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Quantitative Approaches for Causality Assessment of Adverse Events Following Immunisation for COVID-19 Vaccines

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ABSTRACT

Vaccine safety surveillance is important to identify and manage adverse events following immunisation (AEFI) and avoid vaccine hesitancy. Currently, COVID-19 vaccines are administered to large numbers of people to try and curb the pandemic. In this paper, quantitative methods for causality assessment of AEFI are described. Qualitative methods for causality assessment involve an expert panel reviewing each AEFI report to determine whether the AEFI can be attributed to the vaccine. Each AEFI is determined to be classified as consistent, inconsistent, indeterminate or unclassifiable in terms of causality. Quantitative approaches can strengthen causality assessment outcomes. However, the potential for bias and errors should be considered for each safety signal identified. Vaccine and population specific factors may affect AEFI incidence, with a need to obtain background rates to frame safety signals identified into the local context. Several case scenarios from the vaccine safety surveillance in Brunei are used to illustrate the practical application of quantitative approaches for AEFI causality assessment (including comparison of AESI incidence to background rates and disproportionality analysis), which complement the traditional qualitative methods.

Citation:

INTRODUCTION

Globally, the COVID-19 pandemic has wide-reaching consequences, causing disruptions to healthcare services, economies and personal freedom due to social restrictions and 'lockdowns' to curb the spread of the virus. As of 1st October 2021, there were 233,503,524 confirmed cases of COVID-19, including 4,777,503 deaths reported to the World Health Organisation (WHO) [1]. It is hoped that mass-vaccination programes with COVID-19 vaccines will help end this pandemic. As of 28th September 2021, a total of 6,143,369,655 vaccine doses have been administered worldwide [1].

While the overall benefit-risk assessment weighs significantly in favour of vaccination, vaccine safety surveillance is important to identify and manage adverse outcomes from vaccines. This is necessary to avoid vaccine hesitancy, which can significantly impact public health measures to ensure a good uptake of immunization and herd immunity [2].

An adverse event following immunization (AEFI) is defined as 'any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease' [3].

It should be emphasized that an AEFI does not necessarily mean the vaccine caused the adverse reaction; it simply means that the side effects occurred temporally after vaccination. The AEFI then requires further review and assessment to determine whether it was a consequence of receiving the vaccine. It is recommended that healthcare professionals report suspected AEFI to their national pharmacovigilance centres to perform causality assessment and investigate reports of vaccine quality and safety concerns.

In this paper, quantitative methods for causality assessment of AEFI are described, with illustrative examples from the COVID-19 vaccination programme in Brunei used to demonstrate how safety signals may be assessed using background rates.

Causality Assessment – Qualitative Versus Quantitative Approaches:

Causality assessment aims to evaluate reported AEFI and determine the likelihood of the vaccine causing the adverse event. This requires an expert panel to review each AEFI report, which determines by consensus whether the AEFI can be attributed to the vaccine. The panel members should have updated knowledge and expertise of vaccine safety profiles and

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the type of AEFI in question. For example, if a patient presents with chest pain and had a confirmed diagnosis of myocarditis after appropriate investigations and cardiologist review after receiving an mRNA vaccine, one may reasonably attribute this AEFI to the vaccine. Other potential causes of myocarditis, such as viral infections, including COVID-19 infections should be ruled out. This is straight forward given the available literature reporting this known complication [4].

A global collaboration called the Brighton Collaboration was set up to standardize case definitions and provide guidelines on AEFI in response to the variability in data collection, analysis and presentation of immunization safety data [5]. This standardization allows AEFI data across different settings to be comparable. For example, the case definition of anaphylaxis systematically outlines the diagnostic criteria, symptoms based on organs affected (dermatologic or mucosal, cardiovascular, respiratory, gastrointestinal) and laboratory investigations to levels of diagnostic certainty for anaphylaxis [6].

A case study found that application of these Brighton Collaboration case definitions improved the ability of clinicians to provide descriptions of the adverse event and enabled consistent reporting across regional and national levels [7]. An accurate diagnosis is crucial before causality assessment is performed. A study reviewing ICD-10 coded patients with anaphylaxis found that almost 20% did not meet level 1 to 3 criteria for the diagnosis when these case definitions were applied [8].

