Descriptive analysis of COVID-19-related spontaneous reports from VigiBase: interim results

Report from the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre

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Summary

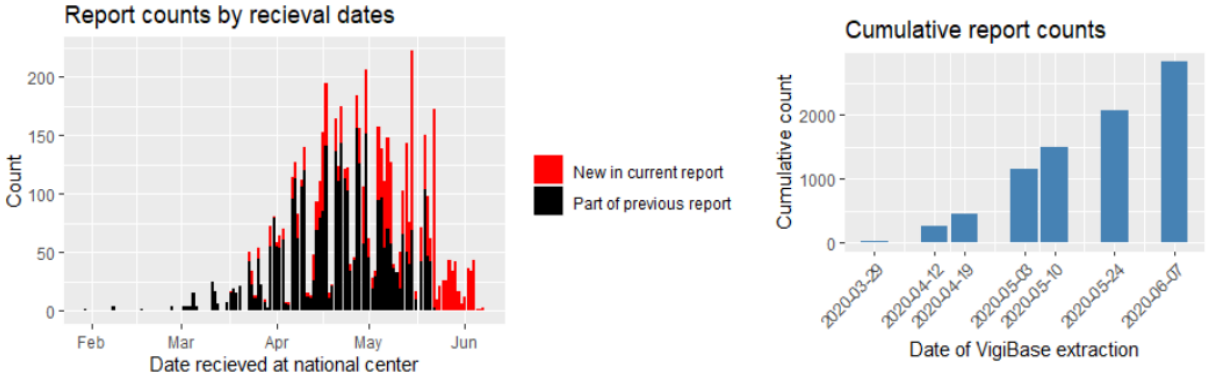
This seventh report of global reporting of ADRs for drugs used to treat COVID-19 is mainly descriptive in nature. It includes reviews for the drugs in the WHO Solidarity trial and other drugs used for a COVID-19 indication where the number of reports exceeds 100.

Reports have so far been shared from five of the six WHO regions, with the largest number still originating in the WHO European Region. Additional cases of rhabdomyolysis secondary to the known, labelled interaction between lopinavir;ritonavir and atorvastatin have been received. Reactions of interest for remdesivir are renal and skin events which are not currently included on available product information from the US FDA or the EMA.

Reports in VigiBase

The methodology of search is the same in this seventh review, as in the sixth. Reports were screened for drugs given on a corona or COVID-19 indication, by relevant free-text terms and laboratory tests. Reports without a decisive COVID-19 indication were reviewed manually before inclusion. Reports were considered for inclusion if they were received at the National Centres between 1 November 2019 and 7 June 2020 and were reported to VigiBase no later than 7 June 2020.* Reports were considered for inclusion when they reported as suspected/interacting drugs included in the SOLIDARITY trial or drugs considered clinically relevant based on medical-expertise and reported to VigiBase on a Corona or COVID-19 indication. See (Table 3) in appendix.

Note that there is country-specific reporting delay after receipt of reports at National Centres, thus the reporting date to VigiBase should not be considered as proxy for reporting date to National Centres or the date of adverse events. See Figure 1 for a visualisation of the arrival dates at National Centres for this reviewing period.



* If the arrival date at the National Center was not reported, the date of latest update at the National Center was used instead.

Figure 1. Number of reports by dates received at national center (left), and cumulative number of reports in VigiBase at the dates of extractions for reports. The rightmost bar (right panel) shows the total number of reports received so far.

Characteristics of the reports

Since the last analysis, 928 new case reports have been identified using the selected search strategy (Table 1). Cumulatively, there have been a total of 2824 reports from six WHO regions with the large majority from the European region (64.1%). 51.9% of the reports were classified as “serious” (Table 2) but not all reporting standards include seriousness (e.g. INTDIS). Males accounted for 55.7% of the reports and females 38.8%.

Most of the reports described at least one drug or substance in the WHO Solidarity trial, i.e. hydroxychloroquine or chloroquine, azithromycin, remdesivir and lopinavir;ritonavir reported as either suspected or interacting. The search also identified a smaller number of additional reports describing other drugs known to be used in the treatment of COVID-19 disease. Tocilizumab and oseltamivir were the most reported (>100 reports) among these drugs and they were therefore included in the more detailed analysis. Overall reporting demographics are shown in Figure 2. In line with males being more affected by COVID-19 infection globally, for all drugs except chloroquine and oseltamivir the reporting was most prevalent for males. Patient ages were similar between drugs, although oseltamivir had the lowest median age.

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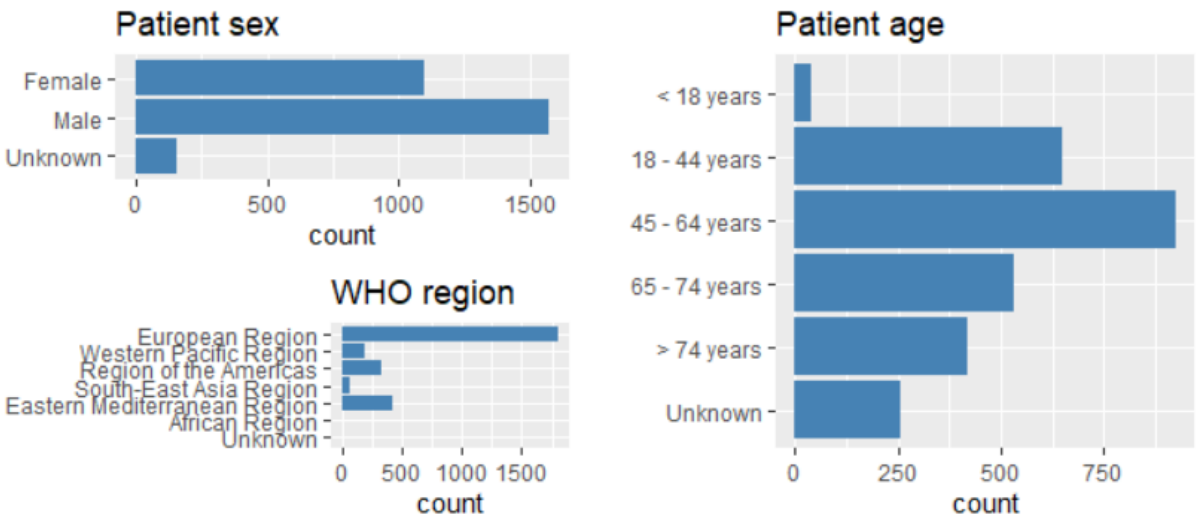

