UK      | 21–77     | 1st          | 23 cases                                 | CVT(13), stroke(2), AMI(1), PE(4), thrombotic thrombocytopenia(23), venous(4), arterial(1) thrombosis, death(7) | – | P(22), N(1) | Scully et al.[60] | NA | NA | NA | NA | NA | NA |
| 4 AZ          | UK      | NS        | NS           | 21.2 million persons                     | CVST(77) | 3 × 10^-6 | NS   | Bikdeli et al.[61] Mehta et al.[62] | ( ) | ? | ? | ? | ? | ? |
| 5 AZ          | UK      | 32, 25/M  | 1st          | 2 cases                                  | CVST, ICB, SAH, thrombocytopenia, stroke(2) | – | P(1) | Van de Munckhof el al[68] | NA | NA | NA | NA | NA | NA |
| 6 AZ          | UK      | 54/M      | NS           | 1 case                                   | CVST, VITT, venous thrombosis(1) | – | P | | | | | |
| 7 AZ          | UK      | 27/M      | 1st          | 1 case                                   | CVST, ICB, thrombocytopenia, death(1) | – | P | Suresh et al.[64] | NA | NA | NA | NA | NA | NA |
| 8 AZ          | UK      | 30/F      | NS           | 1 case                                   | CVST, venous thrombosis(1) | – | P | Talbøl Sorensen et al[65] Al-mayhani et al[66] | NA | NA | NA | NA | NA | NA |
| 9 AZ          | UK      | 35/F, 37/F, 43/F, 29/F, 38/M, 50/F, 35/F | NS           | 3 cases                                  | CVST(2), VITT(3), ICB(2), venous(2), arterial(1) thrombosis, death(1) | – | P(3) | | | | |
| 10 AZ         | Ireland | NS        | 4 cases      | VITT(4), CVST(1), venous thrombosis(1), PE(1) | – | P(4) | Lavin et al[67] | NA | NA | NA | NA | NA | NA |
| 11 AZ         | Europe  | NS        | NS           | NS                                       | CVST, thrombocytopenia(243) | – | NS | Van de Munckhof el al[68] Greinacher et al.[69] | NA | NA | NA | NA | NA | NA |
| 12 AZ         | Germany, Austria | 22–49 | NS           | 11 cases                                  | CVST(9), ICB(1), venous thrombosis(4), PE(3), death(6) | – | P(9) | | | | |
| 13 AZ         | Germany | 29/M      | 1st          | 1 case                                   | CVST, VITT, venous thrombosis(1) | – | NS | Graf et al[70] | NA | NA | NA | NA | NA | NA |
| 14 AZ         | Germany | 41–67/F  | 1st          | 5 cases                                  | CVST(5), ICB(1), stroke(1), venous(1), arterial(12) thrombosis. | – | P(5) | Tiede et al[71] | NA | NA | NA | NA | NA | NA |
| 15 AZ         | Germany | 30/F      | 1st          | 1 case                                   | CVST, ICB, VITT(1) | – | P | Ikenberg et al[72] | NA | NA | NA | NA | NA | NA |
| 16 AZ         | Germany | 55/F      | 1st          | 1 case                                   | Venous thrombosis, stroke, thrombocytopenia(1) | – | N | Bayes et al[73] | NA | NA | NA | NA | NA | NA |
| 17 AZ         | Germany | 31/M      | 1st          | 1 case                                   | Stroke, arterial thrombosis(1) | – | P | Walter et al[74] | NA | NA | NA | NA | NA | NA |