Once an AEFI diagnosis is confirmed, this can be classified within four categories. Firstly, the evidence is convincing for a causal relationship; secondly, the data favours or suggests a causal relationship; thirdly, the evidence supports rejection of a causal relationship; and finally, more data or monitoring is required as there is inadequate information to accept or reject a causal relationship [9]. The World Health Organisation has developed an assessment tool to support causality assessment of AEFI, harmonized with the Clinical Immunisation Safety Assessment. This tool requires the consideration of eligibility for assessment, requiring a review of the AEFI diagnosis and confirmation of the administered vaccine. There is also a checklist for assessors to systematically obtain information regarding the AEFI; and a decision support algorithm to enable assessors to classify each individual AEFI. The final classifications are consistent, inconsistent, indeterminate or unclassifiable. These outcomes help guide assessors to recommend public health decisions for action, particularly if the AEFI is deemed as a vaccine product related reaction [10].

However, it may be less certain whether an AEFI is caused by a vaccine if there were no previous reports confirming an association. In an Israeli nationwide case-control study with 884,828 people in each group to evaluate the safety profile of BNT162b2 mRNA vaccine, an association was found between vaccine recipients and myocarditis, lymphadenopathy, appendicitis and herpes zoster infection [11]. It would be difficult for clinicians to consider whether a patient presenting with herpes zoster infection could be attributed to the vaccine, without a confirmed association based on population data. Thus, the use of quantitative approaches is a useful adjunct to causality assessment, and may add further weight as to whether an AEFI is caused by a vaccine or not. The outcome from this causality assessment is important, as this may have implications on compensation claims for injuries due to vaccination [12].

The following scenario illustrates how quantitative approaches may aid causality assessment. A vaccine recipient's car accidentally slid off the road and landed into a ditch. As this unfortunate event occurred after vaccination, it could be considered as an AEFI. Based on qualitative analysis, heavy rain causing slippery roads and poor visibility could easily account for this accident (*i.e.*, coincidental). However, if there was an increase in reports of car accidents among vaccine recipients which was out of proportion to the expected background rates of car accidents in the area, this would indicate a safety signal warranting further investigation. Additional weight is given to this association if there was a supporting mechanism or hypothesis for the AEFI, such as lethargy post-vaccination contributing to the increased risk of road traffic accidents. Thus, any AEFI should reported regardless if the reporter thinks the adverse event is caused by the vaccine or not. In addition, quantitative approaches can be used to supplement findings of causality from qualitative approaches of each AEFI report.

Considerations for Causality Assessment of AEFI Using Quantitative Approaches:

1. The Potential for Bias and Errors Should be Considered for each Safety Signal Identified:

There are several considerations that should be taken into account when using quantitative approaches, particularly reporting bias. A study reviewing the trends in reported AEFI globally found a significant fluctuation in AEFI reporting between countries and over time, with the least AEFI reports received from South-East Asia and Africa [13]. This may reflect the strength of their vaccine safety surveillance and pharmacovigilance systems. Additional information is also required regarding the quality of the reporting system and the capacity to detect and manage vaccine safety problems at a national level.

In Ontario, Canada, gender-specific trends were found within their passive vaccine safety surveillance programme. There was a female:male reporting ratio of 1.9, with the most gender-specific differences in adults between 18 to 64 years. All the event categories were predominantly reported by females. The highest discrepancy between genders were for oculo-respiratory syndrome, paraesthesia and anaphylaxis [14].

While most AEFI are reported by healthcare practitioners, a study from Victoria, Australia reviewed the contribution of consumer reporting for vaccine safety monitoring. This study found that consumer reports were 5% more likely to describe AEFI and 10% more likely to result in specialist clinic attendance compared to those reported by healthcare professionals. There was a preference of consumers to report by phone (85%) rather than online, which suggests that opportunities to report AEFI may affect incidence rates [15]. Therefore, a robust system is required, including linking the database for real world active safety surveillance across multiple points of community vaccine delivery and across the continuum of vaccine recipients, pharmacists, doctors in clinics and hospitals, as well as schools and workplaces. [16].

2. Vaccine or Population Specific Factors May Affect Incidence of AEFI

AEFI can be classified as general, vaccine platform-specific (e.g., mRNA, viral vector, protein) or population specific (e.g., children, pregnant women, older adults). Adverse

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events of special interest (AESI) for COVID-19 mass vaccination schedule mostly occur within six weeks; those with long latency periods require different approaches and specialized quantitative methods for monitoring. It is also important to collect disease epidemiology data in healthy people, people with underlying disease, in addition to vaccine coverage and vaccination status of people with AEFIs to put background rates into the appropriate context [17].