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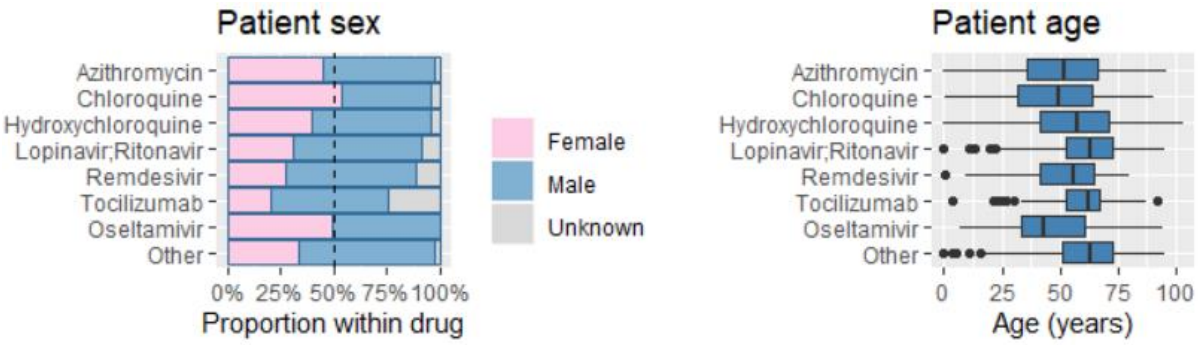

Figure 2. Overall demographics of case safety reports sent into VigiBase in treatment of COVID-19. A) All reports. B) Reports by drug. The B) graphs rely on counts of reports which include each drug as suspected or interacting. Reports including several drugs will be counted once for each reported drug. Patient age boxes show medians and interquartile ranges.

Characteristics of the reports on WHO Solidarity trial drugs

Hydroxychloroquine alone or in combination with azithromycin

There were 592 new reports for hydroxychloroquine during this reviewing period, adding to a cumulative total of 1536 reports. The new reports included 304 men, 248 women and 40 with unknown sex. The new reports were shared from the European region (422), Region of the Americas (97), Eastern Mediterranean region (47), South East Asia (22) and Western Pacific region (2). In the new reports there were 187 reports in the age group 18-44 years, 166 reports in the age group 45-64 years, 92 reports in the age group 65-74 years, 88 reports in the age group 75 years and above and 53 reports of unknown age. For the new reports, hydroxychloroquine was a single suspected drug in 235 cases. An overview of the cumulative reporting demography is shown in Figure 3.

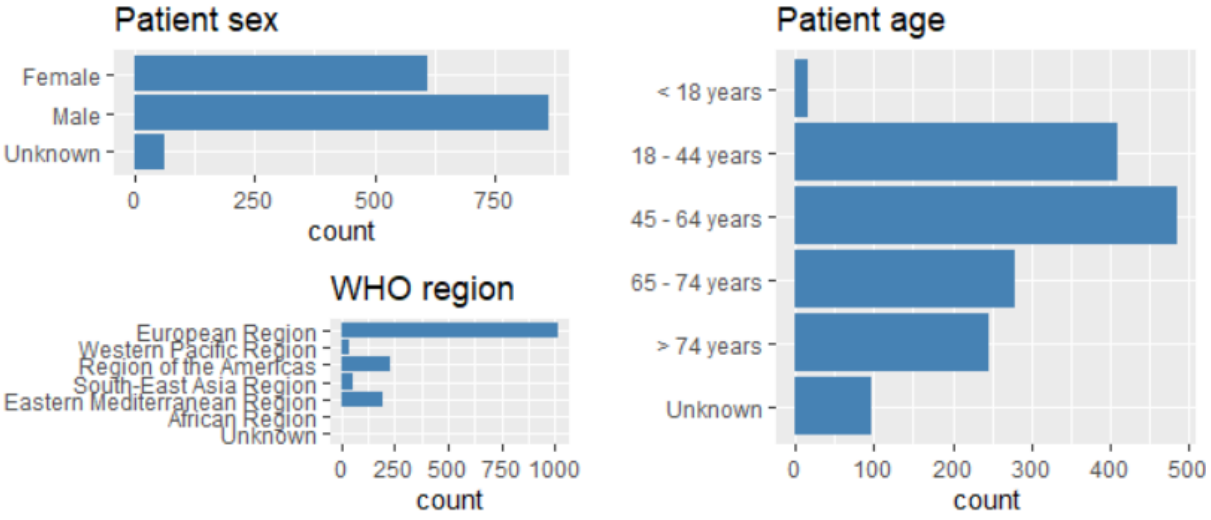

Figure 3. Demography of VigiBase reports received cumulatively so far on hydroxychloroquine as suspected or interacting drug.

Adverse events

Among the reported preferred terms that had the highest increase in the number of reported cases to VigiBase during this period includes intentional product use issues which mainly is that drug has been used for unapproved indication, vomiting, nausea, diarrhoea and headache. These terms are labelled for the drug[1] or for the concomitant drugs that have been administered together with hydroxychloroquine. The reporting pattern for the drug seem to be consistent with what has been reported previously weeks.

Electrocardiogram QT-prolongation: 87 cases during the review period, 358 cases cumulatively. The cases have been submitted from 10 countries spread over three regions. A percentage of 60.9% concerned males, 36.8% females and in 2.3% of the cases the gender was unknown. The age group with the highest proportion of cases (33%) for this period was ≥75 years of age. The dose range among the patients was between 400 mg a day which is what is clinically approved for the drug up to 1600 mg a day. Electrocardiogram QT-prolongation was reported within a relatively short period of time (from the same day up until a couple of days) after starting to take hydroxychloroquine. A majority of the cases (54 out of 87) were reported as serious, five cases with life-threatening consequences and three death cases. One of the serious cases involved a 12 years old patient that took 540 mg hydroxychloroquine together with the drugs azithromycin, levetiracetam and ceftriaxone. The same day, the patient experienced electrocardiogram QT-prolongation but recovered after hydroxychloroquine was withdrawn. A second patient that was standing on the drugs hydroxychloroquine, azithromycin and oseltamivir, experienced electrocardiogram QT-prolongation one day after starting the treatment. The patient was recovered after the withdrawal of azithromycin.

Other concomitant drugs that have been administered and reported as either suspected, interacting or concomitant on the submitted cases includes azithromycin (69 cases), oseltamivir and favipiravir, six cases each.

Hepatitis: Four cases during the review period, 67 cases cumulatively. All cases being reported as serious. The ADR is not labelled for hydroxychloroquine, but in all cases that had been submitted from the same country, the drug azithromycin which is known to have the potential to cause hepatitis was given in all four cases and tocilizumab that can reactivate the viral Hepatitis B-virus, was co-reported in two cases.