(continued on next page)
| Vaccine brand | Country | Age group | Vaccine dose | Total vaccine administered/Reported cases | Total cases | Incidence of thrombosis | PF4 Study | Risk of bias | Applicability concerns |
|---------------|---------|-----------|--------------|------------------------------------------|-------------|------------------------|-----------|-------------|------------------------|
|               |         |           |              |                                          |             |                        |           |             |                         |
| 18 AZ         | France  | 19–99 NS  | 639 cases    | CVST(6), CVT(1), PE(211), DVT(111), venous(92), arterial(308) thrombosis, stroke(219), AMI(81), death(82) | – NS        | Smadja et al.[75]     | NA        | NA          | NA          |
| 19 AZ         | France  | 69/F 1st  | 1 case       | CVST, PE, thrombocytopenia, ICB, death(h1) | – P         | Jamme et al.[76]      | NA        | NA          | NA          |
| 20 AZ         | France  | 21/F 1st  | 1 case       | CVT, stroke, VITT, PE, venous thrombosis(1) | – NS        | Bersinger et al.[77]  | NA        | NA          | NA          |
| 21 AZ         | Norway  | 32–54 NS  | 1st NS       | CVST(4), CVT(3), VITT(5), venous thrombosis(1), death(h3) | – NS        | Schultz et al.[78]    | NA        | NA          | NA          |
| 22 AZ         | Norway  | 30/F NS   | 1 case       | CVST, ICB, PE, thrombocytopenia, death(h1) | – P         | Bjørnstad-Tuving et al.[79]  | NA        | NA          | NA          |
| 23 AZ         | Spain   | 47/M NS   | 1 case       | CVST, CVT, VITT, PE(1) | – P         | Varona et al.[80]     | NA        | NA          | NA          |
| 24 AZ         | Denmark | 60/M 1st  | 1 case       | Stroke, thrombocytopenia, death(h1) Thrombocytopenia, PE, venous thrombosis(1) | – NS        | Muster et al.[82]     | NA        | NA          | NA          |
| 25 AZ         | Austria | 51/F NS   | 1 case       | CVST, CVT, ICB, thrombocytopenia, death(h1) | – N         | Castelli et al.[83]   | NA        | NA          | NA          |
| 26 AZ         | Italy   | 50/M 1st  | 1 case       | CVST, VITT, venous thrombosis, death(h1) | – NS        | Gentonze et al.[84]   | NA        | NA          | NA          |
| 27 AZ         | Italy   | 32/F 1st  | 1 case       | CVST, ICB, SH, venous, arterial thrombosis, PE, MI, death(h1) | – NS        | D’Agostino et al.[85] | NA        | NA          | NA          |
| 28 AZ         | Italy   | 54/F NS   | 1 case       | CVST, CVT, IC, PE(1) | – P         | Bonato et al.[86]     | NA        | NA          | NA          |
| 29 AZ         | Italy   | 26/F 1st  | 1 case       | CVST, CVT, ICB(1) | – P         | Franchini et al.[87]  | NA        | NA          | NA          |
| 30 AZ         | Italy   | 50/M 1st  | 1 case       | CVST, ICB, death(1) | – P         | Gardiner et al.[88]   | NA        | NA          | NA          |
| 31 AZ         | Austria | 39/F 1st  | 2 cases      | CVST(1), CVT(1), ICB(1), thrombocytopenia(2). CVST(1), VITT(3), stroke(1), venous(3), arterial(3) thrombosis, PE(2) | – P(2)     | Bourguignon et al.[89] | NA        | NA          | NA          |
| 32 AZ         | Canada  | 72/F 63/M, 69/M NS | 3 cases | CVST(1), VITT(3), stroke(1), venous(3), arterial(3) thrombosis, PE(2). | – NS        | de Mello Silva et al.[90] | NA        | NA          | NA          |
| 33 AZ         | Brazil  | 57/F 1st  | 1 case       | ICB, VITT(1) | – NS        | Zsba et al.[91]       | NA        | NA          | NA          |
| 34 AZ         | Saudi Arabia | 40/M, 61/F | 2 cases      | CVST, thrombocytopenia(1) | – NS        | Aladdin et al.[92]    | NA        | NA          | NA          |
| 35 AZ         | Saudi Arabia | 36/F 1st  | 1 case       | CVST, VITT, stroke, venous thrombosis(1) | – NS        | Guan et al.[93]       | NA        | NA          | NA          |
| 36 AZ         | Taiwan  | 52/M NS   | 1 case       | CVST, VITT, venous thrombosis(1) | – P         | Wang et al.[94]       | NA        | NA          | NA          |
| 37 AZ         | Taiwan  | 41/F 1st  | 1 case       | CVST, thrombocytopenia, PE(1) | – P         | Choi et al.[95]       | NA        | NA          | NA          |
| 38 AZ         | Korea   | 33/M 1st  | 1 case       | CVST, ICB, thrombocytopenia, death(h1) | – P         | NA        | NA          | NA          | NA          |
| Vaccine brand | Country | Age group | Vaccine dose | Total vaccine administered/Reported cases | Total cases | Incidence of thrombosis | PF4 | Study | Risk of bias | Applicability concerns |
|---------------|---------|-----------|-------------|-------------------------------------------|-------------|-------------------------|-----|-------|-------------|-----------------------|
|               |         |           |             |                                           |             |                         |     |       |             | Patient selection | Index test | Reference standard | Flow & timing | Patient selection | Index test | Reference standard |
| 39 AZ         | India   | 51/M      | 1st         | 1 case                                    | CVT(1)      | –                       | N   | Dutta et al.[96] | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          |
| 40 AZ         | India   | 44/F      | 1st         | 1 case                                    | CVST, SAH, stroke, trombocytopenia(1) | –           | P   | Maramattom et al.[97] | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          |
| 41 Janssen    | US      | NS        | 1 dose      | 12.6 million doses                        | Thrombotic trombocytopenia syndromes(38) | 3 x 10^6    | NS | Rosenblum et al.[98] | @          | @          | ?           | ?           | ?           | ?           | ?           | ?           | ?           |
| 42 Janssen    | US      | NS        | 1 dose      | 6.85 million persons                      | CVST(6)     | 8 x 10^7                | NS | Bikdeli et al.[61] | @          | @          | ?           | ?           | ?           | ?           | ?           | ?           | ?           |