In terms of vaccine platforms, it was observed that the AstraZeneca vaccine (Vaxzevria) had more AEFI after the first dose, while mRNA vaccines (BNT162b2 by Pfizer-BioNTech) and mRNA-1273 by Moderna) had more AEFI reported after the second dose [18-21]. A cross- sectional study found that vaccines containing adjuvants are also associated with an increased risk of autoimmune and inflammatory AEFI, particularly in the first 3 days post-vaccination [22]. Heterologous vaccination, which has been associated with increase immunogenicity may also have a correspondingly higher risk of reactogenicity and AEFI [23].

There are also population specific considerations. Reviewing safety and efficacy data for COVID-19 vaccines should take into account the population in which the vaccines were studied. It is also important to note the subgroups of the population excluded from studies [24]. For older people, immune senescence raises a concern regarding poor vaccine efficacy, albeit a lower risk of developing AEFI [25]. However, older people also have a higher rate of comorbidities, which may affect the safety profile of vaccines.

For pregnant women, the Global Alignment of Immunisation Safety Assessment in pregnancy (GAIA) project produced case definitions for pregnancy and neonatal outcomes after maternal vaccination. Standardized definitions and diagnostic certainty are required to facilitate the availability of consistent and comparable data. A study found that only 50% of stillbirths could be assessed for diagnostic certainty, with a need for more information to distinguish between antepartum and intrapartum stillbirth [26]. There were also challenges with interpreting physiological changes, difficulties in mother-child linkage and a lack of longer-term follow-up for children. In addition, there were potential sources of bias, such as differential access and utilization of antenatal care, a seasonal timing for pregnancy in some localities and unmeasured determinants of pregnancy outcomes [27] For paediatrics AEFI monitoring, there should also be concomitant disease surveillance to determine the risk-benefit between post-immunisation adverse events and vaccine-preventable infections [28].

3. Background Rates Are Useful to Identify Safety Signals for AEFI Monitoring

As medical events still occur before implementing vaccination programmes, it is useful to know the background rate so that when cumulative AEFI triggers the suspicion of a safety signal, there is a frame of reference available to compare rates. These rates vary over time, by geography, gender, age and socioeconomic status [29]. The Brighton Collaboration established a list of Adverse Events of Special Interest (AESI), which are potential adverse events previously linked to other vaccines. For example, aseptic arthritis is considered an AESI due to previous associations with the rubella vaccine [30] Ipsilateral axillary lymphadenopathy has been attributed to mRNA vaccines, thus is currently monitored for subsequent COVID-19 vaccines [31]. Therefore, even if a particular AEFI is under-reported; an increase in the incidence of specific AESI after a mass immunization programme should trigger the consideration of a potential safety signal.

There were large variations in observed rates of AESI based on age, gender and location when databases and electronic health records from eight developed countries were reviewed. Thus, each locality should consider collecting its own background rates of AESI, to take into account population level heterogeneity and the lack of stratification or standardization based on demographic factors [32].

4. Other Sources of Spurious Safety Signals from AEFI

The Vaccine Safety Datalink (VSD) from the United States monitors 9.2 million people annually in eight geographically diverse healthcare organisations. It monitors vaccination safety and compares cases to background rates, with signals of potential vaccine-safety issues identified once the test statistic exceeds a fixed threshold. Spurious safety signals were often identified due to inaccuracy of estimated background rates, changes in incidence or coding over time, inappropriate comparison groups, miscoding of outcomes in electronic records, or by chance alone [33]. These false signals are unavoidable, thus quantitative approaches to causality assessment and data interpretation should take into account the qualitative analysis of each case. Thus, both approaches are complementary, rather than to be used alone for causality assessment.

Practical Application of Quantitative Approaches for Causality Assessment:

This section contains several case scenarios and background rates from the vaccine safety surveillance in Brunei to demonstrate how quantitative approaches can be useful for AEFI causality assessment.

