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Appendicitis as a possible safety signal for the COVID-19 vaccines

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ABSTRACT

This study reviewed cases of appendicitis following administration of COVID-19 vaccines reported to VigiBase, the WHO database of individual case safety reports (ICSRs). Three hundred fifty-eight cases were identified, and disproportionate reporting was noted, with 329 calculated expected cases. Upon review, 24 ICSRs were excluded, so 334 unique ICSRs underwent clinical review from 19 countries. Forty-eight percent of ICSRs reported imaging and 69% noted surgical intervention. The cases were clinically coherent, with an apparent increase in reporting in the four days post-vaccination and a possible dose–response relationship. Appendicitis has been suggested as an adverse event of special interest post-vaccination against COVID-19 after a numerical increase in the vaccine arm of a clinical trial. The case series may be affected by differences in global patterns of reporting, and it is not possible to prove nor disprove causality from this case series. Global longitudinal studies are required to clarify any possible relationship.

Appendicitis is one of the most common surgical abdominal conditions. Typical presentation is of a central abdominal pain that intensifies and radiates the right iliac fossa over the first 24 h, however, this occurs only in approximately 50% of appendicitis cases and there is no specific diagnostic finding [9]. Appendicitis is mentioned in the product information of Pfizer-BioNTech vaccine approved by the FDA, due to a numerical increase of appendicitis cases in the vaccine arm of a large clinical trial [7]. No causal relationship has been established, and it is not labelled for the other COVID-19 vaccines. Appendicitis has been suggested to be an adverse event of special interest post-vaccination for the COVID-19 vaccines [11].

This study aimed to explore the relationship of COVID-19 vaccines and appendicitis by using VigiBase, the WHO database of individual case safety reports (ICSRs), to identify relevant cases of appendicitis with COVID-19 vaccines as the suspected medicinal product from spontaneous reports. ICSRs are anonymised prior to uploading to VigiBase. On 27th May 2021, a search was performed for terms specific to the diagnosis of appendicitis; "Appendicitis", "Appendicectomy", "Appendicitis perforated", and "Complicated appendicitis"; in conjunction with "COVID-19 vaccine". Disproportionality, a statistical measurement of the imbalance of reports for a drug-event pair that compares an observed number of reports to a calculated expected number based on all medicinal products [15,23], was calculated in VigiBase. To the best of our knowledge there is not a case definition or clinical criteria to help determine the likelihood of appendicitis in the cases identified. However, the identified cases were analysed, and narratives clinically reviewed. Where there was uncertainty from the narrative as to whether the patient was diagnosed with appendicitis after clinical review and investigation by a physician the report was excluded. Reasons for exclusion included multiple differential diagnoses being reported in the narrative or if clinical findings such as laboratory tests, imaging studies and surgical findings were reported and not supportive of appendicitis. When there was a difference in time-to-onset (TTO) of appendicitis or suspected symptoms of appendicitis, the shortest TTO was used. Seriousness of the ICSR is determined by the case reporter, prior to uploading to VigiBase, and is defined by the International Conference of Harmonisation seriousness criteria (results in death, is life threatening, caused or prolonged hospitilisation, results in persistent or significant disability, is a congenital birth defect or is a medically important condition) [10].

As of 27th May 2021, an estimated 1.82 billion doses of COVID-19 vaccines had been administered [14,19], there were 900,695 ICSRs in VigiBase for COVID-19 vaccines, and of these 358 ICSRs reported appendicitis. The terms "Appendicitis", "Complicated appendicitis", and "Appendicectomy" had statistically significant disproportional reporting with "COVID-19 vaccines". When stratified by vaccine manufacturer there was significant disproportionate reporting for seven combinations of terms and the vaccines

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from Pfizer-BioNTech, Moderna and Janssen. Full details of disproportionality are in Table 1.