| 43 Janssen    | US      | 18–48     | 1 dose      | 6.86 million doses                        | CVST, trombocytopenia(6), venous thrombosis(3), PE(1), DVT, death(1) | 8 x 10^7    | NS | ACP[99] | @          | @          | ?           | ?           | ?           | ?           | ?           | ?           |
| 44 Janssen    | US      | 12–60/F   | 1 dose      | 12 cases                                  | –           | P(11), NS(1)            | N   | See et al.[100] | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          |
| 45 Janssen or AZ | US  | NS        | NS         | NS                                        | CVT(77)     | –                       | NS | García-Azorín et al.[101] | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          |
| 46 Janssen    | US      | 40/F      | 1 dose      | 1 case                                    | Thrombocytopenia, CVST, PE(1) | –           | P   | Clark et al.[102] | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          |
| 47 Janssen    | US      | 24/M      | 1 dose      | 1 case                                    | VITT, venous thrombosis(1) | –           | P   | Dhoot et al.[103] | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          |
| 48 Janssen    | US      | 48/F      | 1 dose      | 1 case                                    | CVST, ICB, trombocytopenia, venous thrombosis(1) | –           | P   | Muir et al.[104] | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          |
| 49 Janssen    | US      | 43/F      | 1 dose      | 1 case                                    | TIA, arterial thrombosis, PE, CVST, trombocytopenia(1) | –           | P   | Malik et al.[105] | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          |
| 50 Janssen    | US      | 40/F      | 1 dose      | 1 case                                    | CVST, venous thrombosis, PE, trombocytopenia(1) | –           | P   | George et al.[106] | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          |
| 51 Janssen    | US      | 48/F      | 1 dose      | 1 case                                    | VITT, DVT, PE(1) | –           | P   | Abou-ismael et al.[107] | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          |
| 52 Janssen    | Europe  | NS        | 1 dose      | NS                                        | CVST, trombocytopenia(23) | –           | NS | Van de Munckhof et al.[68] | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          |
| 53 Pfizer     | France  | 18–102    | NS         | 1197 cases                                | PE(211), DVT(111), CVT(3), CV(3) venous (42), arterial(183), thrombosis, stroke(561), AMI(238), death(233) | –           | NS | Smadja et al.[75] | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          |
| 54 Pfizer     | Portugal| 47/F, 67/F | 1st, 2nd    | 2 cases                                   | CVT(2), CVST(1), stroke (1), normal platelet(2) | –           | NS | Dias et al.[108] | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          |
| 55 Pfizer     | Poland  | 86/F      | 1st         | 1 case                                    | MI, death(1) | –           | NS | Tajstra et al.[109] | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          |
| 56 Pfizer or Moderna | Austria | 52/M | 2nd         | 1 case                                    | IQR(1)      | –           | NS | Finsterer et al.[110] | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          | NA          |
| 57 Pfizer     | UK      | NS        | 1st, 2nd    | 46.4 million doses                        | Thrombotic trombocytopenia(29), death(4) | 6 x 10^7    | NS | MHRA[17] | @          | @          | ?           | ?           | ?           | ?           | ?           | ?           | ?           |
| 58 Pfizer     | England | > 16      | 1st         | 9513625 persons                           | Thrombotic trombocytopenia(1010), venous(2054), arterial (9473) thrombosis, CVST(6), stroke(3167) | 0.001       | NS | Hippisley-Cox et al.[59] | @          | @          | ?           | ?           | ?           | ?           | ?           | ?           | ?           |
| Vaccine brand | Country | Age group | Vaccine dose | Total vaccine administered/Reported cases | Total cases | Incidence of thrombosis | PF-4 Study | Risk of bias | Applicability concerns |
|--------------|---------|-----------|--------------|------------------------------------------|-------------|------------------------|------------|-------------|-----------------------|
| Pfizer       | Saudi Arabia | 27/M   | 2nd          | 1 case                                   | PE(1)       | –                      | NS         | Esba et al.[91] | NA NA NA NA NA NA NA NA |
| Pfizer or Moderna | US | < 50/F | 1st, 2nd   | 13.6 million persons                      | 1 case      | Thrombosis(14), stroke (18), MI(11), PE(25) | 1 × 10^6    | NS          | Sessa et al.[111] Lee et al.[112] |
| Pfizer & Moderna | US | 22–74 NS | 1st, 2nd   | 20 cases                                 | 1 case      | Thrombocytopenia(20), ICB, death(1), CVST(1) | –          | NS          | NA NA NA NA NA NA NA NA |
| Pfizer       | Malaysia | 49/M   | 1st, 2nd   | 1 case                                   | CVST(1)     | –                      | NS         | Zakaria et al.[113] Fan et al.[114] |
| Pfizer       | Singapore | 54/M, 62/F | 2nd | 3 cases                                 | CVST(3), ICB(3), SAH(2) | –          | N(1) NS(2) | NA NA NA NA NA NA NA NA |
| Moderna      | US | NS | NS | 84.7 million doses | 1 case | CVST with normal platelet(3) | 4 × 10^8 | ACIP[99] | NA NA NA NA NA NA NA NA |
| Moderna      | US | 65/M | 2nd | 1 case | PE, DVT, thrombocytopenia, CVST, death(1) | –          | N | Sangli et al.[115] |
| Moderna      | US | 45/M | 2nd | 1 case | CVST, ICB, SAH, normal platelet(1) | –          | NS | Syed et al.[116] |
| Moderna      | France | 19–102 NS | 325 cases | 325 cases | Venous(11), arterial(253) thrombosis, CVST(3), stroke(173), PE(53), AMI (67), death(53) | –          | NS | Smadja et al.[75] |