1. Background Rates for Selected AESI

In Brunei, each clinical encounter is recorded in a national electronic health record system. All clinical encounters in outpatient clinics and hospital admissions require an ICD-10 code. Before the COVID-19 vaccines were introduced, background rates were obtained for selected AESI, as shown in Figure 1. While this demonstrates the frequency of selected AESI, potential baseline rates for each condition are also seen. The reduced incidence of encephalomyelitis and Guillain-Barre syndrome in 2020 is due to privatization of neurology services that year, thus there were less neurology AESI coded in the national public health records. Thus the 2018-2019 data should be used to identify the background rate for these conditions [8].

Each national pharmacovigilance centre may select or prioritise specific AESI to focus on. For example, when concerns were raised regarding the risk of cerebral venous sinus thrombosis (CVST) and thrombocytopenia after Vaxzevria, the likelihood of causality was supported by a proposed plausible pathophysiological process. Similar to heparin, the vaccine may induce an abnormal immune response, which was confirmed by identification of antibodies to platelet factor 4 in these patients [34]. This was also found to occur with the Janssen (AD26.COV2.S) vaccine and reported in a case series from the United States [35]. After systematically reviewing the evidence retrospectively, clinicians are now aware of the risk of CVST due to vaccine induced immune thrombotic thrombocytopenia [36].

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A high index of suspicion should be present among clinicians, who should ask 'Could this presenting complaint be contributed by the recent COVID-19 vaccination received by this patient?'. In addition to qualitative review of AEFI, baseline rates of AESI may identify safety signals of rare cases. Subsequent to this, baseline rates of thrombosis were also obtained to facilitate active monitoring of these conditions, regardless of AEFI reporting (as shown in Figure 2).

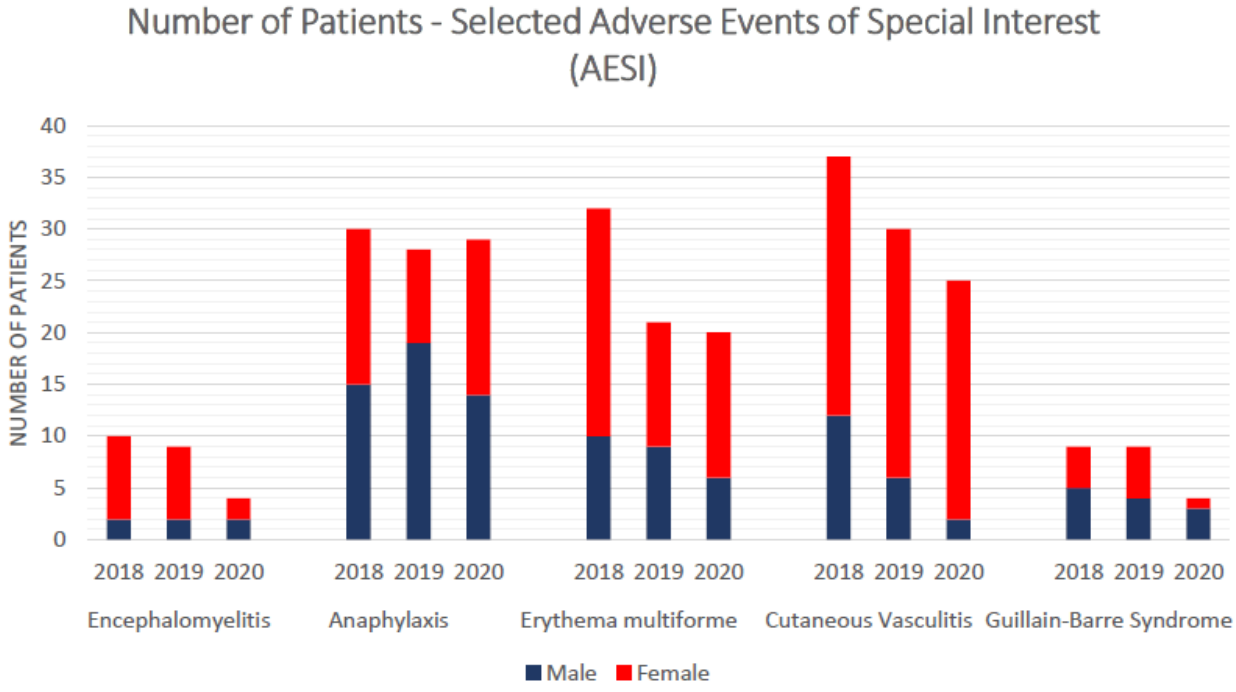

Fig. 1. Frequency of selected AESI (2018 to 2020).
Selected AESI for monitoring at the start of the COVID-19 vaccine programme for active vaccine safety surveillance were: encephalomyelitis, anaphylaxis, erythema multiforme, cutaneous vasculitis and Guillain-Barre syndrome.

