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Title of paper: Impact of COVID-19 vaccine reports on disproportionality analyses for other vaccines

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1. INTRODUCTION

As of 8th February 2022, a total of 549,357 spontaneous UK vaccine reports have been received. Reports for COVID-19 vaccines make up 81.3% (n=446,635) of this total with 44.6% for the Astrazeneca vaccine, 30.1% for the Pfizer vaccine and 6.5% for the Moderna vaccine. Routine signal detection for vaccines relies on disproportionality analyses that compare the observed number reports for a particular vaccine-event combination with an expected number derived from data for all products in the dataset. Currently the routine analyses separate vaccines and drugs so that analyses for a particular vaccine-event combination use a vaccine only comparator dataset and analyses for a drug-event combination use a non-vaccine dataset. With the majority of the vaccine dataset now comprised of reports for COVID-19 vaccines, these have the potential to unduly influence the disproportionality statistics for other vaccines. If the safety/reporting profile for the COVID-19 vaccines differs significantly from other vaccines then this will impact disproportionality statistics and either mask potential signals or result in more false positive signals.

Additionally, there are potential issues with the large volume of COVID-19 vaccine reports impacting the disproportionality analyses for the COVID-19 vaccines themselves. The MHRA currently use the MGPS (Multi-item Gamma Poisson Shrinker) disproportionality method for routine signal detection which calculates the EBGM (Empirical Bayes Geometric Mean) measure of disproportionality. The EBGM is based on another measure, the Relative Reporting Ratio (RRR), which includes the drug/vaccine and event of interest along with all other products/events in the comparator dataset to generate the expected value. The underlying assumption for the RRR calculation is that if the proportion of reports for a particular drug/vaccine or event is negligible then the observed and expected values can be treated as independent. This assumption does not hold if the proportion of reports for a particular drug/vaccine or event is substantial, as is the case for the COVID-19 vaccines. In this scenario potential signals for COVID-19 vaccines could be suppressed. Van Holle et al.[1] describe this situation in their paper and on the basis of a simulation study suggest that a drug/vaccine or event should not make up more than 10% of reports.

This paper presents the findings of MHRA analyses to investigate the impact of COVID-19 vaccines on signal detection for other vaccines and also discusses the impact on signal detection for COVID-19 vaccines themselves when using the EBGM disproportionality measure.

2. METHODS

To investigate the impact of COVID-19 vaccine reports on disproportionality analyses for other vaccines two datamining runs were set up to either include or exclude reports for COVID-19 vaccines. Results from the two runs were compared in terms of absolute disproportionality score (EBGM and EB05), number of signals detected using different thresholds and a qualitative assessment of the signals gained or missed using each approach.

The current threshold for signalling based on disproportionality scores is EBGM≥2.5 and EB05 ≥1.8 with a report count of 3 or more. The numbers of signals based on this threshold generated by each datamining run were determined. A number of additional thresholds were also investigated for EBGM values ≥1.5 and ≥2 and for EB05 values >1 and ≥1.25.

[1] Van Holle & Bauchau V. The upper bound to the Relative Reporting Ratio – a measure of the impact of the violation of hidden assumptions underlying some disproportionality methods used in signal detection. Pharmacoepidemiol Drug Saf. 2014; 23:787-794

Potential issues with signal detection for COVID-19 vaccines when using the EBGM measure of disproportionality were investigated by comparing the distribution of RRR scores with PRR (Proportional Reporting Ratio) scores. The PRR does not include the drug/vaccine and event of interest in the comparator group and therefore is unaffected by the potential violation of independence between the observed and expected counts with the RRR when a drug/vaccine comprises a large proportion of reports in the dataset. Within a large dataset and where no product is over-represented, the differences between PRR and RRR calculations are small. This investigation was conducted using vaccine only and combined vaccine and drugs datamining runs.

3. RESULTS

As of the 08/02/2022, a total of 546,015 vaccine reports were available in the spontaneous vaccine dataset with reports concerning 69 different vaccines. These reports concerned a total of 1,700,442 events. Table 1 provides a breakdown of the numbers of reports and events for COVID-19 vaccines.

