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

Report from the WHO Collaborating Centre for International Drug Monitoring

Report date: 2020-09-23

This twelfth review of global reporting of ADRs for drugs used to treat COVID-19 is presented now more than half a year into the pandemic. For a few drugs, clinical trial results point to some efficacy in the disease. Among these, remdesivir is so far the only antiviral drug[1] while glucocorticoids[2,3] and the heparin class drugs[4] have positive effects on complications of the disease. Other drugs widely used during the first part of the pandemic have by now been reported as ineffective in the patient groups studied[5], while numerous other suggested treatments still lack reliable information on their respective efficacy in COVID-19. The review has been adapted to the current state of knowledge and focus is hence given to remdesivir, the glucocorticoids and the heparin class of drugs for automated and manual reviews following the pattern of previous reviews. In addition, the COVID-19 related reporting into VigiBase for another two substances, favipiravir and ivermectin, has now passed the threshold of 100. A full overview of the reporting for these drugs has also been included.

For all other drugs which have previously been reviewed, including drugs initially part of the WHO Solidarity trial to find an effective COVID-19 treatment, basic statistics, tables and figures are included in this review but no manual analysis has been performed. These drugs are hydroxychloroquine, chloroquine, azithromycin, lopinavir;ritonavir (combination), tocilizumab, sarilumab and oseltamivir. WHO has announced the discontinuation of the hydroxychloroquine (HCQ) and lopinavir;ritonavir arms of the WHO Solidarity trial as per the recommendation from the international steering committee[5].

These COVID-19 related reviews of international spontaneous reporting will continue to be produced during 2020. Decisions on drugs to be manually reviewed, and the format of the report for the PIDM will be flexible and continue to be based on the development of the pandemic, the extent of reporting and new evidence for the usefulness of substances in the treatment of the disease.

Reports have been shared from all WHO regions, with the largest number originating in the WHO region of the Americas with 44% of the reports (table C).

A small number of reports were received for remdesivir following the major increase in reports for the last review. Non-labelled adverse reactions continued to be reported including terms not previously reported.

Concerning the other drugs reviewed, ADR-patterns are consistent with those described in earlier reports and mostly within the labelling for the respective drugs. For favipiravir, where approved labelling was not readily available to us, the pattern appears consistent with what has been described in clinical trials.

World Health Organization

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Reports in VigiBase

The search methodology is with one exception the same in this twelfth review, as in the eleventh. Reports were screened for drugs given on a corona or COVID-19 indication, by relevant free-text terms and laboratory tests. Reports were considered for inclusion if they were received at the National Centres between November 1st 2019 and September 6th 2020 and were reported to VigiBase no later than September 6th.* Reports were considered for inclusion when they were reported as suspected/interacting drugs initially included in the Solidarity trial (Table B) or drugs considered clinically relevant based on medical-expertise (Table C) and reported to VigiBase on a Corona or COVID-19 indication.

There are country-specific reporting delays after receipt of reports at National Centres and thus the reporting date to VigiBase should not be considered as proxy for the 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.

Assessment of causality in individual cases is for all COVID-19 drugs difficult due to the background disease, the limited data on the drugs as used in this disease and the relatively large proportion of multiple concomitant other COVID-19 treatments and has therefore in most cases not been performed.

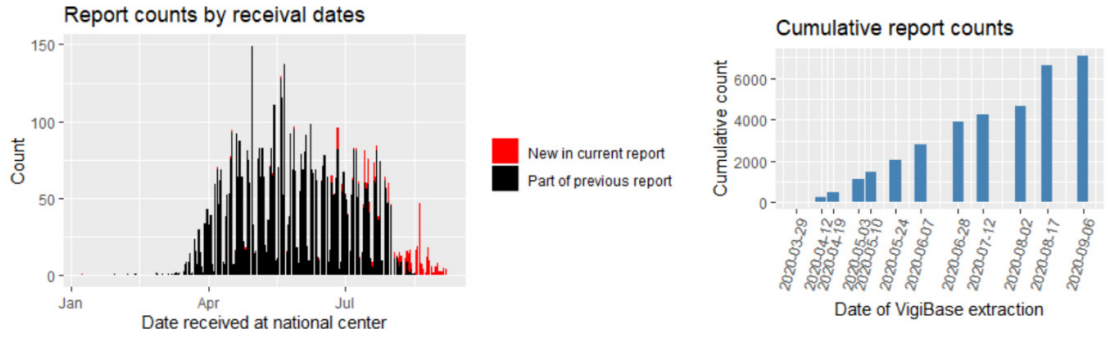


Figure 1. Number of reports by dates received at national center (left), and cumulative number of reports in VigiBase at the dates of extractions for reports. The rightmost bar (right panel) shows the total number of reports received so far.

Overview of patient characteristics

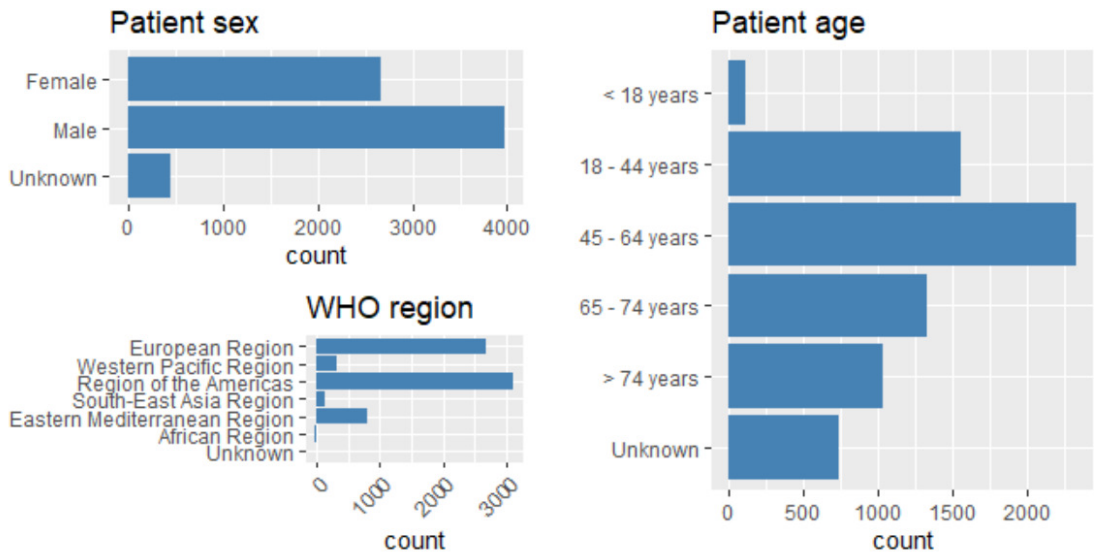
Since the last analysis, 391 new case reports have been identified using the selected search strategy (Table A). Cumulatively, a total of 7092 reports have been received from six WHO regions, namely the Region of the Americas (44%), European Region (37.6%), Eastern Mediterranean Region (11.5%), Western Pacific Region (4.6%), South-East Asia Region (2%), and African Region (0.2%). 57% of the reports were classified as “serious” (table C) but not all reporting standards include seriousness (e.g. INTDIS). Males accounted for 56 % of the reports and females for 37.6 %.