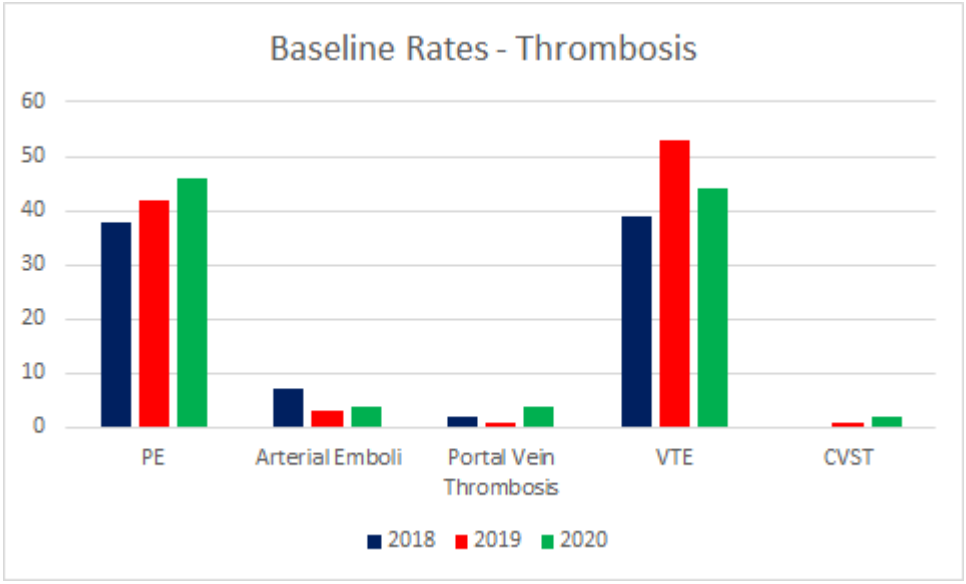

Fig. 2. Frequency of thrombosis-related AESI (2018 to 2020).
PE: Pulmonary Embolism; VTE: Venous Thrombo-Embolism; CVST: Cerebral Venous Sinus Thrombosis.

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2. Community death as an AEFI

A death after vaccination is a serious concern, particularly if it occurred within a short time frame after vaccination. Causality assessment is important to rule out the vaccine causing such an unfortunate event. The WHO outlines an approach for causality assessment of death as an AEFI, with an updated version for COVID-19 vaccines [37-38]. The cause of death can only be confirmed through a post-mortem examination, which includes histology, biochemical, microbiology and toxicology analysis. However, post-mortem examination may not be accessible or accepted in some cultural settings.

In this case example, a person collapsed in the community and passed away despite attempts at cardiorespiratory resuscitation. A few days later, it was realized that the person received a COVID-19 vaccine more than two months earlier. Subsequently, there were queries whether this death was vaccine related. While this was unlikely given the length of time between vaccination and death, a qualitative approach was applied to assess whether there was an increase in community deaths since the use of COVID-19 vaccines.

Figure 3 shows the total collapsed cases in the community from national paramedic records. Data collection only started in 2018, thus records were more complete from 2019 onwards. Taking into account the incident occurred in June 2021 (6 months of the year only), the number of community collapsed cases appear to be consistent with previous background rates from 2019 and 2020.