Table 1. Number of reports and events for COVID-19 vaccines

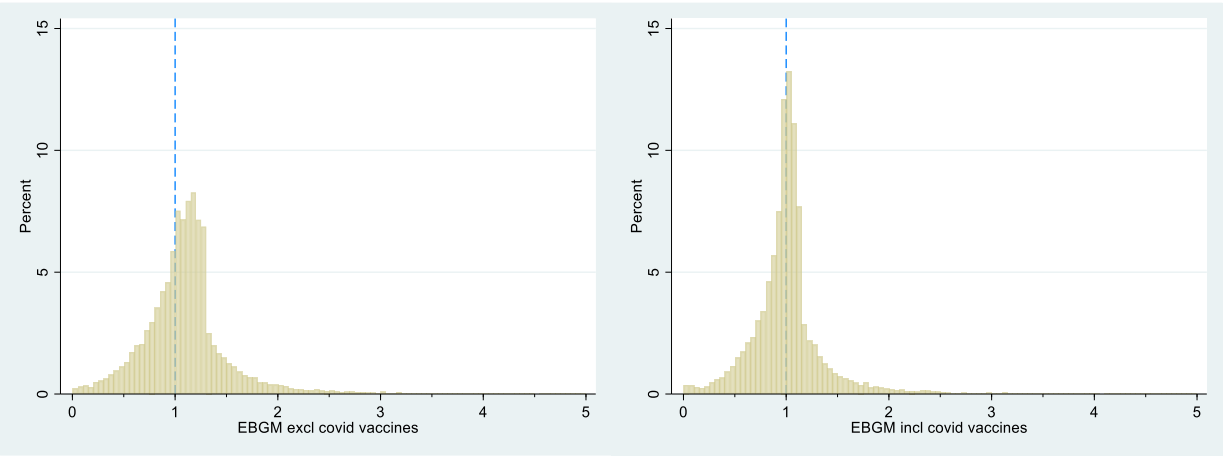
Vaccine	No. Reports	% of total vaccine reports	No. Events	% of total vaccine events
CHADOX1 NCOV-19 (Astrazeneca)	243466	44.6	862306	50.7
TOZINAMERAN (Pfizer/BioNTech)	164536	30.1	472455	27.8
MRNA-1273 (Moderna)	35532	6.5	118346	7.0
SARS-COV-2 VIRUS (brand unknown)	1519	0.3	4651	0.3
AD26.COV2.S (Janssen)	9	0.002	21	0.001

Two datamining runs were set up to generate disproportionality statistics for vaccine-event pairs for non-COVID-19 vaccines. The runs either included or excluded COVID-19 vaccines so that any differences in disproportionality statistics with including or excluding the COVID-19 vaccine reports in the comparator group could be analysed. A total of 22,808 vaccine-event pairs for non-COVID-19 vaccines were available for the analysis.

3.1 Comparison of EBGM and EB05 scores between datamining runs

Overall excluding COVID-19 vaccines from the background comparator group resulted in higher EBGM values (16,207 vaccine-event pairs had higher scores vs 6,375) but lower EB05 values (5,846 vaccine-event pairs had higher scores vs 16,819). Figures 1-4 show the distribution of EBGM and EB05 scores for each datamining run and table 2 shows the mean, median and range of values for each.

Figures 1 and 2. Distribution of EBGM scores for datamining runs including and excluding COVID-19 vaccines



Figures 3 and 4. Distribution of EB05 scores for datamining runs including and excluding COVID-19 vaccines

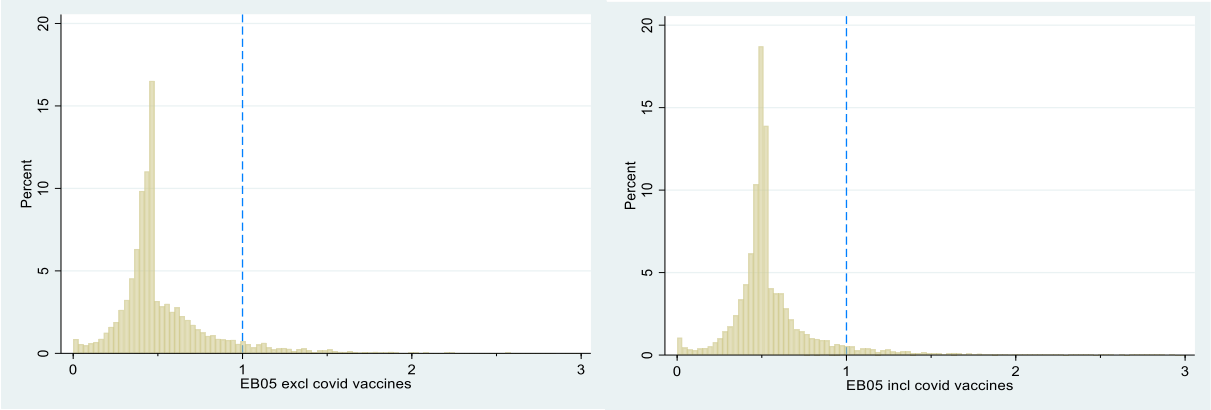


Table 2. Mean, median and range of EBGM and EB05 values datamining runs including and excluding COVID-19 vaccines