Hepatotoxicity: 13 new cases for this period where of 11 reported as serious, cumulatively 15 cases. 12 out of the 13 new cases submitted from one specific country. The cases involved 10 male and three females. Azithromycin was co-reported in 11 of the 13 cases. Hepatoxicity is not labelled for hydroxychloroquine, however the major elimination path for azithromycin is the liver which can be a potential explanation to the event.

Tachycardia: 12 new cases for this period, 21 cases cumulatively. The reports have been submitted from seven different countries. Nine cases concerned female patients while three male patients. Half of the cases was reported as serious with two fatal outcomes. The ADR is labelled in the overdose section for hydroxychloroquine.

Psychiatric adverse events: During this review period, we identified seven new reports for the psychiatric adverse events: anxiety (four new reports, eight cumulatively), sudden cardiac death (one new case reported for the first time), suicide attempt (one new case, cumulatively three cases) and depression (one new case, cumulatively two cases).There were no new cases for the term's nightmare (cumulatively two cases), hallucination (cumulatively four cases) and completed suicide (cumulatively four cases).

Chloroquine

During this reviewing period 41 new reports in which chloroquine was reported as suspecting or interacting drugs were reviewed. These concerned 15 male and 22 female patients; median age of patients described in the new reports was 50 years (four reports had age unreported). 24 reports originated from the WHO Eastern Mediterranean Region, three from the WHO Western Pacific region. An overview of the cumulative reporting demography is shown in Figure 4.

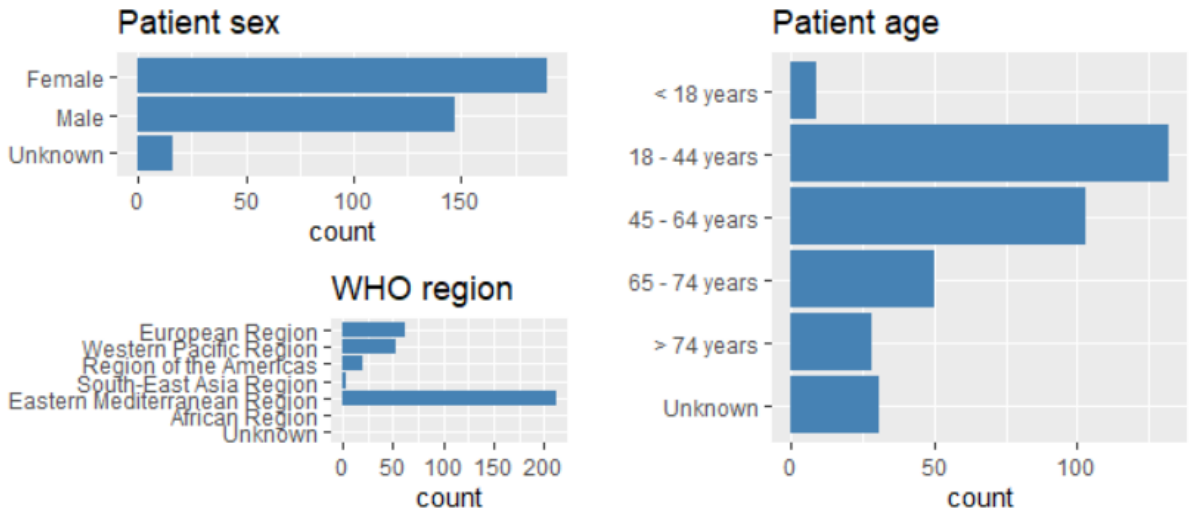

Figure 4. Demographics of VigiBase reports received cumulatively so far for chloroquine as suspected or interacting drug.

Adverse events

The 10 most frequently reported MedDRA Preferred Terms were: Vomiting (19 reports), followed by vertigo (eight reports), abdominal pain upper (eight reports), vision blurred (seven reports), nausea (seven reports), insomnia (six reports), headache (five reports), diarrhoea (four reports), electrocardiogram QT prolonged (four reports), decreased appetite (four reports).

Of the 13 serious reports, a minimum of two reports included at least one of the following Preferred Terms: Vomiting (four reports), Nausea (three reports), Diarrhoea (two reports), Electrocardiogram QT prolonged (two reports), Off label use (two reports)

Among other serious reports, a case of methaemoglobinaemia has been reported to VigiBase. This literature report[2] presents an African-Caribbean 56-year-old man with pre-existing Glucose 6-Phosphate deficiency (G6PD) deficiency, type-2 diabetes mellitus who was treated with a loading dose of chloroquine of 600mg, followed by 300mg twice a day for five days. Twelve hours later, the patient experienced severe haemolysis ascertained by peripheral blood smear. The treating physicians withdrew chloroquine under the suspicion of G6PD deficiency, later confirmed by genetic analyses, and the patient recovered. In a previous report, dated 2020-04-19, another patient with similar demographics experienced fatal methaemoglobinaemia, though no additional information were available on their ancestry or genetic mark-up. The SmPC of chloroquine[1] cautions against the use in patients affected by G6PD; given the recent increase in use of this medicinal product and the potential for fatality, patients (particularly those where G6PD is more prevalent) and health carers should be reminded of the symptoms of haemolysis.

Another serious report concerns an asthmatic woman in her 20s in her third trimester of pregnancy. She was treated with 450mg every 12 hours for the first day and 450mg every 24 hours for four days, starting upon admission for emergency caesarean section due to suspected COVID-19 – later ascertained by swab/PCR. Over time, her infection worsened to acute respiratory insufficiency. Comorbidity included urinary tract infection, developed post-partum. Additional treatments included ceftriaxone, oxacillin, oseltamivir (all later withdrawn after she tested positive for COVID-19), azithromycin, piperacillin;tazobactam, teicoplanin, meropenem, anidulafungin, polymyxin B. She experienced “Cardiac disorder” one day after treatment with chloroquine, characterised by an ejection fraction of 35%, diffuse hypokinesia leading to LV systolic dysfunction; based on the report’s narrative, the treating physicians suspected different aetiologies for her cardiomyopathy: COVID-19-related, pregnancy-related, Takotsubo-like due to COVID, and chloroquine-related. At the time of the report, the patient was recovering though it is unclear whether chloroquine was withdrawn.

A third serious report was sent by a patient in their 40s, who experienced “Cardiac murmur” at an unspecified point in time after treatment with chloroquine at 1000mg per week had been ongoing for two months.