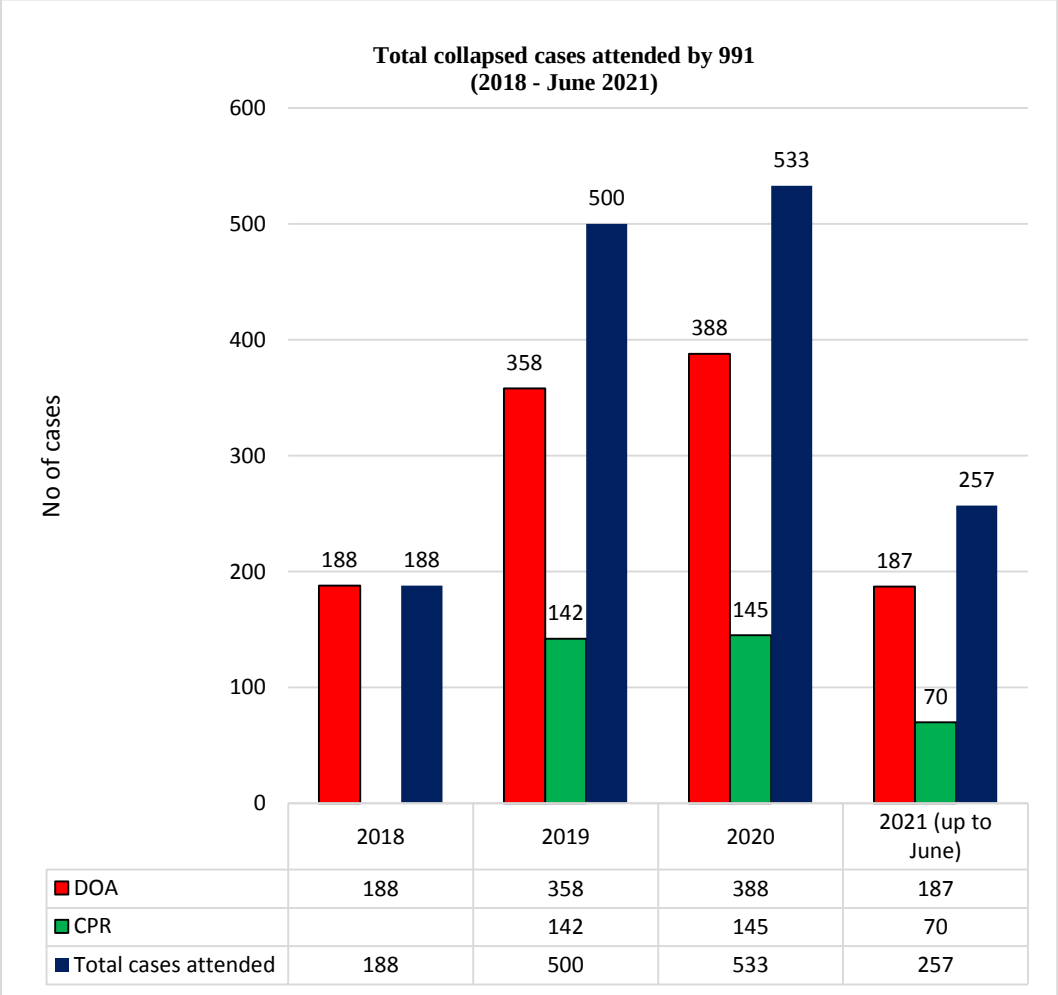

Fig. 3. Collapsed cases from the community attended by 99 1 paramedics (2018 to June 2021).
Cases found collapsed in the community were identified and categorized as DOA or CPR: DOA – Dead on Arrival; CPR- Cardiopulmonary resuscitation attempted.

Given that the vaccination programme started 3 months prior, the monthly trend of community deaths was also analysed and shown in Figure 4. This did not identify a spike or increase in community deaths since the implementation of COVID-19 vaccinations. Therefore, the coincidental nature of this community death as an AEFI was supported by quantitative analysis.