	COVID-19 vaccine reports included	COVID-19 vaccine reports excluded
Mean EBGM	1.258	1.209
Median EBGM	1.01	1.1
Minimum EBGM	0.004	0.004
Maximum EBGM	129.8	73.7
Mean EB05	0.688	0.591
Median EB05	0.507	0.459
Minimum EB05	0	0
Maximum EB05	88.2	53.4

Further exploration was also conducted on the absolute differences in EBGM and EB05 values between datamining including and excluding COVID-19 vaccines. The mean, median and range of absolute difference in values between the two datamining runs were calculated and are shown in table 3 below.

Table 3. Mean, median and range of absolute difference in EBGM and EB05 values between datamining runs including and excluding COVID-19 vaccines

	EBGM	EB05
Mean absolute difference	0.049	0.096
Median absolute difference	-0.08	0.047
5-95% percentile range	[-0.358-0.22]	[-0.162-0.159]
Range absolute difference	[-20.51-118.9]	[-16.07-80.76]

3.2 Differences in signalling between datamining runs including and excluding COVID-19 vaccines

The difference in signalling between the two datamining runs that either included or excluded COVID-19 vaccines was investigated. The current threshold for a signal based on disproportionality scores is EBGM≥2.5 and EB05 ≥1.8 with a report count of 3 or more. The numbers of signals reaching this threshold and additional thresholds based on EBGM or EB05 generated by each datamining run were determined. The results are shown in table 4 below.

Table 4. Numbers of vaccine-event pairs the met different EB05 signalling thresholds

	COVID-19 vaccine reports included	COVID-19 vaccine reports excluded
EBGM≥2.5, EB05≥1.8 & n≥3	436	399
EBGM>2	960	1113
EBGM>1.5	1938	2766
EB05≥1.25	986	1084
EB05≥1	1660	1917

The vaccine-event pairs that met the current signalling criteria (EBGM≥2.5, EB05≥1.8 & n≥3) were further investigated to determine the importance or otherwise of the differences. A total of 496 vaccine-event pairs met the signalling criteria from one or other datamining run. Of these, 339 pairs met the criteria in both datamining runs that included and excluded COVID-19 vaccines, 60 vaccine-event pairs flagged only in the dataset that excluded COVID-19 vaccines and 97 only in the dataset that included COVID-19 vaccines. The vaccine-event pairs that were only flagged in one or other dataset but not both were examined in more detail to determine what types of event might be gained or missed. Particular attention was paid to signals where the one approach signalled much more strongly than the other. Table 5 provide details of the events that would potentially gained as a signal or missed by either including or excluding COVID-19 vaccines.

Table 5. Vaccine signal events (MedDRA PTs) that would be gained or missed by including or excluding COVID-19 vaccine reports

Events flagged in dataset with COVID-19 vaccine reports included only	**Events flagged in dataset with COVID-19 vaccine reports excluded only**
Pregnancy outcomes (Exposure during pregnancy, Live birth, Breech presentation, Caesarean section, Foetal death, Abortion spontaneous, Abortion induced, Morning sickness)	Menstrual & gynaecological disorders (Menstruation delayed, Amenorrhoea, Vaginal haemorrhage, Vaginal discharge)
Injection site reactions (Administration site swelling, Application site pruritis, Injection site oedema, Injection site induration, Injection site bruising, Injection site erythema)	Chromaturia
	Oxygen saturation decreased
	Flatulence
	Fatal (Special PT Group)
Non-specific events (Adverse drug reaction, Therapy non-responder, Product use issue)	
Extra dose administered	
Circulatory collapse	
Loss of personal independence in daily activities	
Infective aneurysm	
Infective pulmonary exacerbation of cystic fibrosis	
Upper respiratory tract infection	
Hepatitis B	