To a high extent reports still describe at least one drug originally included in the WHO Solidarity trial, i.e. with hydroxychloroquine (in some regions replaced by chloroquine), azithromycin, remdesivir or lopinavir;ritonavir reported as either suspected or interacting. While these drugs, except remdesivir, at this point are used less as a result of negative study outcomes[5], reports on ADRs connected to their use are still arriving, partly because of the delay from the occurrence, reporting and coding of

* If the arrival date at the National Centre was not reported, the date of latest update at the National Centre was used instead. Reports referred to as "new" during the current time interval may be reports with an initial entry into Vigibase during the time interval or an update of a report which had been previously received into the database prior to the current reporting period.

the events to the sharing of the reports by the national centres into VigiBase. Reports describing all other drugs used in the treatment of COVID-19 disease and reported more than 100 times into the database have previously been included in a more detailed review. With an increasing number of drugs belonging to the 100+ group, a decision was made to focus the extent of manual reviews, this time to drugs with evidence of efficacy in COVID-19 and drugs reaching a threshold of 100 reports for the first time. Manual reviews are hence this time performed for the following drugs and drug groups with positive treatment results: remdesivir[1] the glucocorticoid group[2,3] and the heparin group[4], and in addition for ivermectin and favipiravir. A disproportionality analysis using drugs reported for COVID-19 as a background rather than the whole database, was used to attempt to minimise highlighting events related to the disease rather than the drug specific ones. Overall reporting demographics for the drugs are shown in Figure 2. In line with males being more affected by COVID-19 infection globally, all drugs except chloroquine, oseltamivir and ivermectin are clearly more reported for men than women. Patient ages are similar between drugs, with patients with reported treatment with oseltamivir and ivermectin appearing to have the lowest median age.

A)



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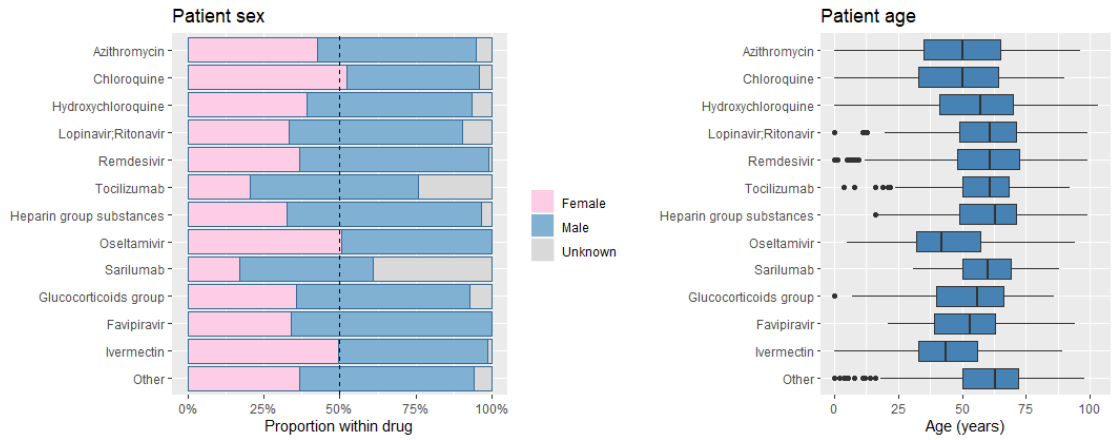

Figure 2. Overall demographics of case safety reports sent into VigiBase in treatment of COVID-19. A) All reports. B) Reports by drug. The B) graphs rely on counts of reports which include each drug as suspected or interacting. Reports including several drugs will be counted once for each reported drug.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

Characteristics of reporting on drugs in focus

Remdesivir

There were 43 new reports for remdesivir during this reviewing period, adding up to a cumulative total of 2018 reports. The new reports included 34 men, eight women and one with unknown sex. The new reports originated from the European Region (N=36), South-East Asia Region (N=3), Western Pacific Region (N=3) and Region of the Americas (N=1). In the new reports the median age was 53 years. For the new reports remdesivir was the single suspected drug in 39 reports. Related cumulative counts are found in Table B and an overview of the cumulative reporting demography is shown in **Error! Reference source not found.**. A cumulative overview of other COVID-19 drugs co-administered with the drug, or drug group, is available in Table E. The most frequently reported COVID-19 drugs co-administered with remdesivir were heparins (741), glucocorticoids (585), azathioprine (318) and tocilizumab (140).