Abbreviation: ACIP, Advisory Committee on Immunization Practices; AMI, acute myocardial infarction; AZ, AstraZeneca; CVST, cerebral venous sinus thrombosis; CVT, cerebral vein thrombosis; DVT, deep vein thrombosis; FDA, food and drug administration; ICB, intracerebral bleeding; MHRA, Medicine and healthcare products regulatory agency; N, negative; NS, not specified; P, positive; PE, pulmonary thromboembolism; SAH, Subarachnoid hemorrhage; VITT, vaccine induced immune thrombotic thrombocytopenia; Ⓜ, low risk; Ⓜ, high risk; NA, not applicable.
allergic skin reaction, laryngeal edema and hyperinflated lungs with mucus plugging. Mast cell and eosinophil infiltration of the injection site, airway, lungs, spleen, and gastrointestinal tract are remarkable histological findings. Technically, morphological study and calculating the number of mast cells is important to confirm the mast cell infiltration and to differentiate it from other conditions, such as systemic mastocytosis, myelodysplastic syndrome or mast cell leukemia.

For the biochemistry investigation, serum tryptase should be taken immediate for analysis. Tryptase is rapidly released from mast cell with peak level within 1–2 h after exposure to allergen. Serum tryptase has a half-life of 2 h, its level is rapidly depleted if the survivor period or postmortem interval are prolonged [124]. The normal level of tryptase level does not exclude the possibility of anaphylaxis. On the contrary, serum tryptase levels can be elevated in a variety of non-anaphylactic conditions, for example Gaucher’s disease, parasitic infections, haematological malignancies, cardiovascular disease, chronic kidney disease etc [125].

Testing of specific IgE toward PEG or anti-PEG IgG may demonstrate the PEG-mediated allergic reaction. However, non-IgE activation of mast cells should be considered, it was previously known as anaphylactoid reaction. They shared similar clinical features and responses to epinephrine treatment. The non-IgE mediated pathways, such as complement activation, C3, or C5 might trigger allergic reactions even on the first exposure of allergen [3].