3.3 Comparison between RRR and PRR scores for COVID-19 vaccines

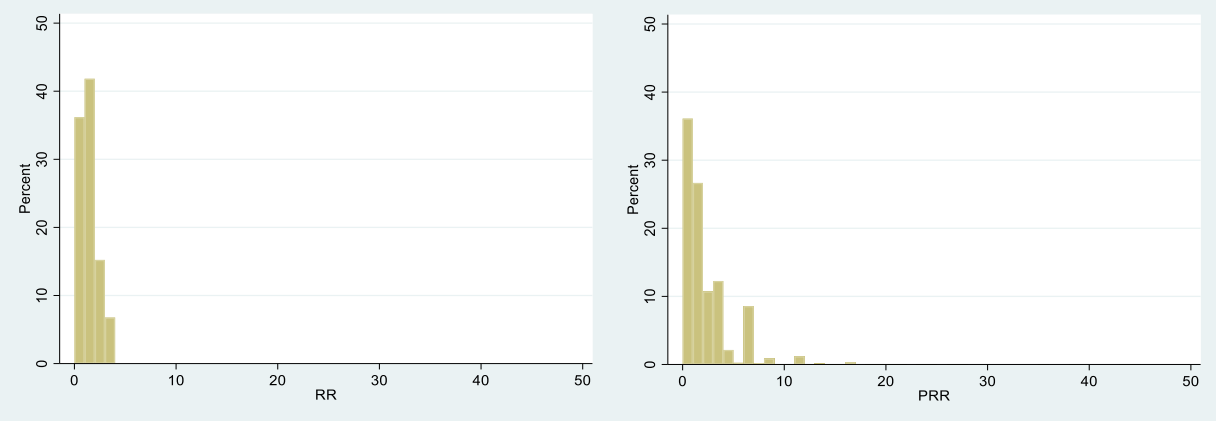
To investigate the potential issue with COVID-19 vaccines being over-represented in the vaccine dataset resulting in a suppression of the EBGM values, RRR and PRR scores were compared for COVID-19 vaccine-event pairs from both a vaccine-only datamining run and a combined vaccine and drugs datamining run. Table 1 shows that the COVID-19 vaccines that contribute a large amount of data to the vaccine dataset are CHADOX1 NCOV-19 (Astrazeneca) and Tozinameran (Pfizer/BioNTech) so this analysis focuses on these two vaccines.

The comparison between the RRR and PRR scores from a vaccine only datamining run showed considerable differences with the PRR of scores having a much wider range than the distribution of RRR scores. Table 6 shows the mean, median and range of RRR and PRR scores and the distribution of scores are shown in figures 5 and 6.

Table 6. Mean, median and range of RRR and PRR scores for CHADOX1 NCOV-19 and Tozinameran from a vaccine-only datamining run

	RRR	PRR
Mean	1.37	2.37
Median	1.12	1.24
Minimum	0.004	0.003
Maximum	3.32	44.1

Figures 5 and 6. Distribution of RRR and PRR scores for CHADOX1 NCOV-19 and Tozinameran from a vaccine-only datamining run.



Whilst the majority of vaccine-event pairs did not differ substantially between RRR and PRR, 25% of pairs had an absolute difference of 1.5 or more and 10% of 3.5 or more. A more detailed evaluation of individual vaccine-event pairs with the highest difference between RRR and PRR revealed the following examples:

Vaccine	Event	n	rr	prr	ebgm
CHADOX1 NCOV-19	Thrombosis with thrombocytopenia syndrome	17	2.24	43.5	1.83
CHADOX1 NCOV-19	Heparin-induced thrombocytopenia	15	2.24	38.5	1.79
TOZINAMERAN	Device defective	9	3.32	44.1	2.01
TOZINAMERAN	Liquid product physical issue	12	3.06	27.8	2.09

CHADOX1 NCOV-19	Cerebral mass effect	10	2.24	26.1	1.65
TOZINAMERAN	Necrotic lymphadenopathy	[redacted]	3.32	20.9	1.52

Results for the datamining run that combined drugs and vaccines showed more concordance between the RRR and PRR, persistent differences remained for 15% of vaccine-event pairs.

4. DISCUSSION

Currently reports for COVID-19 vaccines make up a large proportion of the UK spontaneous vaccine dataset (over 80%) with the Astrazeneca and Pfizer/BioNTech vaccines contributing the most reports. This volume of reports has the potential to affect signal detection for other vaccines but may also impact signal detection for these two vaccines as well.

In order to assess the potential impact on signal detection for other vaccines of the large volume of COVID-19 vaccine reports, comparisons in disproportionality measures (EBGM/EB05) were conducted for datasets either including or excluding the COVID-19 vaccine reports. This analysis showed that there were differences in EBGM/EB05 between the two datasets with EBGM values tending to be higher in the dataset that excluded COVID-19 vaccines but the EB05 values tending to be higher in the dataset that included these. The absolute magnitude of the difference in values was small however for the majority of vaccine-event pairs and suggests that overall the safety profile of the COVID-19 vaccines is broadly comparable to other vaccines in the dataset.