Remdesivir is an adenosine nucleotide prodrug that is metabolized within host cells to form the pharmacologically active nucleoside triphosphate metabolite. Remdesivir triphosphate acts as an analogue of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into forming RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase which results in abnormal replication of the viral RNA.[6]

Remdesivir has shown broad spectrum activity against human and zoonotic coronaviruses in pre-clinical models and has been included in clinical trials for COVID-19 infection.[7]

In a randomised controlled trial of 1063 patients with advanced COVID-19 infection and lung involvement remdesivir shortened recovery time and conferred a small mortality benefit.[1]

During the pandemic, remdesivir has been authorized for use in the indication of COVID-19 in several countries. Publicly available information on its side effects and precautions for its use are therefore still limited and include hypersensitivity including infusion-related and anaphylactic reactions (frequency designated as rare for both), transaminase elevations (very common), nausea (common), headache (common), rash (common) and renal impairment (precaution) and interactions including risk of decreased antiviral activity when co-administered with hydroxychloroquine and chloroquine.[6] It is likely that labelling is currently being updated.

Other interactions are theoretically possible as remdesivir is a substrate for various plasma and tissue esterases, CYP isoenzymes and transporters.[6] However, to date, we have not found evidence in VigiBase of relevant pharmacokinetic interactions.

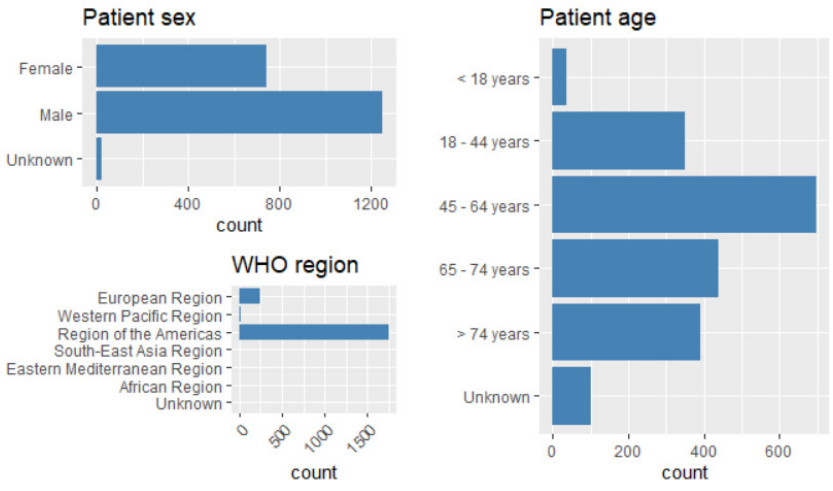

Figure 3. Demographics of VigiBase reports received cumulatively so far for remdesivir as suspected or interacting drug.

Adverse Reactions

This review should be read in conjunction with the 11th period review since a very large number of additional reports were received for that period and the in depth review was largely based on disproportionality of reporting for remdesivir compared with the background of reporting for COVID-19 drugs. This report builds on that review.

Up until the last review reporting for hepatobiliary and renal investigations and conditions and for skin reactions were predominant. The additional reports in the last review contributed further information regarding these system organ classes (SOCs) and expanded to other conditions not previously labelled.

The 43 new reports received for this period contain 52 preferred terms of which 11 are reported for the first time. These are pancreatitis acute, rash morbilliform, symmetrical drug-related intertriginous and flexural exanthema, dysgeusia, pulmonary imaging procedure abnormal, fungaemia, pseudomonas infection, hypogammaglobulinaemia, ill-defined disorder, acute myocardial infarction and thrombocytosis, each reported once. Acute pancreatitis is of interest since it was noted in the tenth review that other pancreatic terms had been reported. Twelve pancreatic terms have now been reported occurring in 12 reports. However, there is evidence that COVID-19 infection may also cause increased pancreatic enzymes and pancreatitis[8] so the reports require closer scrutiny to assess causality.

There were nine reports of fatalities in this period for patients taking remdesivir and these included the terms shock, respiratory failure (four reports), oxygen saturation decreased, pulmonary embolism, renal failure, cerebral haemorrhage, off-label use, sepsis, COVID-19 pneumonia, bacteraemia, fungaemia, pseudomonas infection, death, multiple organ dysfunction syndrome, drug ineffective and cardiac arrest. The report of renal failure occurred in the context of sepsis. Fatality appeared to be related to serious overwhelming COVID-19 and/or other opportunistic infections in five reports. The patient with cerebral haemorrhage was receiving concomitant anticoagulants.

Additional hepatobiliary disorders reported were cholestasis (one new, three in total), hepatitis (2/9), hepatotoxicity (1/7). Hepatotoxicity is disproportionately reported compared with the COVID--19 background reporting. Investigations reported in this period included hyperbilirubinaemia (1/4) and various reports indicating increased hepatic enzymes which are well documented as adverse reactions.

As already noted in previous reviews, reports of renal dysfunction, including renal failure, are frequent and in this review period there was one report each for renal failure (one new, 42 in total), renal impairment (1/66), both statistically disproportionate to the COVID-19 drug background reporting, and polyuria (1/2). There are also 240 previous reports for acute kidney injury. There is no coherent evidence for a consistent underlying renal pathology but previous reports include renal tubular necrosis (0/9) or injury (0/1), renal ischaemia (0/2), hydronephrosis (0/2) and crystal nephropathy (0/1).

A range of skin reactions have been reported including the two newly reported for this period. There are two reports of blisters together with rash but no definite reports to date of any serious cutaneous adverse reactions (SCARs).

Regarding immune system reactions there was one more non-fatal anaphylactic reaction (one new, three in total) and hypogammaglobulinaemia was reported for the first time.

Acute myocardial infarction (one new, ten total) was reported for the first time in the last review and is disproportionately reported compared with the COVID-19 drug background reporting.

Respiratory reports received in this period included respiratory failure (four new, 85 in total) and dyspnoea (1/43). Both are disproportionately reported compared with the COVID-19 drug

background reporting. Respiratory reports may be over-represented for remdesivir since, at least in Europe, it is indicated for patients with COVID-19 infection already requiring supplemental oxygen. [6]

A new report of seizure (one new, 11 in total), was mentioned in the last report as one of an especially noted list of PTs not being disproportionately more reported for remdesivir than for the COVID-19 background *and* not previously mentioned *and* reported more than once. The new report means that the remdesivir/seizure combination has now exceeded the IC_{025} value and is therefore disproportionately reported. These reports require further study.

