NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

VACCINE BENEFIT RISK EXPERT WORKING GROUP

Title of paper: Bell's palsy and myocarditis: Update from rapid cycle analysis and observed vs expected analyses

Type of paper: For advice

Active(s) rINN	Pfizer/BioNTech COVID-19 vaccine BNT162b2 COVID-19 Vaccine AstraZeneca solution for injection (ChAdOx1 S [recombinant])
Product name(s)	
Marketing Authorisation Holder(s)	Pfizer/BioNTech AstraZeneca
Legal status	Prescription Only Medicines
Therapeutic classification (ATC) code	
Previous assessments	1) Risk of Guillain Barre Syndrome (GBS) and facial paralysis with Pfizer/BioNTech COVID-19 vaccine VBR EWG 22nd December 2020 2) Update on the safety data for the Pfizer/BioNTech COVID-19 vaccine VBR EWG 13th January 2021
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1. Introduction

Bell's Palsy and myocarditis/pericarditis have been pre-identified as adverse events of special interest (AESI) for COVID-19 vaccines and are therefore subject to enhanced surveillance by the MHRA.

The Commission for Human Medicine has previously endorsed the MHRA Proactive Safety Monitoring of COVID 19 Vaccines Strategy. In summary, the strategy has four main strands, 1) enhanced passive surveillance using observed vs expected analyses to place Yellow Card reports into context, 2) targeted active surveillance in the Yellow Card Vaccine Monitor, 3) ecological and rapid cycle analyses of select AESI following vaccination using data from the Clinical Practice Research Datalink, and 4) epidemiological studies.

This paper presents an update on the findings on the enhanced passive surveillance and proactive use of the CPRD through ecological and rapid cycle analyses for the AESI Bell's Palsy and myocarditis / pericarditis.

2. Methods

Enhanced passive surveillance

AESI are being routinely monitored through enhanced passive surveillance using the Yellow Card scheme through the implementation of observed vs. expected analyses using the sequential Maximised Sequential Probability Ratio Test (MaxSPRT)[1]. These analyses place the spontaneous reports into the context of size of the vaccinated population and the background rate of the AESI. Age group specific background rates for each adverse event of special interest have been calculated using data from the Clinical Practice Research Datalink (CPRD) including linked secondary care data available through Hospital Episode Statistics. Sensitivity analyses for different levels of under-reporting of adverse events are considered.

Ecological analyses

Sequential ecological analyses are being conducted within the CPRD primary care data. Such analyses compare trends in event rates over time before and after the introduction of a vaccine within cohorts targeted and not targeted for vaccination. The interpretation of ecological analyses may be complicated by effects of the pandemic on patterns of healthcare seeking behaviour particularly during periods of lockdown.

Rapid cycle analysis

Rapid cycle analysis is the approach implemented by the US FDA and CDC utilising sequential methods such as the MaxSPRT within the longitudinal patient records available to the Vaccine Safety Datalink. This approach identifies events occurring within a risk window following vaccination and compares the observed number to the expected number based on

[1] Li L, Kulldorff M. A conditional maximised sequential probability ratio test for pharmacovigilance. Stat Med. 2010; 29: 294-95.

background rates. Within the rapid cycle analyses, as implemented within the CPRD, adjustments are made to the follow up time within the post-vaccination risk window to account for delay in records of events presenting or being diagnosed within secondary care making it into the primary care record. MHRA and CPRD have established the transfer of data on vaccinations and AESI on a weekly basis to support the implementation of rapid cycle analyses in the CPRD for COVID-19 vaccines.

3. Results

3.1. Vaccine exposure

Table 1 provides a summary of the number of vaccinations by brand, age, and dose administered in the UK until end 31st January 2021. These estimates have been extrapolated from England data provided by PHE to UK estimates based on population sizes as reported by the Office for National Statistics.

Table 1: Estimates of vaccine exposure numbers (millions)

Vaccine		**<50 years**	**50-69 years**	**70-79 years**	**80+ years**	**Total**
Pfizer / BioNTech	1st dose	[redacted]	[redacted]	[redacted]	[redacted]	6.64
	2nd dose	[redacted]	[redacted]	[redacted]	[redacted]	0.56
	Total	[redacted]	[redacted]	[redacted]	[redacted]	7.20
AstraZeneca	1st dose	[redacted]	[redacted]	[redacted]	[redacted]	3.10
	2nd dose	[redacted]				
	Total	[redacted]	[redacted]	[redacted]	[redacted]	3.10

3.2. Bell's Palsy

Yellow Card reports of Bell's Palsy for the Pfizer/BioNTech vaccine

Up to and including the 27th January 2021, the MHRA has received 79 cases reporting the PT facial paralysis and/or the PT facial paresis with the Pfizer/BioNTech vaccine; with 7 cases reporting both terms, 7 reporting facial paresis alone and 65 reporting facial paralysis alone. Patient sex was reported in 76 cases, of which 56 were female and 20 male. Where age was provided and sensical, it ranged from 20 to 90, with 37 reporting ages 50 and under and 37 were above 50 years old, and the remaining 5 cases not reporting age or reporting an unlikely age of 1 years.

