Inconsistent safety outcome reporting in randomized clinical trials of COVID-19 vaccines complicates informed medical decisions

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In recent months there has been extensive reporting of interim efficacy results of several COVID-19 vaccine randomized clinical trials. Considerably less attention has been placed on the safety outcomes of these trials. Before large-scale observational studies became available, individual patients and clinicians needed to make indirect comparisons between COVID-19 vaccines in regions-such as Hong Kong-where patients may choose among vaccine products. The early results of COVID-19 vaccines trials published in top medical journals[1-4] were some of the first publicly available data reporting vaccine safety outcomes, yet the reporting of these outcomes in journal articles should be more consistent, comprehensive, and transparent to allow for informed comparisons between different vaccines.

Ramasamy et al. reported local and systemic adverse reactions for Vaxzevria (COVID-19 Vaccine (ChAdOx1-S [recombinant]); AstraZeneca AB, Sweden) versus control (MenACWY vaccine).[3] However, we note that the detailed adverse reaction data for the controls appears to be missing from the supplementary tables. In their studies of CoronaVac (COVID-19 Vaccine (Vero Cell), Inactivated; Sinovac Life Sciences, China), Wu et al. and Zhang et al. define the primary safety endpoint as *adverse reactions*.[1,2] The International Conference on Harmonisation defines adverse events as “Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”.[5] In contrast, an adverse reaction is an event that is judged to be caused by the vaccine under study. In the published papers by Wu et al. and Zhang et al., there appears to be a lack of clarity in the reporting as both terms are used somewhat interchangeably. There are also discrepancies between the primary outcome of *adverse reactions* in the study protocols and *adverse events* in the statistical analysis plans.

To date, the Government of Hong Kong has purchased three COVID-19 vaccines which use three different vaccine platform technologies: Comirnaty (COVID-19 mRNA Vaccine

(nucleoside-modified); BioNTech Manufacturing GmbH, Germany), CoronaVac, and Vaxzevria. To emphasize the importance of consistent, clear, and transparent reporting of safety outcomes in published articles of COVID-19 vaccine randomized clinical trials, a summary of the frequency of adverse events or reactions reported in clinical trials after the first dose of these three vaccines is shown in the Table. Published rates of adverse reactions for CoronaVac appear to be lower when compared with Comirnaty and Vaxzevria. It is not clear to us whether the investigators of CoronaVac used different definitions or different processes to ascertain whether an adverse event qualified as an adverse reaction, which could have resulted in a much lower frequency of reported adverse reactions when compared with Comirnaty and Vaxzevria, but this is difficult to ascertain from the published article. Tools created by the Brighton Collaboration,[6] which establishes consistent definitions for adverse events following immunization, have been endorsed and recommended by the WHO's Global Advisory Committee on Vaccine Safety.[7] If vaccine developers used the safety templates and reported accordingly, it would greatly facilitate this area of discussion.

Moreover, we encourage the authors and their sponsors to clearly report the frequency of pooled and stratified *adverse events* and *adverse reactions* for all COVID-19 vaccine trials. Similarly, we also encourage journal reviewers and editors to carefully assess the reporting of these safety data. By providing this much needed information, patients and clinicians will be able to meet the challenge of indirectly comparing vaccine safety profiles. This safety information will enhance informed decisions about vaccine selection at the individual level, taking into consideration not only efficacy, but also the overall frequency and severity of adverse events. We note that some regulatory authorities, such as the US Food and Drug Administration and the European Medicines Agency, have made detailed COVID-19 vaccine safety data publicly available. These data, in addition the rapidly emerging evidence from large-scale observational studies and spontaneous reports, will enhance our understanding of the

comparative safety of the available COVID-19 vaccines. Observational studies are essential for assessing COVID-19 vaccine safety in populations with limited inclusion in randomized clinical trials such as very old and frail adults, pregnant women, and patients who are immunocompromised. To better inform the public, clinicians, and policy makers about the real-world comparative safety of COVID-19 vaccines, the Department of Health of Hong Kong has commissioned the COVID-19 Vaccines Adverse Events Response & Evaluation (CARE) Programme: a comprehensive real-time surveillance study that aims to closely monitor the known and potential adverse events following immunization of COVID-19 vaccines in Hong Kong.[8]

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Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

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Code availability

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Authors' contributions

Joseph E Blais: Literature search (English), writing (original draft and editing), conceptualization, data extraction.

Yue Wei: Literature search (Chinese), writing (original draft and editing), data extraction and data validation.

Celine SL Chui: Writing (editing), comments and revision.

Esther W Chan: Conceptualization, writing (original draft and editing), supervision.

Ian CK Wong: Comments and revision, supervision.

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1 **Table**

Table. Frequency of overall and selected vaccine adverse events (Comirnaty[a]) and adverse reactions (CoronaVac[b] and Vaxzevria[c]) as reported in published COVID-19 vaccine clinical trials.

Adverse Event/Reaction	Vaccine	18-59/16-55/18-55 years of age		≥ 60/56 years of age	
		Intervention (%)	Control (%)	Intervention (%)	Control (%)
Injection site pain	CoronaVac	8	7	7	3
	Comirnaty	83	14	71	9
	Vaxzevria	61	NR	29	NR
Fatigue	CoronaVac	7	2	3	0
	Comirnaty	47	33	34	23
	Vaxzevria	76	NR	44	NR
Fever	CoronaVac	3	2	2	1
	Comirnaty	4	1	1	0
	Vaxzevria	24	NR	0	NR
Headache	CoronaVac	2	0	0	0
	Comirnaty	42	34	25	18
	Vaxzevria	65	NR	44	NR
Overall (any adverse event)	CoronaVac	17	15	15	15
	Comirnaty	27	12	NR	NR
	Vaxzevria	98	74	85	48

NR: not reported.

[a] Outcomes are for the two-dose regimen of Comirnaty 30 μg given 21 days apart. Adverse events within 7 days of the first dose were extracted from Figure 2 of Polack et al.[4] The overall frequency of any adverse event was only reported for the overall safety population and not stratified by age group.

[b] Outcomes are for the two-dose regimen of CoronaVac 3 μg given 28 days apart (low dose). Adverse reactions were extracted from supplementary table 3-12 for the combined phase 1/2 trials (Zhang et al)[2] and from supplementary table 3-3 for the phase 2 trial (Wu et al).[1] reported within 28 days of the first dose.

[c] Outcomes are for the two-dose regimen of Vaxzevria (standard dose: 3·5–6·5 × 10^{10} virus particles) given 28 days apart. Adverse reactions were solicited up to 7 days after the first dose. Specific adverse reactions were extracted from supplementary table S5-S7, while overall adverse events indicate any local or systemic adverse reaction for the priming dose (supplementary table S12).[3] Results for the 56-69 and 70+ age groups were pooled.

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