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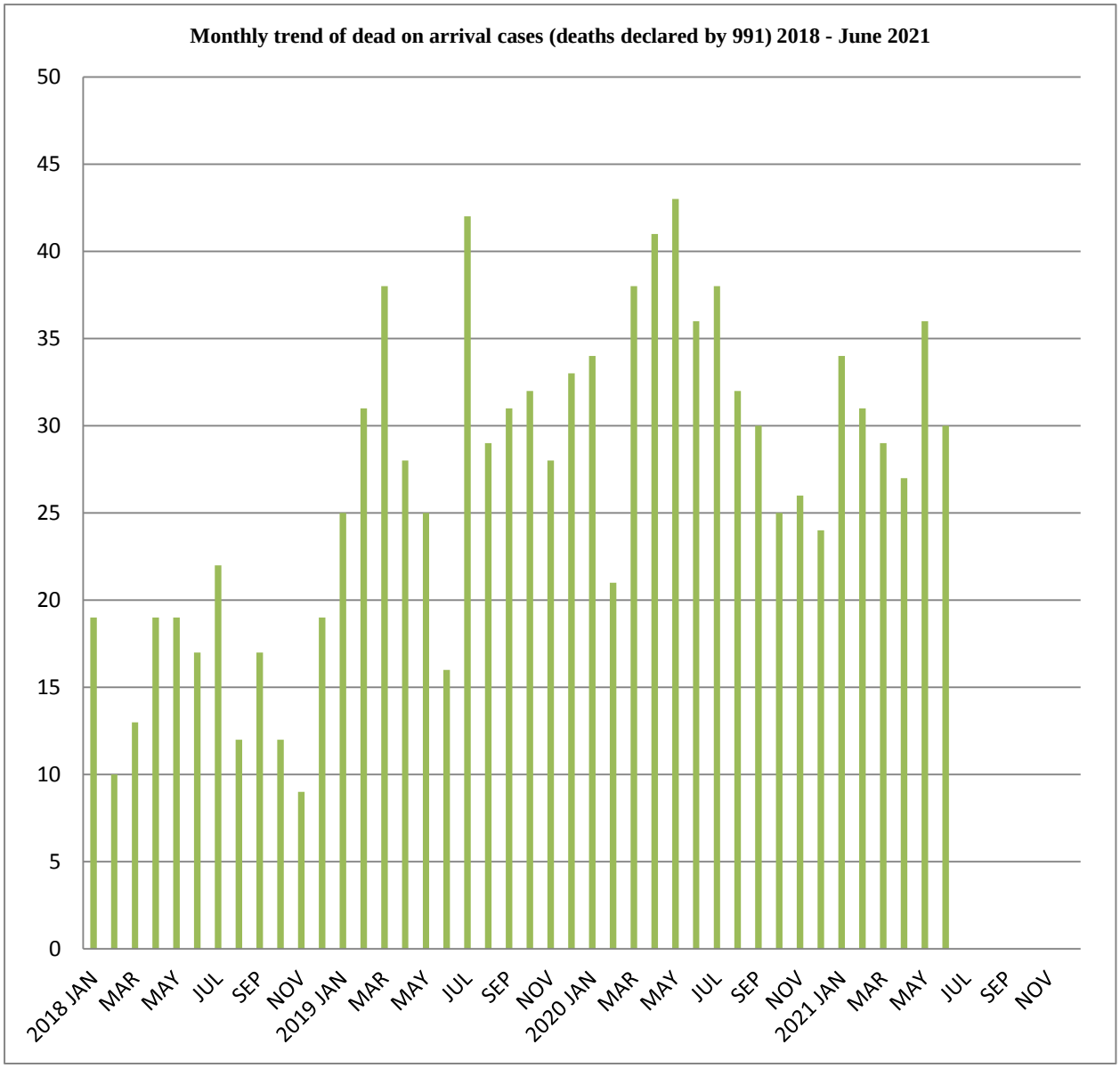

Fig. 4. Monthly trend of dead-on-arrival cases including background rates 2018 to 2021 (as of 30 June 2021).

3. Intracerebral Haemorrhage (ICH)

Concerns were also raised regarding ICH as a potential safety signal due to the large number of reported ICH as an AEFI. However, absolute numbers of AEFI reports should not be used (incidence rates are preferred) as an indicator of safety concerns. A national study found that more than a third of adults were hypertensive, of which 28.6% were not previously diagnosed. This places a significant proportion of the population at risk for developing ICH [39].

The frequencies of ischaemic and haemorrhagic strokes are shown in Figure 5. Although the number of ICH cases (in red) appear stable, there was a concern regarding a possible increase in 2021, given that there are still four months remaining when this data was obtained (*i.e.*, if the cases are diagnosed at a uniform rate over the year, this could indicate a 25% increase in ICH for 2021).

As the number of local reports for ICH are relatively small, a larger database for quantitative analysis would be useful to assess this safety signal further. Disproportionality analysis of haemorrhagic and ischaemic stroke AEFI following COVID-19 vaccination was performed based on data from the World Health Organisation Uppsala Monitoring Centre (WHO-UMC) Global database, Vigibase as of 15th September 2021 [40]. The results are summarized in Table 1. This showed that while there was a potential signal for ischaemic stroke (particularly with BNT162b2 with positive IC and IC025 scores of 1.8 and 1.7), this was not the case for ICH (with negative IC and IC025 scores for all vaccines).