Incorrect dose administered (one new, seven in total) adds to a range of previous reports for incorrect product preparation, dispensing and administration. The reports examined so far are sparse in detail and countries are encouraged to investigate such reports for preventable events.

Fatal and other serious reports for remdesivir include conditions that could be attributed to COVID--19 infection itself or other medicines used to treat it, eg, respiratory failure, sepsis, shock and organ failure. Nevertheless there needs to be continued scrutiny including discovery of preventable adverse reactions where errors are reported.

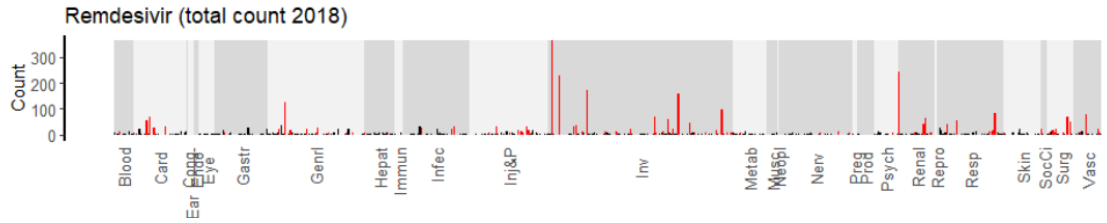

Figure 4. Cumulative report counts for remdesivir in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

PT	Reports (Total)	%
Alanine aminotransferase increased	364 (2018)	18.0
Acute kidney injury	240 (2018)	11.9
Aspartate aminotransferase increased	229 (2018)	11.3
Blood creatinine increased	174 (2018)	8.6
Liver function test increased	159 (2018)	7.9

PT	Reports	IC025_COVID
Blood creatinine increased	174	1.5
Glomerular filtration rate decreased	70	1.4
Therapy cessation	71	1.4
Alanine aminotransferase increased	364	1.3
Therapy interrupted	49	1.3

PT	Reports	IC025_VigiBase
Liver function test increased	176	6.3
Glomerular filtration rate decreased	76	5.8
Therapy interrupted	54	5.8
Alanine aminotransferase increased	393	5.6
Aspartate aminotransferase increased	250	5.2

Figure 5 Remdesivir. Left subtable: Top 5 reported Preferred Terms (PT). Reports (Total) shows the cumulative number of reports in the COVID-19-dataset with both the drug and PT and the total count with drug respectively. Middle subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on COVID-19-reports. Reports-column shows the cumulative number of reports with the drug and PT in the COVID-19-dataset. Right subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on VigiBase (ie not limited to use in COVID-19). Reports-column shows the cumulative number of reports with the drug and PT in VigiBase. An IC025-value above 0 indicates that the observed value is disproportionately high compared to the expected count. Ties might result in more than 5 PTs.

Glucocorticoid group (GCG)

There were 34 new reports for the glucocorticoids group (GCG) during this reviewing period, adding up to a cumulative total of 251 reports. The most common substances were prednisone, methylprednisolone and dexamethasone accounting for nearly 90% of these drugs (Figure 7). The

new reports included 14 men and 20 women. The new reports originated from the region of the Americas (N=17), European Region (N=8), Eastern Mediterranean Region (N=7) and Western Pacific Region (N=2). In the new reports the median age was 52 years. For the new reports, a glucocorticoid was the single suspected drug in six reports. Related cumulative counts are found in Table C and an overview of the cumulative reporting demography is shown in Figure 6. A cumulative overview of other COVID-19 drugs co-administered with the drug, or drug group, is available in Table .

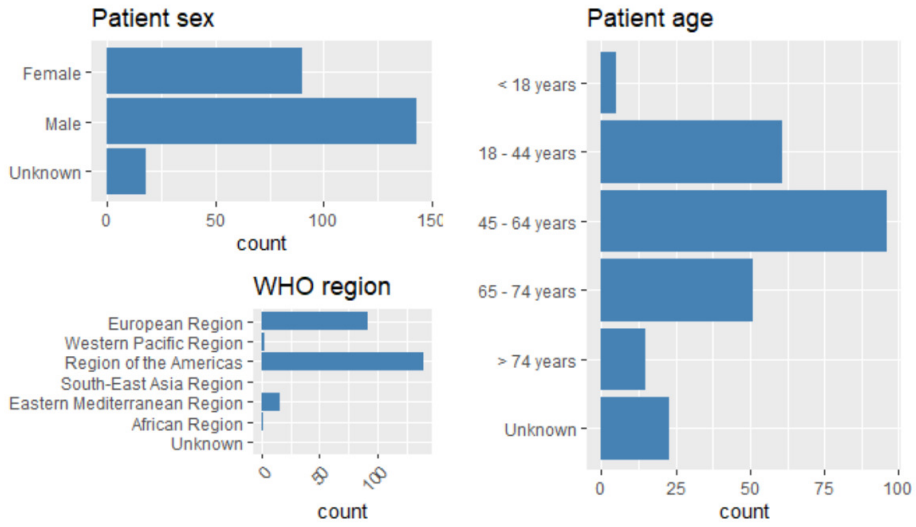

Figure 6. Demographics of VigiBase reports received cumulatively so far for glucocorticoid group drugs as suspected or interacting drug.

Drug	Count	%
Prednisone	80	32.0%
Methylprednisolone	73	29.2%
Dexamethasone	69	27.6%
Prednisolone	11	4.4%
Hydrocortisone	8	3.2%
Betamethasone	8	3.2%
Beclometasone	1	0.4%

Figure 7. The drugs that have been reported from the glucocorticoids group. Note that these counts are not mutually exclusive, since more than one of these drugs could appear on the same report.

First isolated in the late 1940s and subsequently synthesized, drugs representing the glucocorticoid hormonal group have a very well established and similar profile regarding potential harms and benefits in their numerous pre-COVID-19 indications. The use in COVID-19, has been studied primarily for dexamethasone and been shown to bring beneficial clinical outcomes.[2,3]

ADRs reported for GCG in COVID-19 use are dominated both cumulatively and for new reports in this review by MedDRA preferred terms (PT) expected either as being labelled for GCGs, or terms of a regulatory-administrative nature such as *off-label use* and *intentional product use issue*. Another common group of PTs are reports of indication spillover, ie, miscoding of the indication as an ADR *COVID-19, COVID-19 pneumonia, acute respiratory distress syndrome* etc.