Due to duplication or unclear reporting 24 cases were excluded, leaving 334 cases from 19 countries for analysis. Case demographics are shown in Table 2. The cases described in the narratives followed that of typical appendicitis, with patients presenting with abdominal pain often accompanied by nausea, vomiting, diarrhoea, or fever. There was often a delay of several days between onset of symptoms and diagnosis. Three hundred and one (90%) of ICSRs were marked as serious, with most of these being noted as causing or prolonging hospitalisation (n = 283, 85%); the other criteria reported were life threatening (n = 87, 26%), other medically important condition (n = 15, 4.5%) and persistent or significant disability (n = 6, 1.8%). One ICSR (0.3%) described a fatal case, the patient having been found to be profoundly thrombocytopenic, and dying before their delayed surgery. In the ICSRs, no other medications were suspected to have caused appendicitis.

Fig. 1 shows that most of the cases reported a TTO of 0–4 days with a median of four days, despite a very wide range in TTO (0–71 days). The only cases reported after the second dose were for the Pfizer-BioNTech and Moderna vaccine, but this is likely to be heavily influenced by the vaccination programmes, with a typically longer interval between doses for AstraZeneca, for example. When looking at the differences in TTO between the first and second dose in general, the median was three days for both, however, for the Pfizer-BioNTech and Moderna vaccines there was a notable difference in TTO between first and second dose (Pfizer-BioNTech four and three days respectively; Moderna three and two days respectively). This is a relatively small difference, and we are not able to compare this to the other vaccines, but it could suggest a dose–response relationship. However, more cases were reported after the first dose (n = 178) than the second dose (n = 97) and this remains true, if less pronounced, for both Pfizer-BioNTech (n = 83 and n = 70, respectively) and Moderna (n = 39 and n = 27, respectively).

Fifty-two cases reported a negative COVID-19 test at the time of symptoms, with two reporting a positive COVID-19 test, in one of these ICSRs the exact timeline is unclear but occurred after receiving the AstraZeneca vaccine, while the other describes a positive COVID-19 test four days after the first dose of the Moderna vaccine before developing the onset of appendicitis five days later. Seven ICSRs described a previous COVID-19 infection with the time between infection and vaccination being reported as 29 days, five months, six months, ten months and 11 months with it being unreported in two ICSRs. COVID-19 status is an important consideration as previous infection may enhance the immune response to vaccination [13]. Furthermore, multisystem inflammatory syndrome, initially described in children as a COVID-19 complication, can present as abdominal pain and both mimic and cause appendicitis [1]. However, only two of the cases in this series describe being COVID-19 positive at the time of appendicitis.

The exact pathophysiology of appendicitis is unknown, but it is thought to most commonly occur due to obstruction of the appendiceal lumen, classically due to fecalith [4,16]. Five ICSRs mention appendicoliths, as a reported term or in the case narrative, and all reports of appendicolith with COVID-19 vaccine are in this case series. Lymphoid hyperplasia has also been identified as an important cause of appendicitis [2,24] as it can cause obstruction and lead to appendicitis [16]. Appendicitis has presented simultaneously in different underlying causes of lymphadenopathy and lymphoid hyperplasia, such as viral infection, leukemia and lymphoma [4,18,24]. Lymphadenopathy is listed as a side-effect of the vaccines. Five ICSRs mention lymphadenopathy as occurring, two mentioning abdominal lymphadenopathies specifically. It is possible that abdominal lymphadenopathy, and similarly appendicolith, would be under-reported, as they are typically diagnosed after abdominal imaging and not often identified as a serious adverse event. One hundred sixty-one ICSRs (48%) mention imaging being performed to support the diagnosis. In VigiBase to date, there are nine ICSRs mentioning abdominal lymphadenopathy after COVID-19 vaccinations, including the two in this series. There are also 29,191 ICSRs with lymphadenopathy after COVID-19 vaccines, the median TTO is one day, and 16% report a TTO as zero days. This suggests that such a mechanism is temporally plausible even for the cases where onset of symptoms was very quick. Additionally, the immune response may also contribute to the onset of appendicitis. The COVID-19 vaccines produce robust Th1 immune responses [3,5,17,22] and there is a hypothesised link between

Table 1
Disproportionality Tables for COVID-19 vaccine and appendicitis with stratification by vaccine manufacturer. Abbreviations: IC – Information Component, IC_{025} – Lower endpoint of the credibility interval for the Information Component. Above 0 is considered statistically significant. [15,23] * denotes statistical significance.