The Vigilyze component of Vigibase from the Uppsala Monitoring Centre is accessible by affiliated national pharmacovigilance centres, which also contribute AEFI reports to the global database. Disproportionality analysis is a validated approach to explore and generate signals. Positive 'Information Component' (IC) indicates disproportionate reporting of the AEFI for the vaccine, which helps to identify whether a reported vaccine-AEFI combination is reported more often than expected. The IC_{025} is the lower 95% credibility interval for IC, which is the threshold used for statistical significance. Thus, a positive IC and IC_{025} suggests a potential safety signal [40].

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However, the finding of a disproportionality ratio does not confirm causality. It should trigger a case-control or cohort analysis or reinvestigation of data acquired from pharmacology and randomized controlled trials [41]. In addition, disproportionality analysis should use a minimum number of reports (500 for national databases, 5000 for databases that are not country specific) to avoid spurious associations identified through disproportionality analysis [42].

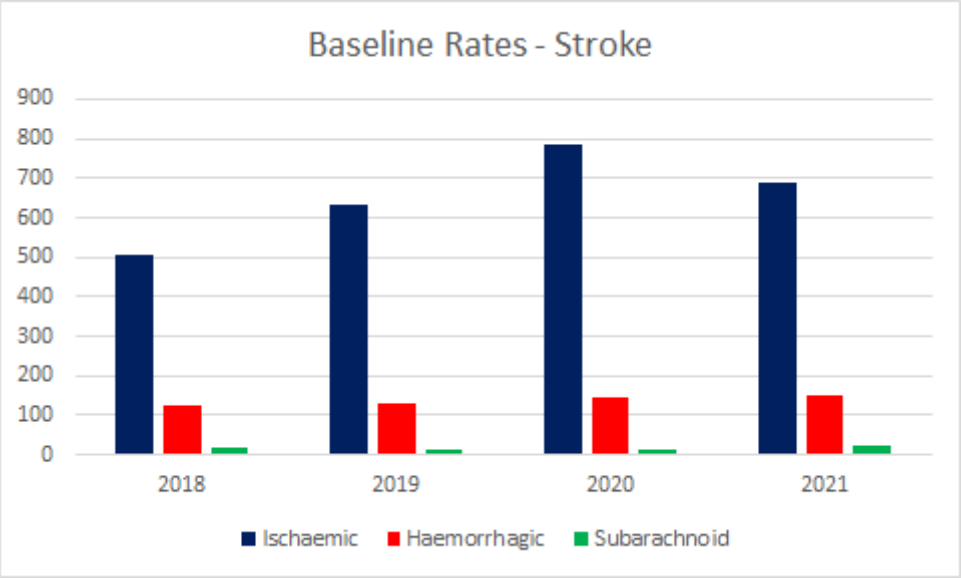

Fig. 5. Baseline rates of ischaemic and haemorrhagic strokes 2018 to 2021 (as of 30 August 2021)

Table 1. Disproportionality analysis of COVID-19 vaccination haemorrhagic and ischaemic stroke AEFI

All COVID-19 vaccines	AstraZeneca	mRNA-1273	BNT162b2	Other Vaccines
Haemorrhagic Stroke:				
n (Total = 404)	101 (25.0%)	52 (12.9%)	219 (54.2%)	32 (7.9%)
IC	-0.7	-1.0	-0.1	
IC_{025}	-0.9	-1.4	-0.3	
Ischaemic Stroke:				
n (Total = 2472)	605 (24.5%)	309 (12.5%)	1433 (58.0%)	125 (5.1%)
IC	1.1	0.8	1.8	
IC_{025}	1.0	0.6	1.7	

IC: Information Component; **IC_{025}:** lower end of 95% credibility interval for IC.

CONCLUSION

Causality assessment is an important process in pharmacovigilance to evaluate the likelihood whether an AEFI could be caused by a vaccine. While qualitative approaches are often used for this, it is hoped that this paper will encourage the use of quantitative approaches. The illustrated examples demonstrate the potential of reviewing whether there has been any increase in AESI compared to background rates, and applying disproportionality analysis using large databases such as Vigibase to strengthen conclusions from causality assessment.

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CONFLICT OF INTEREST

The author has no conflicts of interests to declare

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