4.2. Myocarditis

Myocarditis is generally observed in mRNA vaccine cohort, predominantly in adolescent male and onset within 2–4 days after 2nd dose of vaccination. In clinical setting, patient may present with acute myocardial infarction like syndrome, new onset of arrhythmia or heart block, fulminant heart failure and sudden cardiac death. Laboratory investigation included endomyocardial biopsy (Dallas criteria), elevated cardiac enzymes and inflammatory biomarkers eg ESR, d-dimer and CRP. Routine clinical imaging study eg cardiac MRI, Echocardiography and ECG will also aid in diagnosis [126].

Postmortem diagnosis of myocarditis requires histology confirmation of myocardial damage and inflammatory cells infiltration [127]. However, histological study is insufficient to determine the etiology and there is no specific testing to link the myocarditis to vaccination. Biological markers, such as Troponin or Creatine Kinase (CK)-MB could be utilized in supporting the diagnosis of myocarditis [127]. Microbiological analysis of serum, pericardial fluid, and myocardium should be collected as soon as practicable [128]. As viral infection is the most common cause of myocarditis, RT-PCR or viral culture could be useful in identifying the type of infectious agent and ruling out the possibility of post-vaccine death.

Ascertained with other cardiac pathology, for example, ischemic heart disease is important. Although exacerbation of underlying cardiac conditions has been reported with the vaccination, the causality between vaccination and underlying heart disease has yet to be established.

4.3. Vaccine-induced immune thrombotic thrombocytopenia (VITT)

VITT is a life-threatening thrombosis with thrombocytopenia syndrome (TTS) characterized by venous or arterial thrombosis with mild to severe degree of thrombocytopenia. Thrombocytopenia was reported to have a higher occurrence in adenoviral-based vector vaccines [129]. Furthermore, a higher incidence of VITT was observed in women with a mean age of 35-year-old [67]. The onset of VITT is reported within 5–24 days after AstraZeneca or Janssen vaccination [130].

Clinically, Brighton Collaboration case definition of thrombosis and thromboembolism is used in evaluation of adverse reaction following vaccination, which included scoring system: Wells score and revised Geneva score, d-dimer, targeted organ biopsy, compression ultrasonography (DVT), CT pulmonary angiography (pulmonary thromboembolism) and contrast CT, MR venography (CVST, stroke) etc. [131].

The primary focus of an autopsy is to seek evidence of thrombosis in damaged organs. Careful dissection of arteries and veins is needed to detect the thrombus and demonstrate ischemic or hemorrhagic infarction in serial sections of organs especially cerebral venous sinuses. Of note, Hippisley-Cox et al. (2021) study reported an increased risk of thrombocytopenia, venous thromboembolism, and arterial thrombotic events in a short time interval after AstraZeneca vaccination, while arterial thromboembolism and ischemic stroke is more frequently observed after Pfizer vaccination [59].

Several studies reported the detection of anti-PF4 antibodies in cadaveric blood in post-SARS-CoV-2 vaccination patient blood [79,132]. Therefore, immediate collection of fresh blood for the analysis of anti-PF4 antibodies is recommended. Postmortem confirmation of thrombocytopenia is difficult as the level of platelet is normally depleted after death, especially in prolong postmortem intervals. Functional platelet activation assays such as PF4 induced platelet activation test (PIPA) and heparin-induced platelet activation test (HIPA), could serve as alternative way to identify identification of VITT, which is not significantly affected by postmortem interval [69,133].

Finally, to ascertain the causal relationship of death with vaccination, a multidisciplinary approach is required for assessing each case of death after vaccination by integrating epidemiological data, risk factors, clinical information, postmortem findings, and laboratory studies. (Tables 4 and 5).

| Table 4 | Summary of order of incidence and total number of reported cases. |
|---|---|
| **Adverse reaction** | **Parameter** | **First** | **Second** | **Third** | **Fourth** |
| Anaphylaxis | Total number of cases | Pfizer | AstraZeneca | Moderna | Janssen |
| Incidence | Incidence | Moderna | Pfizer | AstraZeneca | Janssen |
| Myocarditis | Total number of cases | Pfizer | Moderna | AstraZeneca | Janssen |
| Incidence | Incidence | Moderna | Pfizer | AstraZeneca | Janssen |
| Thrombosis | Total number of cases | Pfizer | Janssen | Janssen | Moderna |
| Incidence | Incidence | AstraZeneca | Pfizer | Janssen | Moderna |
5. Conclusions

This study presented the incident, onset, histopathology and biochemistry analysis of major post-vaccination lethally side effects.