A fourth serious report concerns an elderly patient (75 years and above) who weighed more than 50kg, who experienced congestive heart failure six days after a loading dose of 900mg for one day, followed by 450 mg twice a day for four days. Concomitant treatment included 500mg azithromycin for five days. Underlying conditions were hypertension and type-2 diabetes mellitus (unclear management). The Emergency Use Authorisation for chloroquine phosphate recommends up to 1000mg loading dose followed by 500mg daily for four to seven days in patients weighing 50kg or more [3]. This case report reinforces the importance of monitoring elderly patients, as recommended in the SmPC of chloroquine phosphate. Additional evidence on the appropriate dosing of chloroquine in patients with underlying conditions is needed.

Lastly, a serious report of grand mal convulsions occurring two days after chloroquine and azithromycin in a patient without clinical history of epilepsy. The SmPC of chloroquine phosphate suggests that chloroquine may lower the seizure threshold of epileptic patients or increase the risk of convulsions in combination with mefloquine, as rare cases of convulsions have been reported in association with chloroquine. Other serious reports were in line with the SmPC of chloroquine.

Azithromycin

Reports including azithromycin are largely described in the sections of chloroquine, hydroxychloroquine or lopinavir;ritonavir.

We identified 16 new cases in the period (cumulatively 25 cases) where azithromycin was taken as the only drug for COVID-19. The cases, four serious and 10 non-serious case, have been submitted from five different countries involving 11 female patients, two male patients and one unknown case. The top reported adverse drugs reactions were electrocardiogram QT prolongation, diarrhoea, nausea and intentional product use issue, same as for hydroxychloroquine. The number of new cases where azithromycin is being used as a single drug for COVID-19 seems to increase compared to the previously weeks.

All the reported reactions and their level of seriousness are (cumulatively and for this period) available on an HLGT level in attachment 1 [separate file]. An overview of the cumulative reporting demography is shown in Figure 5.

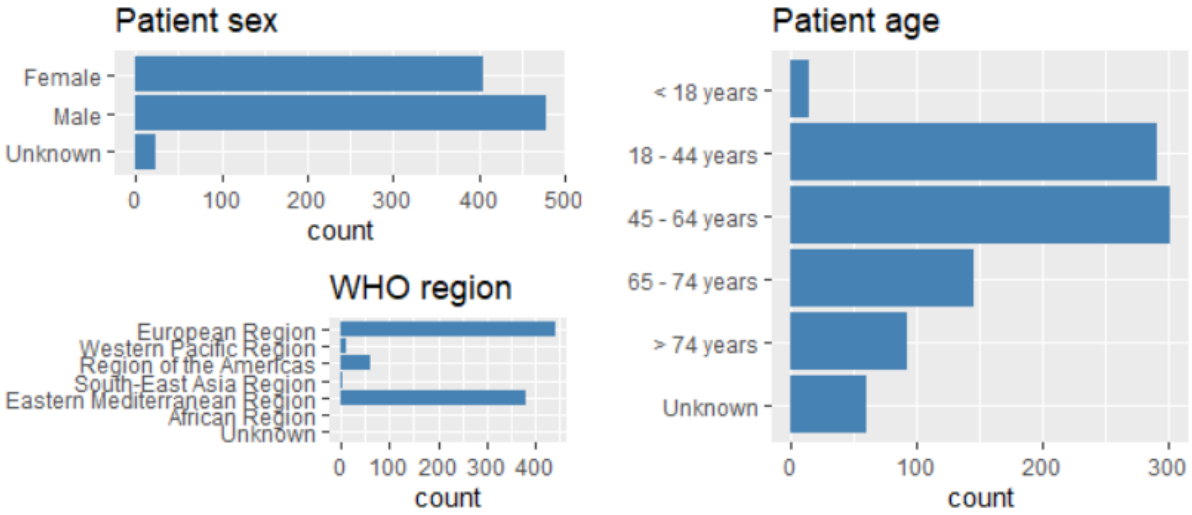

Figure 5. Demography of VigiBase reports received cumulatively so far on azithromycin as suspected or interacting drug.

Lopinavir;ritonavir

During this reviewing period 132 new reports in which lopinavir;ritonavir were reported as suspecting or interacting drugs were reviewed. These concerned 55 male and 45 female patients; median age of patients described in the new reports was 62 years (34 reports had age unreported). 119 reports originated from the WHO European region and two from the WHO Western Pacific region.

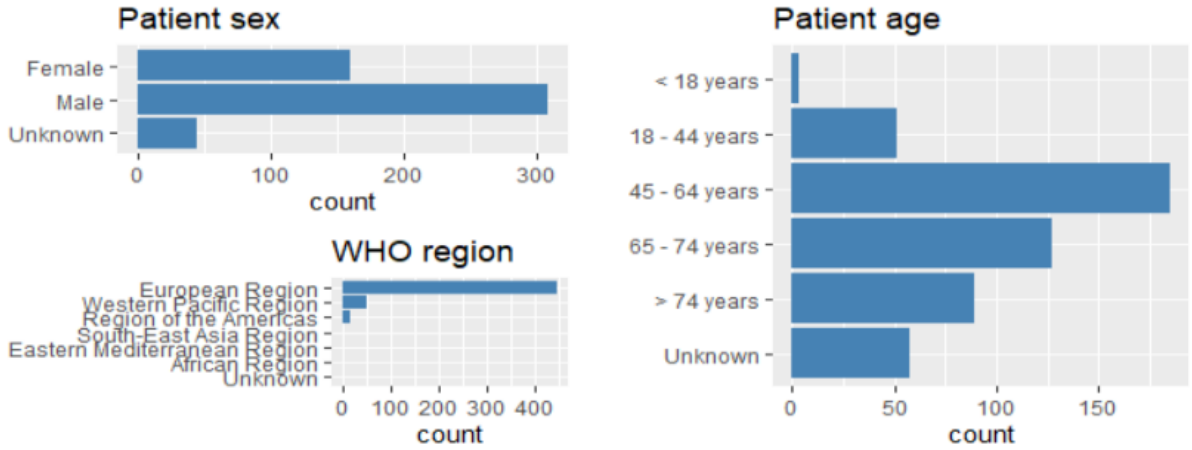

Figure 6. Demographics of VigiBase reports received cumulatively so far for lopinavir;ritonavir as suspected or interacting drug.

Adverse events

The most commonly reported ADRs continued to be those which are included on the product labelling for lopinavir;ritonavir.[4]

The most commonly reported ADRs during the review period were therapeutic response unexpected (32 reports, 57 cumulative), pre-existing condition improved (31 reports, 31 cumulative), diarrhoea (29 reports, 134 cumulative), nausea (14 reports, 58 cumulative), and long QT syndrome (13 reports, 16 cumulative).

The most commonly reported ADRs cumulatively are: diarrhoea (134 reports), nausea (58 reports), therapeutic response unexpected (57 cumulative), hepatocellular injury (47 reports), vomiting (37 reports).