Four of the 79 cases were in the context of cerebral infarction, cerebrovascular infarction, transient ischemic attack or haemorrhagic stroke which are considered alternative explanations for the facial paralysis reported; the one fatal case reported is the haemorrhagic stroke report. Of the remaining cases, four also report concurrent infection (COVID-19 (n=2), nasopharyngitis (n=1) and Herpes zoster (n=1)) which are also possible alternative aetiologies for the facial paralysis reported.

Of the remaining 71 cases, onset times were reported in 68 cases, and 35 of these reported onset within 1 day of vaccination, 13 were 2-3 days after vaccine, 10 were 4-7 days post vaccination and the remaining 10 cases ranged from 8-18 days post vaccination. In these 71 cases, the outcome for the facial paralysis and/or facial paresis was reported as recovered in 12 cases, recovering in 13 cases, not recovered in 41 cases and the outcome was unknown in 4 cases.

Overall, of the 79 cases identified, 8 had alternative aetiologies present for the facial paralysis or facial paresis reported in the cases, and suspected COVID-19 was reported in the medical history of a further 10 of the cases and one with a positive prior COVID-19 test. Additionally, a large number of cases reported an onset time of one day from vaccination which would not be plausible for vaccine involvement as there would not be sufficient time for an immune response to play a role in the events. The events are predominantly reported in females and the age range is evenly spread rather than being concentrated in the younger age group where Bell's palsy is more common.

In conclusion, a large number of the reports of possible Bell's palsy either report potential confounding factors or have an onset time that is implausible for being related to the vaccine. While causality has not been established in the remaining cases, it also is not confirmed based on this analysis. "Acute peripheral facial paralysis" is included as a rare side effect in the Pfizer/BioNTech COVID-19 vaccine UK product information based on 4 cases seen in the clinical trial vaccine arm vs none in the placebo arm, although this rate was not outside of the background rate expected in the trial population.

Yellow Card reports of Bell's Palsy for the AstraZeneca vaccine

Up to and including the 27th January 2021, the MHRA has received 10 cases reporting facial paralysis with the AstraZeneca vaccine. One of these cases also reports facial paresis. 9 of the patients were female and one male. Ages reported include [redacted] (age not reported in 2 cases). The time to onset was within 1 day in 5 cases, 2 days in 3 cases and 3 days in 2 cases. The facial paralysis was reported to have recovered in 2 cases, with the reaction recovering the same and following day, recovering in 2 cases and not recovered in the remaining cases.

A diagnosis of Bell's Palsy is given in 5 of the cases. In 2 cases it doesn't specify that medical advice was sought (in one of these cases [redacted] so this may not be indicative of Bell's Palsy), in 1 case the patient [redacted] nd the reactions recovered. No diagnosis of Bell's Palsy was made. In 1 sparse case the report is made by a healthcare professional, no diagnosis of Bell's Palsy is specifically made, and the reaction is reported as recovering. The remaining case is too sparse for assessment.

Overall, cases reporting facial paralysis are so far low however there are 5 cases with a diagnosis of Bell's Palsy and an absence of alternative aetiologies reported. Facial paralysis is not currently listed in the AstraZeneca product information. In clinical trials, 3 cases reporting facial paralysis were seen in each arm (AstraZeneca and control, which was either Meningococcal A,C,W,Y vaccine or normal saline). Of note, 2 of the 3 cases in the AZ arm had features arguing against causative association with vaccination.

Observed vs Expected analyses of Bell's Palsy

Both a broad and a specific definition of Bell's Palsy have been used to estimate background rates and to allow the analysis of Yellow Card reports specifying Bell's Palsy and those reporting a less specific facial weakness. Based on the data above and the estimates of background risk we estimate we would have expected the following number of cases compared to the number observed with 7/42 days of any dose of the vaccine (see Tables 2i and 2ii). First and second doses are combined for the purposes of these analyses and the expected is adjusted for incomplete follow up in those vaccinated within the last 7 or 42 days. Data includes all Yellow Card reports committed to the database by the end of 2nd February 2021.

Table 2i: Observed vs expected analysis of Bell's Palsy Yellow Card reports (Pfizer)

Definition	**Risk window**	**Expected**	**Observed**
Broad definition	7 days	74	73
	42 days	229	93
Specific definition	7 days	55	35
	42 days	169	50

Table 2ii: Observed vs expected analysis of Bell's Palsy Yellow Card reports (AZ)

Definition	**Risk window**	**Expected**	**Observed**
Broad definition	7 days	28	16
	42 days	46	16
Specific definition	7 days	21	8
	42 days	35	8

From Table 2i and ii we can see that we are not yet seeing more cases of Bell's Palsy than we would expect to see.