Table 5
Checklist for postmortem examination in vaccination-related death.

| Category                          | Details                                                      |
|----------------------------------|--------------------------------------------------------------|
| Past medical history and vaccine information | General: Comorbidity, heart disease, pulmonary disease, coagulopathy |
|                                  | History of COVID-19 infection                                 |
|                                  | Vaccine related information                                  |
|                                  | Number of vaccination dose                                    |
|                                  | Type and batch of vaccine                                     |
|                                  | Data and time of onset of symptom                             |
|                                  | Time interval between vaccination and death                   |
| Anaphylaxis                      | History of an allergy reaction, type of reaction, and allergen|
|                                  | History of exposure to allergen other than vaccine e.g., food, medication |
|                                  | Clinical symptoms of wheezing, shortness of breath, cough, cyanosis, rhinorrhea, tachycardia, hypotension, syncope, nausea, vomiting, abdominal pain, of diarrhea. |
| Myocarditis                      | History of recent fever, upper respiratory tract infection, arthralgia, pharyngitis, tonsillitis, medication, or toxin exposure. |
|                                  | Medical history of diabetes mellitus, obesity, antiphospholipid syndrome, coagulopathy |
| Internal & external examination  | Injection site reaction                                       |
|                                  | Local or generalized skin rash e.g., urticaria, erythema, angioedema |
|                                  | Pneumothorax assessment                                       |
|                                  | Respiratory tract: laryngeal edema, hyperinflected lung, mucus plugging |
|                                  | Gastrointestinal tract abnormality                            |
| Laboratory investigation         | General investigation                                          |
|                                  | Upper (nasopharyngeal, oropharyngeal) and lower (sputum, tracheal, lung) respiratory tract swab for COVID-19 |
|                                  | Blood culture for bacterial and fungal organism               |
|                                  | Toxicology analysis                                           |
|                                  | Extensive histopathological examination of targeted organs and representative sampling of other organs. |
| Anaphylaxis                      | Serum tryptase, Total Ig E, specific IgE (PEG), anti-PEG antibody, interleukin-6, CRP, complement factor 3.5 [344] |
|                                  | Histopathological examination of injection site (skin, deltoid muscle, axillary lymph node), respiratory tract (pharyngeal mucosa, epiglottis, trachea, bronchus, all the lung lobes), GIT tract, myocardium, coronary arteries and spleen for mast cell and eosinophil infiltration. |
|                                  | Mast cell identification and quantification using Giemsa and immunostaining e.g. CD117, anti-tryptase, and anti-chymase antibody. Normal number of mast cell in: Lung (0.051 per HPF), skin (0.79 per HPF), colon (13 per HPF) [135–137] |
| Myocarditis                      | Troponin, CK-MB [127]                                        |
|                                  | Blood, pericardial fluid, myocardium for PCR and viral culture for cardiotropic virus e.g. influenza, adenovirus, enterovirus, cytomegalovirus, Epstein-Barr virus, Herpes simplex virus. Human Herpes virus 6, Mycoplasma, Syphilis, Leptospirosis, Borrelia burgdorferi serology |
| VITT                             | Platelet factor 4 (PF4) concentration                         |
|                                  | Platelet factor 4 (PF4) concentration                         |
|                                  | Proper storage of extra blood and tissue samples for future investigation. |

The prelicensing clinical trial does not represent the incidence of vaccine side effects; passive surveillance, identifying and weighting the potential side effect against the advantages after vaccination are important. An immediate standardized autopsy approach, histopathology and biochemistry analysis is required to improve the investigation the causality of post-vaccination death. Through improving the accuracy of investigation, a guideline of vaccine selection could be suggested and decrease the mortality rate of post-vaccination. The safety of vaccination is the top priority of SARS-CoV-2 battle and gain public confidence in vaccination program.

CRediT authorship contribution statement

Lii Jy Ye Tan: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing.
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Wong Cheng Poh: Formal analysis, Investigation, Resources.
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Declaration of Competing Interest

None.

Acknowledgements

The authors thank the Director-General of Ministry of Health Malaysia, Director of Perak State Health Department, Dean of Faculty of Medicine, Quest University and those who helped and assisted in the preparation and publication of this article.

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