Off-label use has been reported as an ADR in nine reports during the review period and in 158 reports cumulatively.

Newly received during this reporting period are 31 reports of "pre-existing condition improved". All reports co-reported "therapeutic response unexpected". All reports were received from a single country, and there was no information provided on age or sex. All case reports refer to the study by Capra R, De Rossi N, Mattioli F, et.al. [5] in which 85 consecutive patients were enrolled to received standard of care (hydroxychloroquine, lopinavir;ritonavir) or standard of care plus tocilizumab. Conclusion of study was that tocilizumab results to have a positive impact if used early during COVID-19 pneumonia with severe respiratory syndrome in terms of increased survival and favourable clinical course.

Other newly reported ADRs of interest include: agitation (one report), confusional state (one report), and depressed level of consciousness (one report). Concomitantly administered drugs included carbidopa/levodopa, pramipexole, venlafaxine in the report of agitation and sertraline in the report of confusional state and withdrawal syndrome.
Reports related to hepatic system continue to be received. In addition to hepatocellular injury as noted above, there were new reports for hypertransaminasemia (nine new, 29 cumulative), hepatitis (two new, 16 cumulative), hyperbilirubinemia (six new, 25 cumulative), and additional other terms which are less commonly reported.

There were three additional cases of rhabdomyolysis received in the current period. One of the three reported atorvastatin as a concomitant medication, and another case report "hypertriglyceridemia" in the medical history. Interaction with lopinavir;ritonavir and atorvastatin is described in the label.

The reported reactions and their level of seriousness are all (cumulatively and for this period) available on an HLGT level in attachment 1 [separate file].

Remdesivir

There is a total of 96 reports of remdesivir in VigiBase. During this reviewing period, 25 new remdesivir reports were shared, of which 17 the drug was reported as single suspected. These concerned eight female and 10 male patients as well as seven patients of unknown sex. 25 reports originated from the WHO European region. An overview of the cumulative number of reports up until the previous period is available in the previous report.

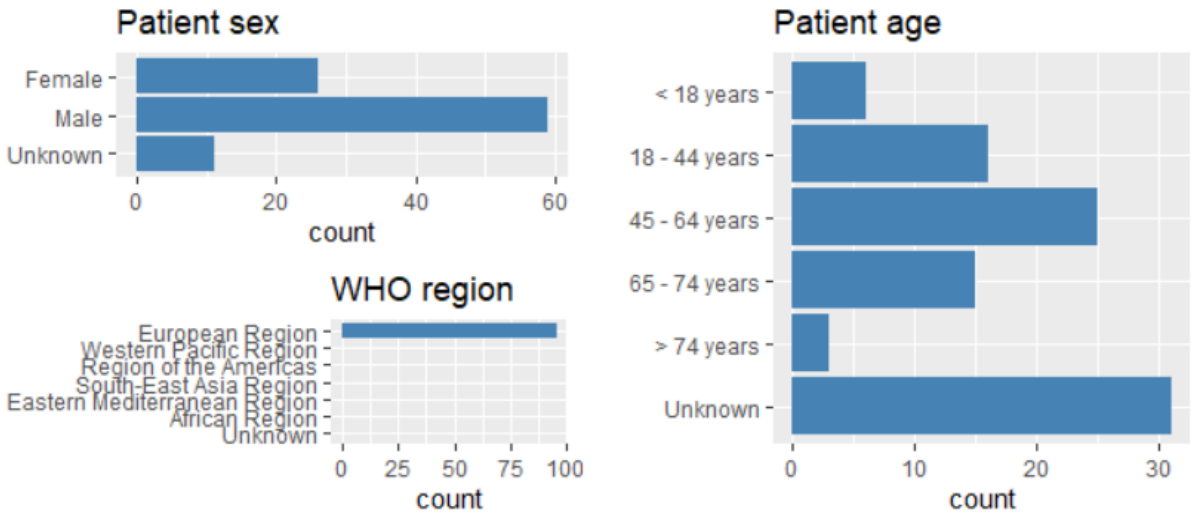

Figure 7. Demographics of VigiBase reports received cumulatively so far for remdesivir as suspected or interacting drug.

Adverse events

The most commonly reported ADRs during the review period are: acute kidney injury (four reports, 12 cumulative), respiratory failure (three reports, seven cumulative), anaemia (two reports, five cumulative), diarrhoea (two reports, seven cumulative), and multiple organ dysfunction syndrome (two reports, five cumulative).

The most commonly reported ADRs cumulatively are: acute kidney injury (12 reports), rash (11 reports), transaminases increased (11 reports), respiratory failure (seven reports), and diarrhoea (seven reports).

The cumulative cases of acute kidney injury and the associated MedDRA PT, renal failure, are here reviewed. There is a total of 15 cases, 12 male and three females, ages ranged between 39 -80 years (four reports with unknown age), originating from eight different European countries. Concomitant medications of note: furosemide (six reports), hydroxychloroquine (four reports), lopinavir;ritonavir (four reports), piperacillin/tazobactam (six reports). In only two cases were an additional agent reported as co-suspected (furosemide). Co-reported ADRs were multiple organ dysfunction syndrome (four reports), septic shock (three reports), hypotension (two reports), respiratory failure (two reports). Time to onset ranged between 1-17 days (information available from 10 cases). Included in the Annex 1 information for compassionate use in Europe[6]: "In nonclinical animal studies, toxicity findings were consistent with dose-dependent and reversible kidney injury and dysfunction. In clinical studies, no evidence of nephrotoxicity has been observed with single doses of remdesivir up to 225 mg or multiple once-daily doses of remdesivir 150 mg for up to 14 days."

Hepatobiliary reactions continue to be reported. Reactions received during this review period include: hepatic function abnormal (one report, two cumulative), hyperbilirubinaemia (one report, two cumulative), acute hepatic failure (one report, one cumulative), hepatitis (one report, two cumulative) and associated PT in the Investigations SOC such as transaminases increased (11 cumulative), hepatic enzymes increased (seven cumulative), ALT increased (seven cumulative), and AST increased (four cumulative)

Included in the Annex 1 information for compassionate use in Europe[6]: "In clinical studies, transient elevations in ALT and AST have been observed with single doses of remdesivir up to 225 mg and multiple once-daily doses of remdesivir 150 mg for up to 14 days, with mild, reversible PT prolongation in some subjects but without any clinically relevant change in INR or other evidence of hepatic effects. The mechanism of these elevations is currently unknown."