However, analyses by age group suggest that a statistical signal is being seen in younger patients aged <50 years where the signal threshold is now just being reached using the broad definition and assuming complete reporting. With moderate levels of under-reporting, a signal is also being seen in older patients aged 50-65 years, but much higher levels of under-reporting are still required in order to see a signal in those age 65+ years. Similar signals are not being seen for the specific diagnosis, where a signal would only be seen if we were receiving 10% of reports.

Ecological analyses of Bell's Palsy

Ecological analyses of the incidence rate of Bell's Palsy in the population, calculated using CPRD data, over time including during the period of the pandemic and vaccine deployment show that the estimated event rate has remained reasonably constant over time.

Rapid Cycle Analyses of Bell's Palsy

1.32 million first doses of Pfizer vaccine have been identified within the CPRD (data until 31st January 2021) along with 0.62 million AstraZeneca vaccines.

In the CPRD, a total of 19 cases of Bell's Palsy have been identified within 42 days of a first dose of a Pfizer vaccination and 4 within 7 days. This is compared to an expected 11 (based on an adjusted follow up time of 39,462 patient years) and 4.5 cases (15,666 pyrs) respectively.

In comparison, a total of 2 cases have been identified within 42 days of a first dose of an AstraZeneca vaccination (both actually within 7 days). This is compared to an expected 1.5 (5,213 pyrs) and 1.2 cases (4,773 pyrs).

In overall analyses combining both vaccinations the observed number of cases of Bell's Palsy is still within the expected range. However, for the Pfizer vaccine we are seeing a statistical signal for the risk of Bell's Palsy after the first dose. The estimated relative risk is 1.71 across the full age range which crosses the threshold for a signal within the sequential group analyses (which combine data across different age groups). This seems to be driven by an increase in patients aged [redacted] although age-specific analyses are not significant (Figure 2).

3.3. Myocarditis

Yellow Card reports of myocarditis/pericarditis for the Pfizer/BioNTech vaccine

Up to and including the 27th January 2021, the MHRA has received 2 reports of pericarditis and 5 reports of myocarditis with the Pfizer/BioNTech vaccine.

The ages in the pericarditis cases are [redacted] Neither of these cases report past medical history.

Of the myocarditis cases, four of the patients are in their 30s and [redacted] and all but one was female. The time to onset was reported in 4 of the cases, and were classified as 12 hours, 2 days, 3 days and 5 days. Troponin was reported to be raised in three of these cases. One case reported [redacted] One case also reports COVID-19 as an ADR, along with one case reporting being antibody positive for SAR-CoV-2 and one with previous suspected COVID-19. A further case reports concurrent tubulointerstitial nephritis which may be a contributing factor.

Overall, there are several cases with a plausible onset time following vaccination, however, relevant information is lacking in many cases and several cases also report relevant confounding factors. There is a predominant reporting in younger ages, and myocarditis is more frequently diagnosed in younger adults. However, this may also be related to a higher likelihood of reporting in this age group, and particularly healthcare workers who are likely to recognise the condition as well as being an age where cardiac events in general are less common and therefore more likely to be noteworthy and reported.

Yellow Card reports of myocarditis/pericarditis for the AstraZeneca vaccine

Up to and including the 27th January 2021, the MHRA has received 1 report of pericarditis and no reports of myocarditis with the AstraZeneca vaccine.

The pericarditis case was in [redacted]

Observed vs Expected analyses of myocarditis/pericarditis

Based on the data above and the estimates of background risk we estimate we would have expected the following number of cases compared to the number observed with 42 days of any dose of the vaccine (see Tables 4i and 4ii)

Table 4i: Observed vs expected analysis of myocarditis/pericarditis Yellow Card reports (Pfizer)

Risk window	Expected	Observed
42 days	82	8

Table 4ii: Observed vs expected analysis of myocarditis/pericarditis Yellow Card reports (AZ)

Risk window	Expected	Observed
42 days	18	1

We are not currently seeing more cases of myocarditis / pericarditis reported to us through the Yellow Card Scheme than would be expected although there is apparent under-reporting in part likely to delays in diagnoses.

Ecological analyses of myocarditis/pericarditis

Ecological analyses of the incidence rate of myocarditis/pericarditis in the population, calculated using CPRD data, over time including during the period of the pandemic and vaccine deployment show that the rate has remained reasonably constant over time, although it is more variable in those aged 80+, with no apparent impact of the pandemic or vaccine deployment.

Rapid Cycle Analyses of myocarditis/pericarditis

As before, 1.32 million first doses of Pfizer vaccine have been identified within the CPRD (data until 31st January 2021) along with 0.62 million AstraZeneca vaccines.