VACCINE	*TERM*	*OBSERVED CASES*	*EXPECTED CASES*	IC_{025}	*IC*
Covid-19 vaccines	*Appendicitis, Appendicectomy, Complicated appendicitis and Appendicitis perforated*	*358*	*329*	*−0.0*	0.1
Covid-19 vaccines	*Appendicectomy*	*145*	*89*	*0.5**	*0.7*
Covid-19 vaccines	*Complicated appendicitis*	*9*	*3*	*0.5**	*1.6*
Covid-19 vaccines	*Appendicitis*	*305*	*198*	*0.5**	*0.6*
Covid-19 vaccines	*Appendicitis perforated*	*47*	*56*	*−0.7*	*−0.3*
By Vaccine Manufacturer					
Moderna	*Appendicectomy*	*50*	*13*	*1.5**	*1.9*
Pfizer-BioNTech	*Complicated appendicitis*	*8*	*1*	*1.3**	*2.5*
Janssen	*Appendicectomy*	*17*	*4*	*1.3**	*2.1*
Pfizer-BioNTech	*Appendicitis*	*170*	*72*	*1.0**	*1.2*
Moderna	*Appendicitis*	*69*	*28*	*0.9**	*1.3*
Pfizer-BioNTech	*Appendicectomy*	*72*	*32*	*0.8**	*1.1*
Janssen	*Appendicitis*	*22*	*8*	*0.7**	*1.4*
Pfizer-BioNTech	*Appendicitis perforated*	*27*	*20*	*−0–2*	*0.4*
Janssen	*Appendicitis perforated*	*5*	*2*	*−0.6*	*1.0*
Moderna	*Appendicitis perforated*	*9*	*8*	*−0.9*	*0.2*
AstraZeneca	*Appendicitis*	*41*	*82*	*−1.5*	*−1.0*
Moderna	*Complicated appendicitis*	*1*	*0*	*−3.0*	*0.8*
AstraZeneca	*Appendicitis perforated*	*6*	*23*	*−3.3*	*−1.9*
Sinopharm	*Appendicectomy*	*1*	*1*	*−3.5*	*0.3*
COVID-19 vaccine	*Appendicitis*	*1*	*1*	*−3.9*	*−0.1*
AstraZeneca	*Appendicectomy*	*5*	*37*	*−4.3*	*−2.8*
Sinopharm	*Appendicitis*	*1*	*2*	*−4.3*	*−0.5*
Sinovac	*Appendicitis*	*1*	*3*	*−5.2*	*−1.4*

Table 2
Case demographics of appendicitis cases after COVID-19 vaccine by vaccine manufacturer.

		ALL CASES (N = 334)	PFIZER-BIONTECH (N = 186)	MODERNA (N = 77)	ASTRAZENECA (N = 42)	JANSSEN (N = 26)	SINOPHARM (N = 1)	SINOVAC (N = 1)	UNSPECIFIED VACCINE (N = 1)
Age (%) (years)	12–17	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	18–44	163 (49)	84 (45)	38 (49)	25 (60)	16 (62)	0 (0.0)	0 (0.0)	0 (0.0)
	45–64	102 (31)	57 (31)	25 (32)	13 (31)	5 (19)	0 (0.0)	1 (100)	1 (100)
	65–74	28 (8.4)	17 (9.1)	7 (9.1)	2 (4.8)	1 (3.8)	1 (100)	0 (0.0)	0 (0.0)
	75+	19 (5.7)	14 (7.5)	3 (3.9)	0 (0.0)	2 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
	Unknown	21 (6.3)	13 (7.0)	4 (5.2)	2 (4.8)	2 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Median age (range)		42 (17–88)	45 (17–85)	42 (20–88)	40 (18–72)	41 (27–79)	73	52	50
Sex (%)	Female	214 (64)	125 (67)	49 (64)	23 (55)	17 (65)	0 (0.0)	0 (0.0)	0 (0.0)
	Male	117 (35)	61 (33)	28 (36)	17 (40)	9 (35)	1 (100)	1 (100)	0 (0.0)
	Unknown	3 (0.9)	0 (0.0)	0 (0.0)	2 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)
Dose (%)	1ST	177 (53)	83 (45)	40 (52)	28 (67)	26 (100)	0 (0.0)	0 (0.0)	0 (0.0)
	2ND	97 (29)	70 (38)	27 (35)	0 (0.0)	N/A	0 (0.0)	0 (0.0)	0 (0.0)
	UNKNOWN	60 (18)	33 (18)	10 (13)	14 (33)	0 (0.0)	1 (100)	1 (100)	1 (100)
Median TTO (range)		4 (0–71)	4 (0–66)	3 (0–71)	4 (0–44)	4 (0–25)	14	N/A	4
Serious (%)		301 (90)	166 (89)	71 (92)	39 (93)	23 (87)	1 (100)	1 (100)	0 (0.0)
Surgical intervention (%)		231 (69)	125 (67)	68 (88)	13 (31)	22 (85)	1 (100)	1 (100)	1(100)
Fatal (%)	Fatal	1 (0.3)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Region (%)	North America	245 (73)	146 (78)	74 (96)	0 (0.0)	25 (96)	0 (0.0)	0 (0.0)	0 (0.0)
	Europe	82 (25)	38 (20)	3 (3.9)	39 (93)	1 (3.8)	1 (100)	0 (0.0)	0 (0.0)
	Oceania	4 (1.2)	2 (1.1)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)
	South America	3 (0.9)	0 (0.0)	0 (0.0)	2 (4.8)	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)