Skin reactions continue to be reported. Reactions received during this review period include: rash (two reports, 11 cumulative), rash maculo-papular (one report, three cumulative), dermatitis allergic (one report, one cumulative), and rash erythematous (one report, one cumulative). There is no

information provided regarding skin reactions in either the available information from the US FDA or the EMA.[7]

The reported reactions and their level of seriousness are all (cumulatively and for this period) are available on an HLGT level in attachment 1 [separate file].

Non-solidarity-drug use for COVID-19 with ADR reporting in VigiBase

Apart from the WHO-solidarity trial, a large number of cases report the use of other drugs for the treatment of COVID-19. As ADR data accumulate for such substances, treatment and patterns of reported adverse events for them will be described. A more detailed review is included once the number of reports for a drug exceeds 100; at this time both tocilizumab and oseltamivir both reached above this threshold and are reviewed separately. The rest of the drugs identified as being used are presented as "other" (Table 3)
The reported reactions and their level of seriousness for all drugs (cumulatively and for this period) available in attachment 1 [separate file]. For the non-solidarity drug reports (marked as "other" in the table) individual case validation has not been performed.

Tocilizumab

Tocilizumab is a monoclonal antibody against the interleukin-6 receptor. Approved indications are all non-infectious in nature and among them and most relevant for its use in COVID-19, is cytokine release syndrome (CRS).[8,9] The drug is used in COVID-19 to alleviate the inflammatory cytokine storm, part of a severe inflammatory response to the viral infection.

During this reviewing period there were 96 new reports in which tocilizumab was reported as suspected or interacting adding up to a total cumulative number of 267 reports (Table 1). The new reports concerned 45 males, 19 females and 32 where sex was not reported; median age of the patients was 64 (with 31 reports lacking information on age). The new reports were shared from the European region (86), Region of the Americas (seve), Eastern Mediterranean region (none), South East Asia (none), Western Pacific region (three) (Table 2).

An overview of other COVID-19 drugs co-administrated with tocilizumab is available in Table 4 where azithromycin, hydroxychloroquine, lopinavir;ritonavir and enoxaparin are the three most common ones. An overview of the cumulative reporting demography is shown in Figure 8.

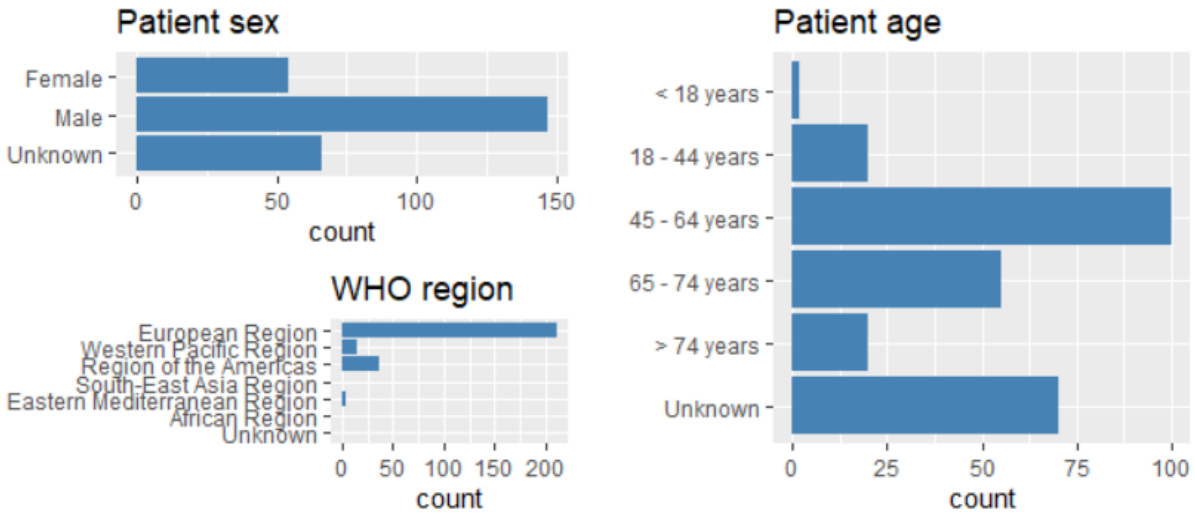

Figure 8. Demographics of VigiBase reports received cumulatively so far for tocilizumab as suspected or interacting drug.

Adverse events

New and unlabelled events

Eosinophilia[8] was reported in two cases with a time to onset of 16 days and two months respectively. In both cases other drugs were co-suspect and in one of the cases pruritus and rash was co reported and a skin test with unknown outcome was mentioned.

Since review # 5 and 6 where coagulopathies and platelet disorders were discussed in more detail a few more similar reports have been shared. A collected assessment of the cases reinforced by the new ones, is one of complicated coagulation system imbalances where the inherent ability of the drug to cause bleedings cannot be excluded as adding to the clinical picture as may have the COVID-19.

In review #4, 5 and 6, case series of hepatic reactions, white blood cell disorders, anaphylactic reactions, cardiac arrhythmias, and severe infections (other than COVID-19) were presented; an update follows: Also for this period several new hepatic reactions including hepatobiliary investigational terms were reported but nut further discussed. Hepatitis in one of the most reported reactions all over with the use of tocilizumab and the most common hepatic term with now 36 reports in total. It is acknowledged in the labelling as a rare side effect for tocilizumab.[8,9] Besides hepatitis, other hepatic reactions noted so far are: cholestasis, drug-induced liver injury, hepatotoxicity, hyperbilirubinemia, hepatitis acute, hepatocellular injury, liver function test increased, gamma-glutamyltransferase increased transaminases increased, hepatic enzyme increased.

Regarding blood disorders, there were again new cases of leukopenia, thrombocytopenia and neutropenia reported. White blood cell disorders are labelled with a frequency of common[9] for the drug and may also be present in the disease.

Besides the above, other haematological disorders reported so far are: anaemia, bi-cytopenia, blood loss anaemia, cytopenia, haemolytic anaemia, lymphopenia.

There were no serious hypersensitivity reactions reported for this review. Previously anaphylactic reactions including shock have been reported. Urticaria, hypersensitivity and (fatal) anaphylaxis are labelled for the drug.

In addition to cases of infection and the discussion related to the inherent risk of infections from tocilizumab use in the last two reviews, there are in this review among reports of infections cases of candida endophthalmitis, cytomegaly virus infection, candida endocarditis, staphylococcal sepsis, and four new cases of septic shock reported three of which were fatal.
The tocilizumab label does not include cardiac events[8,9.] In review #6 myocardial infarction, atrial fibrillation, atrial flutter, bundle branch block, ventricular extrasystole, ventricular tachycardia, cardiac and cardiopulmonary arrest, cor pulmonale were discussed. For this review only one cardiac case, one of atrial fibrillation was added.