A disproportionality analysis using drugs reported for COVID-19 as a background rather than the whole database, was used for the GCG to attempt to minimise highlighting events related to the disease rather than the drug specific ones.[9] Excluding ADRs of the types mentioned above, one drug event combination, *premature delivery* was highlighted by the method as being reported significantly more often than expected:

- cumulatively five cases of *premature delivery,* four of which in neonates and one in a mother have been reported. Birthweight was 0.93-1.05 kg where reported. Co-reported terms are such as would be clinically expected in prematurity. Co-reported drugs with a COVID-19 indication were in all cases hydroxychloroquine and azithromycin. The cases, all reported from the same national centre, contain little to no clinical description thereby precluding any further analysis. None of the cases was fatal at the time of reporting.

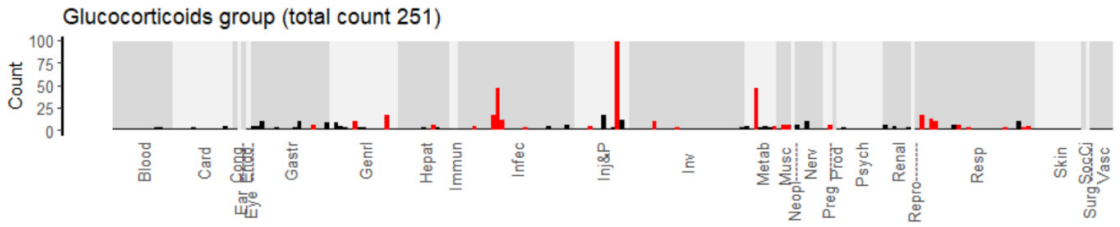

Figure 8. Cumulative report counts for the glucocorticoids group in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

PT	Reports (Total)	%
Off label use	99 (251)	39.4
COVID-19	46 (251)	18.3
Hyperglycaemia	46 (251)	18.3
Acute respiratory distress syndrome	17 (251)	6.8
Coronavirus infection	16 (251)	6.4
Intentional product use issue	16 (251)	6.4
Pyrexia	16 (251)	6.4

PT	Reports	IC025_COVID
Hyperglycaemia	46	3.8
COVID-19	46	2.5
Blood glucose increased	9	2.1
Coronavirus infection	16	2.0
Cough	13	1.8

PT	Reports	IC025_VigiBase
Steroid diabetes	733	6.0
BK virus infection	459	4.6
Hypofibrinogenaemia	118	4.5
Hiccups	3863	4.1
Cytomegalovirus oesophagitis	43	3.9

Figure 9. Glucocorticoid group. Left subtable: Top 5 reported Preferred Terms (PT). Reports (Total) shows the cumulative number of reports in the COVID-19-dataset with both the drug and PT and the total count with drug respectively. Middle subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on COVID-19-reports. Reports-column shows the cumulative number of reports with the drug and PT in the COVID-19-dataset. Right subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on VigiBase (ie not limited to use in COVID-19) . Reports-column shows the cumulative number of reports with the drug and PT in VigiBase. An IC025-value above 0 indicates that the observed value is disproportionately high compared to the expected count. Ties might result in more than 5 PTs.

Heparin group drugs

There were 11 new reports for the heparin group substances during this reviewing period, adding up to a cumulative total of 206 reports. Enoxaparin and heparin reports make up more than 95% of the reporting in the group (Figure 11). The new reports included six men and five women. The new reports originated from the European Region (N=6), Eastern Mediterranean Region (N=4) and Region of the Americas (N=1). In the new reports the median age was 63 years. A substance from the heparin group was the single suspected drug in six of the new reports. Related cumulative counts are found in Table C and an overview of the cumulative reporting demography is shown in Figure 10. A cumulative overview of other COVID-19 drugs co-administered with the drug, or drug group, is

available in Table .

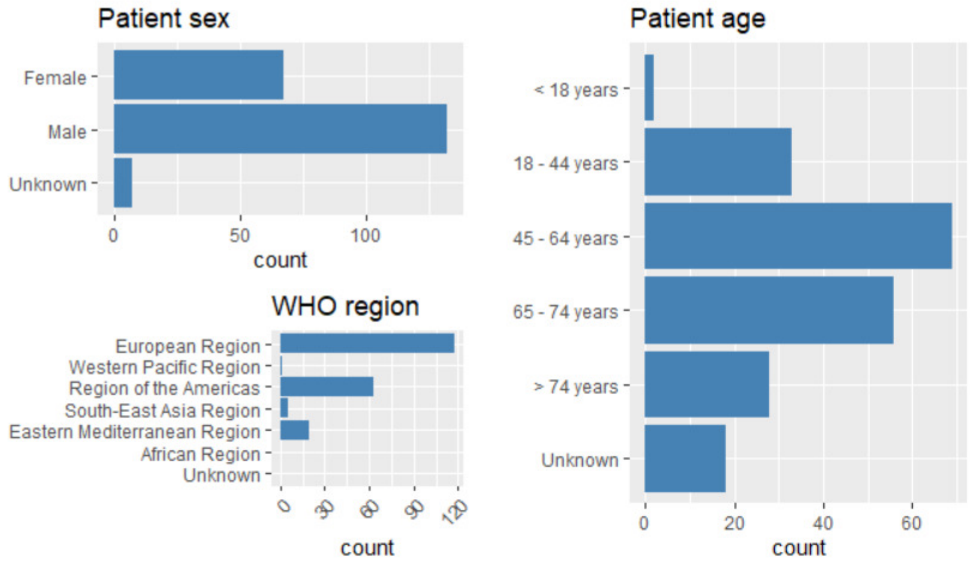

Figure 10. Demographics of VigiBase reports received cumulatively so far for Heparin group substances as suspected or interacting drug.