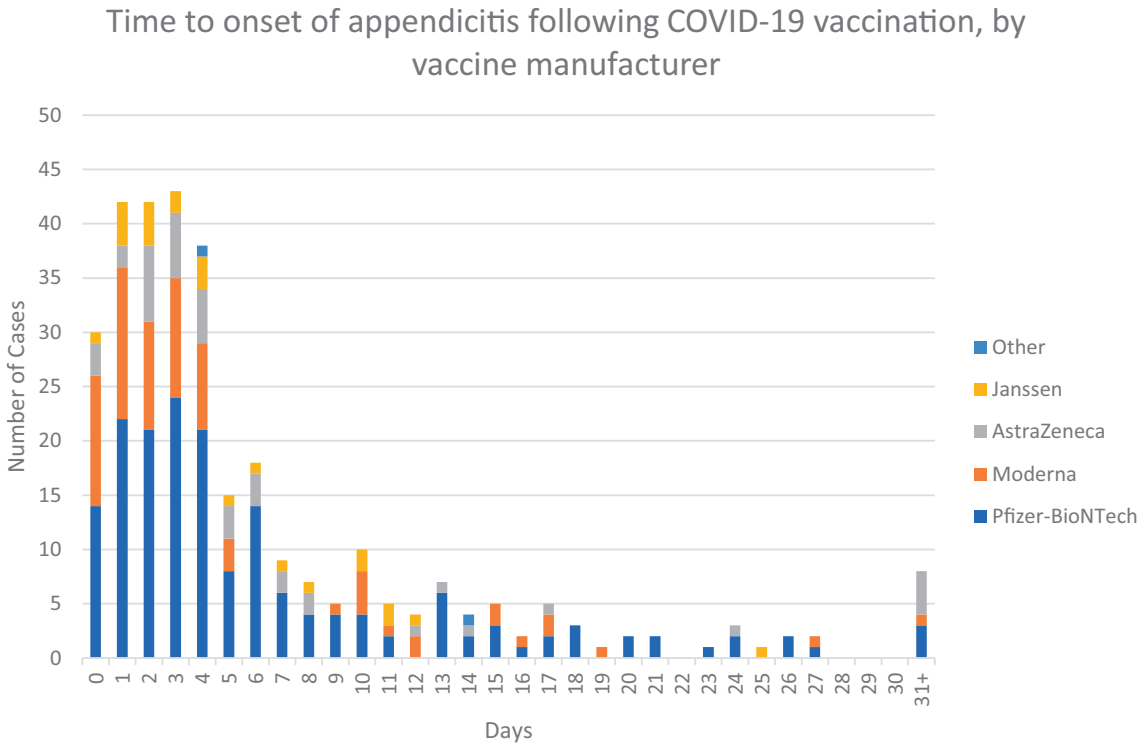

Fig. 1. Time to onset of appendicitis following COVID-19 vaccination, by vaccine manufacturer.

an increased Th1 immune response and a sub-type of appendicitis that is likely to require surgery [12,16,21]. In this study 69% of ICSRs reported surgical intervention, which may be an underestimate as outcomes and management are not always included in the reports.