In review #6 intestinal perforations and gastrointestinal haemorrhages were discussed. Also, during the period of this review similar events have been reported including another four reports of perforation and a case of ischemic colitis and one of melaena. Mouth ulceration, Gastritis, Stomatitis and Gastric ulcer are included in the tocilizumab label[8,9] but not colitis, perforations and haemorrhages per se other than as a complication of diverticulitis; there is a warning regarding treating patients at risk of perforation. The pattern of reported ADRs for lies largely within what is labelled for the drug except for the cardiac events.[8,9] All the reported reactions and their level of seriousness are (cumulatively) available on HLGT level in attachment 1 [separate file].

Oseltamivir

During this reviewing period 93 new reports in which oseltamivir were reported as suspecting or interacting drugs were reviewed. Included in this review are additional 36 reports that had been received previously. These concerned 66 male and 63 female patients; median age of patients described in the new reports was 43 years. 112 reports originated from the WHO European region, seven reports from the WHO Region of the Americas, and one from the WHO Western Pacific region.

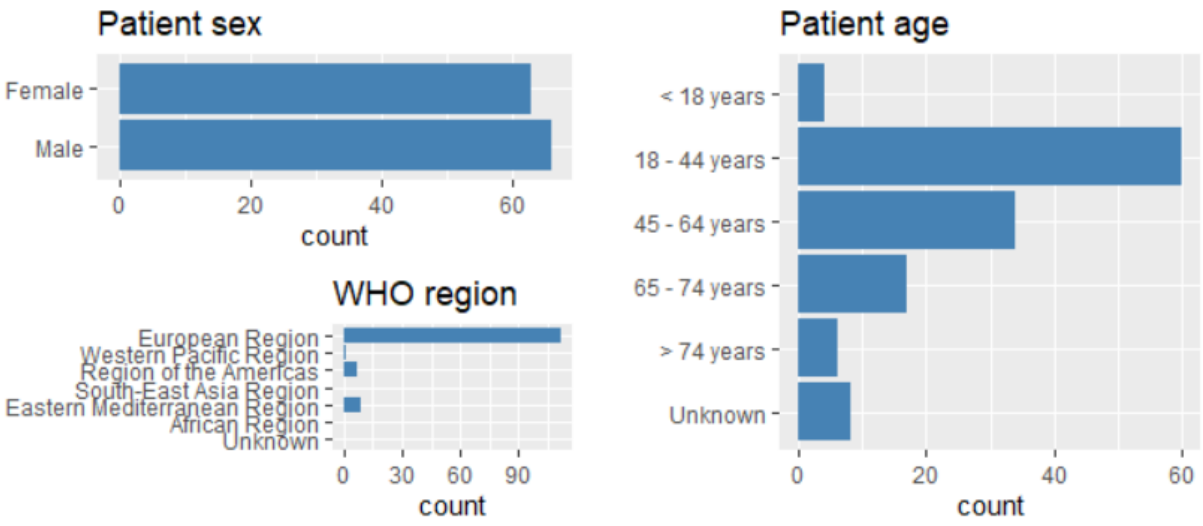

Figure 9. Demographics of VigiBase reports received cumulatively so far for oseltamivir as suspected or interacting drug.

Adverse events

The most commonly reported ADRs are those which are included on the product labelling for oseltamivir.[10]

The most commonly reported ADRs during the review period and cumulatively are: nausea (18 reports, 21 cumulative), vomiting (11 reports, 15 cumulative), diarrhoea (11 reports, 19 cumulative), hepatotoxicity (10 reports, 11 cumulative), and pruritus (10 reports, 12 cumulative).

A review of the 11 cumulative reports of hepatotoxicity revealed that 10 cases arose from a single country in which a regimen of multiple agents was being used to treat COVID-19: oseltamivir, hydroxychloroquine and azithromycin and typically an antibiotic such as ceftriaxone. Four cases within this case series also receive favipiravir.

Included in the label for oseltamivir are neuropsychiatric reactions. There is one case of hallucination report; upon review, the case describes a woman quite ill with COVID -19 disease, with high fevers and gastrointestinal symptoms, and taking multiple medications.

Also included in the label for oseltamivir are skin reactions, including such serious reactions as Stevens Johnsons syndrome and toxic epidermal necrolysis. There are number of skin ADRs which have been reported, including rash (11 reports), skin disorder (one report), dermatitis allergic (one report), hyperhidrosis (one report), skin exfoliation (one report, upon review – not consistent with SJS/TEN), urticaria (one report), and rash maculo-papular (one report).

Disclaimer

Data in the reports are not complete and only a subset of the reports in the analysis contained narratives. With limited data available at this stage of the pandemic and the uncertainty over other confounders (such as the underlying disease), this report is no more than a preliminary overview of cases and reported ADRs. No deduplication was used. Any signals detected from this monitoring will be communicated separately.

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World Health Organization

Appendix

Drug group	N_old	N_new	N_total
Azithromycin	624	282	906
Chloroquine	312	41	353
Hydroxychloroquine	944	592	1536
Lopinavir;ritonavir	381	132	513
Remdesivir	71	25	96
Tocilizumab	171	96	267
Oseltamivir	36	93	129
Other drugs	237	197	434
Unique reports	1896	928	2824

Table 1. N_old display reports described in previous reports, which included reports received to VigiBase no later than the 24th of May. N_new includes reports received to VigiBase no later than the 7th of June. Other drugs are selected from medical expertise from the set of corona virus indicated drugs reported to VigiBase, see Appendix. Counts include suspected or interacting drugs. As one report may contain several drugs, rows are not mutually exclusive.