Drug	Count	%
Enoxaparin	147	71.71%
Heparin	49	23.9%
Tinzaparin	4	1.95%
Dalteparin	3	1.46%
Nadroparin	1	0.49%
Low molecular weight heparin	1	0.49%

Figure 11. The drugs that have been reported from the hetarin group. Note that these counts are not mutually exclusive, since more than one of these drugs could appear on the same report.

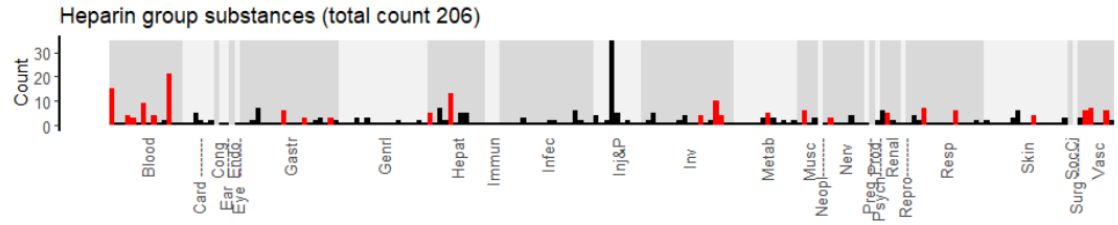

Figure 12. Cumulative report counts for heparin group substances in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

PT	Reports (Total)	%
Off label use	35 (206)	17.0
Thrombocytopenia	21 (206)	10.2
Anaemia	15 (206)	7.3
Hepatocellular injury	13 (206)	6.3
Platelet count decreased	10 (206)	4.9

PT	Reports	IC025_COVID
Heparin-induced thrombocytopenia	9	2.5
Anaemia	15	2.3
Thrombocytopenia	21	2.3
Haematoma muscle	6	2.1
Platelet count decreased	10	2.0

PT	Reports	IC025_VigiBase
Heparin-induced thrombocytopenia	8630	7.7
Retroperitoneal haemorrhage	1503	6.3
Retroperitoneal haematoma	722	6.0
Haematoma muscle	615	5.6
Shock haemorrhagic	1106	5.3

*Figure 13.Heparin group substances. Left s*ubtable: Top 5 reported Preferred Terms (PT). Reports (Total) shows the cumulative number of reports in the COVID-19-dataset with both the drug and PT and the total count with drug respectively. Middle subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on COVID-19-reports. Reports-column shows the cumulative number of reports with the drug and PT in the COVID-19-dataset. Right subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on VigiBase (ie not limited to use in COVID-19). Reports-column shows the cumulative number of reports with the drug and PT in VigiBase. An IC025-value above 0 indicates that the observed value is disproportionately high compared to the expected count. Ties might result in more than 5 PTs.

The heparin class drugs are widely used in COVID-19 to prevent and treat the coagulation complications seen in the disease. The class has a well-established pre-COVID-19 profile[10] regarding potential harms and benefits.

The most commonly reported MedDRA PTs for the group refer to off-label use related terms and labelled terms describing haemorrhages, haematological or hepatic events.

A disproportionality analysis using drugs reported for COVID-19 as a background rather than the whole database was applied also for the review of these drugs. This to detect reactions of interest for the drug group through minimising the number of highlighted combinations likely more related to the disease. Excluding ADRs of the type mentioned above only one drug event combination, *hypofibrinogenaemia* was highlighted by the method as being reported significantly more often than expected compared to other COVID-19 drugs. In all the five reported cases tocilizumab was present as a co-suspect drug for which the reaction is labelled. This finding has been reviewed previously in relation to the use of tocilizumab in COVID-19.

Ivermectin

There were 66 new reports for ivermectin during this reviewing period, adding up to a cumulative total of 131 reports. The new reports included 29 men, 35 women and two with unknown sex. The new reports all originated from the region of the Americas (N=66). In the new reports the median age was 46 years. For the new reports ivermectin was the single suspected drug in 29 reports. Related cumulative counts are found in Table C and an overview of the cumulative reporting demography is shown in Figure 14. A cumulative overview of other COVID-19 drugs co-administered with the drug, or drug group, is available in Table .

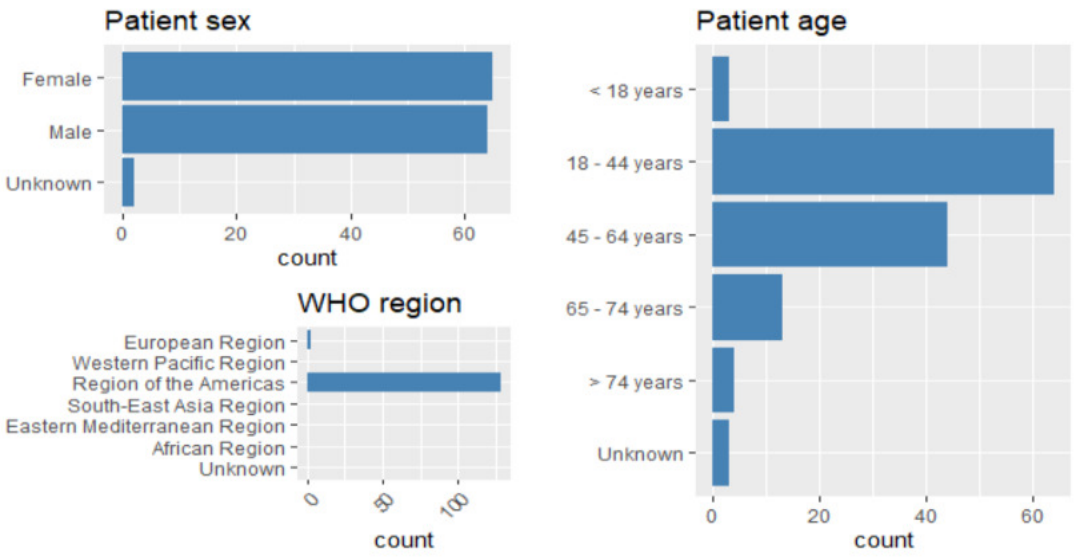

Figure 14. Demographics of VigiBase reports received cumulatively so far for Ivermectin as suspected or interacting drug.