To further assess any potential effect of the COVID-19 reports on signal detection for other vaccines, signalling was investigated between datasets that either included or excluded COVID-19 vaccine reports. For the current signal threshold (EBGM≥2.5, EB05≥1.8 & n≥3) a similar number of vaccine-event pairs were flagged with nearly 70% overlap between the two datasets. For different signal thresholds at lower levels of EBGM and EB05, more signals were detected from the dataset that excluded COVID-19 reports. Further investigation into the signals detected using the current signal threshold that would either be gained or missed by either including or excluding COVID-19 vaccine reports showed that inclusion of the COVID-19 reports would suppress signals for events including menstrual/gynaecological disorders, chromaturia and oxygen saturation decreased. These events likely represent signals for the COVID-19 vaccines for which a higher than expected number of reports has been received and there is therefore a masking effect on signals for these events for other vaccines. This has been an issue in the past for other safety concerns that have generated a large volume of reports e.g. SSRIs and suicidal events. Signals that met the threshold with the inclusion of the COVID-19 vaccine reports only included some pregnancy outcomes, some injection site reaction terms and some non-specific terms. The pregnancy outcome signals likely represent a difference in population between the COVID-19 data and data for other vaccines with other vaccines often targeting pregnant women (e.g. influenza and pertussis vaccines) while the COVID-19 vaccines were administered to all adults. Some of the other events that signal with the inclusion of COVID-19 vaccines are MedDRA terms for which other more informative/appropriate terms are available and these terms may have been used less commonly for COVID-19 vaccine reports in favour of other terms.

Overall differences in disproportionality scores for other vaccines between datasets that either included or excluded COVID-19 vaccine reports were not substantial and the differences did not have a large impact on signalling for other vaccines. The results suggest that the safety profile of the COVID-19 vaccines is broadly similar to that of other vaccines. Caution should be taken for any known safety concerns with the COVID-19 vaccines that will have generated a large excess in reporting as these will have the potential to mask signals for other vaccines but this is not a situation unique to COVID-19 vaccines.

Based on the findings of the IMI PROTECT project on signal detection[2] and in-house studies, the MHRA will be changing signalling threshold criteria in the near future and will be subgrouping data based on time period. Disproportionality analyses will be calculated within each subgroup separately. Time periods have been determined based on numbers of reports received with each subgroup being a roughly similar size. As COVID-19 vaccines generated a very large volume of reports, 2021 is a subgroup on it's own. As such the majority of data for COVID-19 vaccines will be excluded from the majority of data for other vaccines going forward.

The second aspect of this paper was to investigate potential issues with signal detection for COVID-19 vaccines and Astrazeneca and Pfizer/BioNTech vaccines in particular due to the large proportion of reports contributed by these two products. The comparison between the RRR and PRR for these vaccines showed that whilst the majority of drug-event pairs had similar values for RRR and PRR, 25% of pairs had substantially higher PRR values to RRR. The maximum RRR value in the dataset was 3.32 compared with 44.1 for PRR. This suggests that the RRR value is being constrained due to the inclusion of the product of interest being included in the comparator group for the RRR calculation. Furthermore, the MGPS method shrinks the RRR value to generate the EBGM resulting in an even lower value which will make it difficult if not impossible to meet the signalling criteria.

One possibility to address this issue is to use a drugs and vaccines combined dataset for disproportionality for COVID-19 vaccines instead of a vaccines-only one. This has the effect of increasing the size of the dataset and thus reducing the proportion made up by the two COVID-19 vaccines. This approach is already in use for routine signal detection of COVID-19 vaccines that uses both a combined dataset and vaccine-only dataset to generate disproportionality statistics. The combined dataset mitigates some of the issue but large differences between PRR and RRR still exist for 15% of vaccine-event pairs. Another option would be to use the PRR disproportionality measure for the Astrazeneca and Pfizer/BioNTech vaccines to ensure that the statistics are not being suppressed.

5. CONCLUSIONS AND ADVICE SOUGHT

The results of the investigation into the impact of COVID-19 vaccine reports on disproportionality for other vaccines suggest that any impact is small and can be mitigated by assessors applying caution for events that are known safety issues for COVID-19 vaccines. Furthermore, with the imminent change in signalling criteria, the majority of COVID-19 vaccine data will be analysed separately from that for other vaccines through the use of subgroups.

For signal detection for the Astrazeneca and Pfizer/BioNTech vaccines, due to the large proportion of reports received for these vaccines and the impact of this on the RRR scores, it would be prudent to use the PRR as the disproportionality statistic for these going forward.

The Group are asked if they agree with the findings and conclusions of this paper and if they have any additional comments.

[2] Seabroke S, Candore G, Juhlin K et al. Performance of Stratified and Subgrouped Disproportionality Analyses in Spontaneous Databases. Drug Saf. 2016; 39:355-364