		Azithromycin		Chloroquine		Hydroxychloroquine		Lopinavir;Ritonavir		Remdesivir		Tocilizumab		Oseltamivir		Other		Unique reports	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Report characteristics																			
	Total N	906	100	353	100	1536	100	513	100	96	100	267	100	129	100	434	100	2824	100
	Single Susp.	52	5.7	125	35.4	612	39.8	190	37	78	81.2	158	59.2	10	7.8	215	49.5	1440	51
	Serious	410	45.3	119	33.7	822	53.5	296	57.7	53	55.2	183	68.5	31	24	271	62.4	1466	51.9
	Fatal	37	4.1	4	1.1	82	5.3	32	6.2	17	17.7	77	28.8	2	1.6	82	18.9	258	9.1
Sex																			
	Female	404	44.6	190	53.8	612	39.8	160	31.2	26	27.1	54	20.2	63	48.8	146	33.6	1095	38.8
	Male	478	52.8	147	41.6	864	56.2	309	60.2	59	61.5	147	55.1	66	51.2	274	63.1	1573	55.7
	Unknown	24	2.6	16	4.5	60	3.9	44	8.6	11	11.5	66	24.7			14	3.2	156	5.5
Age																			
	Median (Q1-Q3)	52 (36-66)		49 (32-64)		58 (41-71)		63 (53-72)		56 (41-65)		62 (53-67)		43 (33-61)		62 (51-72)		58 (43-70)	
	< 18 years	15	1.7	9	2.5	17	1.1	3	0.6	6	6.2	2	0.7	4	3.1	3	0.7	39	1.4
	18 - 44 years	292	32.2	132	37.4	410	26.7	51	9.9	16	16.7	20	7.5	60	46.5	58	13.4	649	23
	45 - 64 years	302	33.3	103	29.2	486	31.6	185	36.1	25	26	100	37.5	34	26.4	171	39.4	925	32.8
	65 - 74 years	145	16	50	14.2	280	18.2	127	24.8	15	15.6	55	20.6	17	13.2	99	22.8	534	18.9
	> 74 years	92	10.2	28	7.9	247	16.1	89	17.3	3	3.1	20	7.5	6	4.7	79	18.2	419	14.8
	Unknown	60	6.6	31	8.8	96	6.2	58	11.3	31	32.3	70	26.2	8	6.2	24	5.5	258	9.1
WHO region																			
	African Region	1	0.1	0	0	2	0.1	0	0	0	0	0	0	0	0	0	0	2	0.1
	Eastern Mediterranean Region	381	42.1	213	60.3	193	12.6	1	0.2	0	0	3	1.1	9	7	7	1.6	420	14.9
	European Region	442	48.8	63	17.8	1018	66.3	446	86.9	96	100	212	79.4	112	86.8	344	79.3	1810	64.1
	Region of the Americas	63	7	21	5.9	230	15	16	3.1	0	0	37	13.9	7	5.4	34	7.8	336	11.9
	South-East Asia Region	6	0.7	3	0.8	53	3.5	0	0	0	0	0	0	0	0	0	0	60	2.1
	Western Pacific Region	13	1.4	53	15	40	2.6	49	9.6	0	0	15	5.6	1	0.8	49	11.3	195	6.9
	Unknown	0	0	0	0	0	0	1	0.2	0	0	0	0	0	0	0	0	1	0

Table 2. Counts are cumulative and include suspected and interacting drugs. As one report may contain several drugs, columns are not mutually exclusive. Other drugs are selected from medical expertise from the set of corona virus indicated drugs reported to VigiBase, see Appendix. Single susp. = Drug was reported as single suspected or interacting drug, Q1-Q3 = First to third quartile.

Drug	N	%
Unique reports	129	100
Enoxaparin	86	66.7
Favipiravir	64	49.6
Plasma	40	31
Eculizumab	38	29.5
Ritonavir	31	24
Anakinra	24	18.6
Darunavir	22	17.1
Heparin	22	17.1
Ruxolitinib	13	10.1
Apixaban	12	9.3
Interferon beta-1b	12	9.3
Sarilumab	12	9.3
Ribavirin	11	8.5
Baricitinib	9	7
Montelukast	9	7
Canakinumab	8	6.2
Cobicistat;Darunavir	8	6.2
Lopinavir	8	6.2
Metamizole	7	5.4
Ascorbic acid	6	4.7
Ivermectin	5	3.9
Siltuximab	5	3.9
Colchicine	4	3.1
Immunoglobulin human normal	4	3.1
Interferon beta-1a	4	3.1
Rituximab	4	3.1
Epoprostenol	3	2.3
Umifenovir	3	2.3
Zinc	3	2.3
Apremilast	2	1.6
Darunavir;Ritonavir	2	1.6
Nitazoxanide	2	1.6
Ademetionine	1	0.8
Almitrine	1	0.8
Bromhexine	1	0.8
Ciclosporin	1	0.8
Icatibant	1	0.8
Interferon beta	1	0.8
Octreotide	1	0.8
Tofacitinib	1	0.8

Table 3. Drugs included in the Other drugs-category. Counts are cumulative and include drugs reported as suspected or interacting. *As one report may contain several drugs, rows are not mutually exclusive.*

	Azithromycin	Chloroquine	Hydroxychloroquine	Lopinavir;Ritonavir	Remdesivir	Tocilizumab	Oseltamivir
Total (S/I/C)	1084	365	1712	561	96	300	193
Single suspected	201	134	754	229	78	175	53
Azithromycin		229	761	121	8	63	107
Chloroquine	229		7	23	1	6	2
Hydroxychloroquine	761	7		264	29	134	168
Lopinavir;Ritonavir	121	23	264		14	57	13
Remdesivir	8	1	29	14		7	2
Tocilizumab	63	6	134	57	7		8
Oseltamivir	107	2	168	13	2	8	
Anakinra	14		16	2	1	4	
Apixaban	3	2	12	7	2		
Apremilast	1		2				
Ascorbic acid	34	5	42	5	1		14
Baricitinib	2		5			1	
Bromhexine			2				2
Canakinumab			2				
Ciclosporin			4	2			
Cobicistat;Darunavir	6		9	3	1	2	
Colchicine	2		5			2	1
Darunavir	6		20	2	1	2	
Darunavir;Ritonavir			2				
Eculizumab	3		2	1		1	
Enoxaparin	191	15	275	62	25	46	44
Favipiravir	38		62	3	1	12	23
Heparin	6	1	18	20	13	5	2
Immunoglobulin human normal	1		3			2	
Interferon beta			1	2		1	
Interferon beta-1a	1		1	4			
Interferon beta-1b	10	1	12	13		2	
Ivermectin	2		3			2	
Lopinavir	3		10				
Metamizole	11		21	3	6	5	4
Montelukast	3		1	2	1		
Nitazoxanide	2		1				
Ribavirin	4		2	13	1	1	1
Ritonavir	9		31	2	1	2	
Rituximab			1	1			
Ruxolitinib	1		6	2	1	1	
Sarilumab	4		4				
Siltuximab			1	1			
Umifenovir				5			2
Zinc	21	6	16	3	1		
Other	468	78	771	304	74	109	106

Table 4. Co-medication frequencies. First row gives total number of reports including a drug irrespectively of drug role (suspected/interacting/concomitant). Second row gives number of reports on which the drug was the single suspected or interacting drug. Remaining rows give frequencies of co-reporting of a drug pair, irrespectively of drug role.

CAVEAT DOCUMENT

2018-11-20

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

i. recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information
ii. explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases
iii. affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.