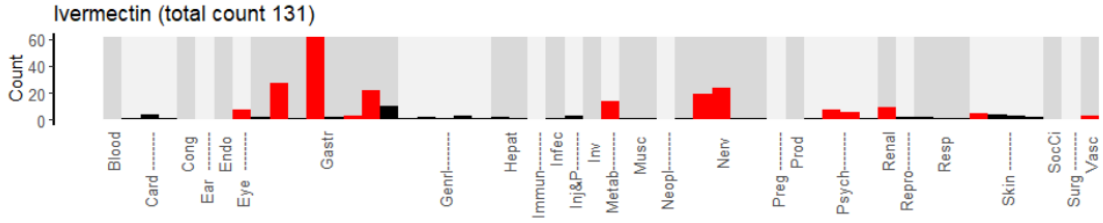

Figure 15. Cumulative report counts for ivermectin in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

PT	Reports (Total)	%
Diarrhoea	61 (131)	46.6
Abdominal pain	27 (131)	20.6
Headache	24 (131)	18.3
Nausea	22 (131)	16.8
Dizziness	19 (131)	14.5

PT	Reports	IC025_COVID
Dizziness	19	2.8
Urine abnormality	9	2.6
Abdominal pain	27	2.5
Decreased appetite	14	2.3
Headache	24	2.2

PT	Reports	IC025_VigiBase
Urine abnormality	11	2.6
Pruritus	926	2.2
Erythema	291	2.0
Dermatitis	42	1.8
Headache	464	1.4

Figure 16. Ivermectin. Left subtable: Top 5 reported Preferred Terms (PT). Reports (Total) shows the cumulative number of reports in the COVID-19-dataset with both the drug and PT and the total count with drug respectively. Middle subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on COVID-19-reports. Reports-column shows the cumulative number of reports with the drug and PT in the COVID-19-dataset. Right subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on VigiBase (ie not limited to use in COVID-19). Reports-column shows the cumulative number of reports with the drug and PT in VigiBase. An IC025-value above 0 indicates that the observed value is disproportionately high compared to the expected count. Ties might result in more than 5 PTs.

Ivermectin is a member of the class of avermectins, which are highly active broad-spectrum, anti-parasitic agents. It is indicated for use in the treatment of strongyloidiasis (Strongyloides stercoralis)

and onchocerciasis (Onchocerca volvulus).[11] It is also commonly used to treat scabies, although usage patterns for this indication vary between countries. In the scabies indication, it is approved for first-line therapy in some countries (within Europe), second-line therapy in others (such as Australia), or only recommended for special circumstances, such as immunocompromised or institutionalized patients or when topical therapy has failed (the United States).[12–14] Furthermore, it has been suggested for use in the treatment of head lice given the recent increase in the burden of this condition in the industrialized world.[15]

One hundred thirty one cases have been shared into VigiBase (cumulatively), 66 new during the last iteration. A total of 121 cases (92%) of all the ivermectin reports in total, originate from one single country and 116 reports from one specific source (study). The 10 remaining reports have been submitted from various regions including the US and Europe. Among the 14 spontaneously submitted reports, we have an age distribution of 18-44y (36%), 45-64y (36%), 65-74y (21%) and >75y (7%) with a slightly higher proportion of female reports (57%) compare to male reports (43%). Ivermectin was co-reported with other COVID-19 associated drugs including azithromycin, hydroxychloroquine, tocilizumab and enoxaparin in more than half of the reports (64 %).

Adverse events

Among the top reported adverse reactions for all 131 individual case safety reports, we have gastrointestinal problems such as diarrhoea, abdominal pain, decreased appetite, vomiting and nausea, terms that are all labelled for the drug.[11] Dizziness, headache, urine abnormality, visual impairment, anxiety and depression are other examples of top reported terms for the drug. These terms are not labelled for ivermectin but may have been caused by the concomitantly reported drugs mentioned in the reports or the underlying disease.

Focusing on the 14 spontaneous reports that did not originate from a specific study, there were two serious cases reporting death. In one of the cases, a patient with type-2 diabetes as the underlying disease died due to respiratory failure. The second fatal case did not report any possible reason for the outcome. Both of the fatal reports included multiple co-reported drugs such as oseltmavir, cefatriaxone and tocilizumab in addition to ivermectin.

Favipiravir

There were 22 new reports for favipiravir during this reviewing period, adding up to a cumulative total of 103 reports. The new reports included 15 men and seven women. The new reports originated from the European Region (N=14), Eastern Mediterranean Region (N=6) and South-East Asia Region (N=2). In the new reports the median age was 49 years. For the new reports favipiravir was the single suspected drug in 15 reports. Related cumulative counts are found in Table C and an overview of the cumulative reporting demography is shown in Figure 17. A cumulative overview of other COVID-19 drugs co-administered with the drug, or drug group, is available in Table .