In the CPRD, a total of 7 cases of myocarditis / pericarditis have been identified within 42 days of a first dose of a Pfizer vaccination. This is compared to an expected 4.3 (based on an adjusted follow up time of 34,020 patient years).

In comparison, no cases have been identified within 42 days of a first dose of an AstraZeneca vaccination.

In combined analyses no signals are raised however a signal is raised in patients aged <50 years where 5 cases have been identified compared to an expected 1.1. This results in an estimated relative risk of 4.5.

4. Discussion

4.1. Bell's Palsy

Overall, the data presented do not provide evidence of an increased risk of Bell's Palsy following a COVID-19 vaccination.

In the observed vs expected analyses of the Yellow Card reports we do see a small signal when using the broader definition of Bell's Palsy. However, it is difficult to align case definitions across CPRD data and YC reports and the fact that we do not see a signal for the more specific and definite diagnosis of Bell's Palsy, nor do we see any consistent signal across age groups, is reassuring.

The small statistically significant finding seen within the rapid cycle analysis is interesting, and indeed we would expect to see a signal first in older patients in the event of a true association as the background risk is greatest in this group, but it is difficult to interpret. Bell's palsy can be triggered by an infection and so understanding the COVID-19 status of

the cases identified is important. Ecological analyses do not suggest any particular association of Bell's Palsy with COVID-19 infection, but such an approach is not particularly sensitive to short term risks in lower proportions of the population.

However, given the interest in this AESI due to the cases seen in clinical trials it seems appropriate based on these data to trigger the implementation of a more robust epidemiological study designed to adjust for potential confounding factors including COVID-19 infection. MHRA are working with the London School of Hygiene and Tropical Medicine (LSHTM) and Public Health England to develop complementary protocols for epidemiological studies to assess the association of COVID-19 vaccination with Bell's Palsy in the CPRD and OpenSAFELY (https://opensafely.org/), a joint initiative between LSHTM and the University of Oxford using data linked to primary care records from GPs using SystemOne software. Use of linked COVID-19 testing data would be important as will the use of appropriate study designs to tease out any change in the background risk of Bell's palsy over the period of the vaccine deployment. Careful consideration would also have to be given to the case definition used and sensitivity analyses implemented to try to ensure records were true cases of Bell's palsy.

Any epidemiological study would include both the Pfizer and AstraZeneca vaccines, and could be extended to other vaccines if needed. The first step would be to conduct power calculations over the two databases to ensure there were sufficient data to estimate small but relevant risks. It is worth noting the strength of the UK for exploring this AESI given the size of the data sets available, the near real time availability of primary care data, and the ability to link in secondary care and other relevant data sets.

MHRA will also continue to monitor Bell's palsy using the observed vs expected, ecological, and rapid cycle analysis approaches presented in this paper alongside conduct of an epidemiological study.

4.2. Myocarditis / pericarditis

Overall, the data presented do not provide evidence of an increased risk of myocarditis / pericarditis following a COVID-19 vaccination.

Only a small number of cases of myocarditis and pericarditis have been reported to the Yellow Card scheme or identified in the CPRD to date which is unsurprising giving the low background incidence of the event.

The only signal is arising from the rapid cycle analysis However, because of the limited experience with this approach to vigilance in the UK and the theoretical potential for immune complex reactions in individuals with prior infection it is important to discuss.

It is highly plausible that the risk seen in the rapid cycle analysis is a chance finding. The ecological analyses show that the incidence of myocarditis/pericarditis in the CPRD, particularly when restricted to older patients is highly variable due to the rarity of the event so would not be surprising to see short-lived outliers in incidence rates compared to the background average. This likelihood is supported by the fact that the strength of the signal, which was first raised in the analyses using data until 24th January 2021, has decreased in the most recent week's data (data until 31st January 2021) as no new cases have been identified. Further, a conservative approach has been taken to the implementation of the rapid cycle analyses in the first instance and the use of the approach across multiple AESI

has not been taken account of to ensure that we have the highest sensitivity for detecting true risks.

Given this the proposal is that myocarditis / pericarditis continues to be monitored through the assessment of individual cases and by using the observed vs expected, ecological, and rapid cycle analysis approaches but that no further epidemiological study is required, or indeed feasible given the numbers of cases being seen, at this time. MHRA have worked with NHS Digital and CPRD to obtain access to linked secondary care data through the Secondary Uses Service data which includes data on admissions to hospital. These data will be fed into the rapid cycle analyses to strengthen the capture of events.

Questions to the EWG

1) Do the group agree with the current assessment of the data presented with regards to the risk of Bell's Palsy and myocarditis/pericarditis?
2) Do the group support the proposed approach to the continued vigilance of these two AESI?