Although there is disproportionate reporting of appendicitis on a global level, most ICSRs in this series are from North America and when stratified by vaccine manufacturer, the vaccines that have disproportionate reporting are those used in the United States of America (USA). This may be related to the mention of appendicitis

in the product information for the USA. Spontaneous reporting systems typically under-report adverse events but there can be an increase when a medicinal product is being scrutinised due to public or media interest in a product [23]. These vaccines are used outside of North America and there is evidence of disproportionate reporting outside of North America, but further investigations are needed to further explore the global pattern of cases and to increase awareness globally.

The overall incidence of appendicitis is approximately 11 cases per 10,000 life years [6,16], with highest incidence reported in late childhood and early adulthood [11,16]. Most cases occurred in the age group 18–44 years (49%), but a significant amount occurred in the 45–64 years age group (31%). The median age of the cases, where reported, was 42 years old. This suggests that the cases identified in this assessment may be occurring at a slightly older age than expected, but this is likely to be heavily impacted by the vaccination programmes in different countries, with many countries prioritising vaccination of elderly and vulnerable populations and healthcare workers. This is an important consideration as vaccination programmes progress toward vaccinating younger populations and it might be expected to see an increase in the rate of reporting for appendicitis as this occurs. This will require special consideration in when establishing if there is an increase in appendicitis cases above the background rate.

One of the main weaknesses of this study is that we were not able to compare the reporting rate to the prevailing incidence as the data is from a passive surveillance system [11]. This is partly because it is not possible to calculate a precise denominator to compare observed reporting rate to an expected incidence rate. Furthermore, there is typically underreporting with spontaneous reporting which varies for each drug-event combination, but one *meta*-analysis estimated the average level of underreporting to be 94% [8]. We do, however, have other ways to compare observed against expected reports in VigiBase. Disproportionality analysis, see Table 1, shows there are more observed reports than a calculated expected number of reports (358 versus 329 cases, respectively). The expected number of reports is automatically calculated based on the total number of reports concerning COVID-19 vaccines and the proportion of cases reporting the selected appendicitis terms in the whole database. However, this increase in number or any statistically significant disproportionate increase in reports does not necessarily indicate a relationship but can help with hypothesis generation and detection of signals, hypothesised risks with a medicinal product that is supported by data and other arguments. As such, it is not possible to distinguish if these cases are vaccine related or part of the background rate of appendicitis. Background rates have shown considerable heterogeneity between geographies and databases [11]. Furthermore, patient behaviour has been affected by the COVID-19 pandemic, with fewer seeking medical attention, presenting later, and at a more severe stage of disease [20]. These changes, as well as the incidence of any COVID-19 vaccine related appendicitis, need to be considered in further investigation of this possible association, with global longitudinal studies that examine cohorts, with an appropriate control group either from unvaccinated individuals or recent historical data, over an extended period. Thus, an incidence could be calculated and compared against the background rate and stratified by vaccine manufacturer, age, gender to identify if any specific risk population exists. .

In conclusion, this study highlights a possible adverse event to COVID-19 vaccines. However, the exact nature of the relationship, if any, needs further longitudinal studies to expand upon this initial report as this series cannot be used to prove or disprove causality. Greater knowledge of this as a possible adverse event will sensitise healthcare workers and those receiving the vaccine to monitor symptoms and seek medical attention in a timely manner when appropriate.

Data Availability

The datasets generated and analysed during the current study are not publicly available due to agreements between contributors of data to the database used (VigiBase) and the custodian of this database. National centres (mainly national drug regulatory authorities) participating in the WHO Programme for International Drug Monitoring (PIDM) contribute data to VigiBase and the Uppsala Monitoring Centre is the custodian in its capacity as WHO Collaborating Centre for International Drug Monitoring. Some subsets of the data may be available from the corresponding author on reasonable request.

Author Contributions

All authors attest they meet the ICMJE criteria for authorship.

CRediT authorship contribution statement

Joseph Mitchell: Methodology, Formal analysis, Investigation, Writing – original draft. **Qun-Ying Yue:** Methodology, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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