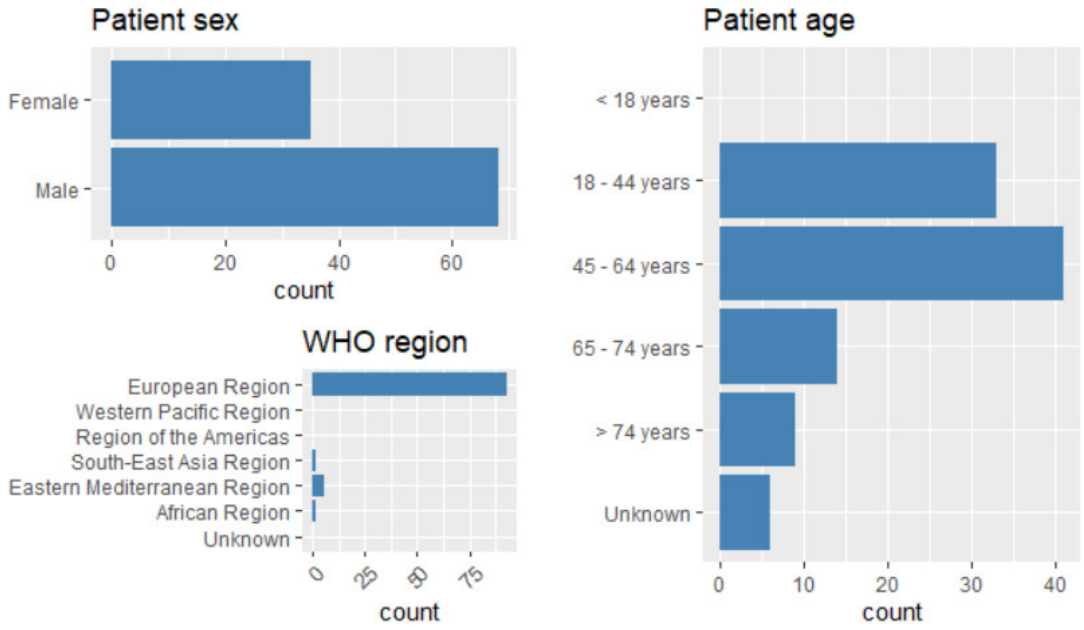

Figure 17. Demographics of VigiBase reports received cumulatively so far for Ivermectin as suspected or interacting drug.

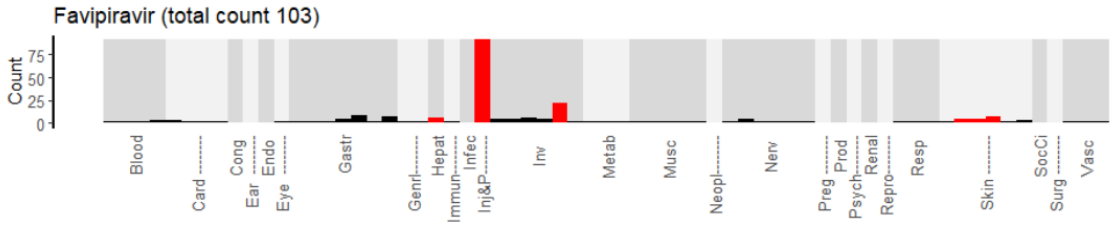

Figure 18. Cumulative report counts for Favipiravir in one bar for each preferred term, sorted by SOC (which is abbreviated as inTable). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

PT	Reports (Total)	%
Intentional product use issue	91 (103)	88.3
Liver function test increased	22 (103)	21.4
Nausea	8 (103)	7.8
Rash	7 (103)	6.8
Vomiting	7 (103)	6.8

PT	Reports	IC025_COVID
Intentional product use issue	91	2.7
Liver function test increased	22	2.0
Hepatotoxicity	6	1.4
Erythema	5	0.7
Rash	7	0.6

PT	Reports	IC025_VigiBase
Intentional product use issue	91	6.8
Liver function test increased	22	4.6
Electrocardiogram QT prolonged	11	3.2
Tachycardia	17	2.9
Hepatotoxicity	6	2.1

Figure 19. Favipiravir. Left subtable: Top 5 reported Preferred Terms (PT). Reports (Total) shows the cumulative number of reports in the COVID-19-dataset with both the drug and PT and the total count with drug respectively. Middle subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on COVID-19-reports. Reports-column shows the cumulative number of reports with the drug and PT in the COVID-19-dataset. Right subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on VigiBase (ie not limited to use in COVID-19). Reports-column shows the cumulative number of reports with the drug and PT in VigiBase. An IC025-value above 0 indicates that the observed value

is disproportionately high compared to the expected count. Ties might result in more than 5 PTs.

Favipiravir is a relatively new antiviral first marketed in 2014 in Japan and is indicated for the treatment of influenza A, B, C. After intracellular phosphorylation, its active metabolite, favipiravir ribosyl triphosphate, inhibits viral RNA-dependent RNA polymerase.[16] Currently, it has found off-label application in the treatment of COVID-19.

Regardless of reporting period, reports in VigiBase have primarily concerned the MedDRA SOCs: injury, poisoning and procedural complications, investigations, gastrointestinal disorders, skin and subcutaneous tissue disorders. The most reported MedDRA PTs have been: intentional product use issue, liver function test increased, nausea, rash, vomiting, electrocardiogram QT prolonged, hepatotoxicity, alanine aminotransferase increased, erythema, pruritus. As shown in **Error! Reference source not found.** (mid pane), since the beginning of the UMC COVID-19 monitoring some of these terms have been highlighted by disproportionality analyses with an $IC_{025} > 0$. Intentional product use issue had the highest disproportionality and upon manual review all reports were found to come from one country in the Eastern Mediterranean Region. Inspection of the corresponding MedDRA LLTs revealed that all reports included "Intentional use for unlabeled indication", which may suggest the reporters meant to indicate the off-label use of favipiravir. Regarding liver adverse events, elevations of aspartate aminotransferase and alanine aminotransferase have been known to occur in humans and animals without alterations of hepatic parenchyma, though this adverse effect was a concern of the Japanese regulatory agency at the time of approval.[16] The six reports including the term 'hepatotoxicity' all came from a country in the Eastern Mediterranean Region and all included time to onset information, which ranged from 2 - 9 days (in one report the administration followed onset of events). Almost all of these reports included co-suspected medicinal products known to affect the liver, such as azithromycin, hydroxychloroquine or oseltamivir, with times to onset comparable to those of favipiravir. In only one report was favipiravir the only suspected medicinal product. However, the term 'hepatotoxicity' lacks specificity. Given the lack of available approved product information, as well as possible confounding by hepatic complications from COVID-19 infection, additional data may be necessary for further assessments of various phenotypes of liver damage.

Of the 22 new reports delivered to VigiBase during this reporting period eight included MedDRA PTs that had never been reported before. These PTs were: neutropenia, tachycardia, abdominal pain upper, constipation, hyperuricaemia, hyponatraemia, loss of consciousness. Tachycardia is further highlighted by disproportionate reporting when considering the entire database as reference group and is possibly related to the known QT-prolonging effects of favipiravir. Decreases in neutrophil counts have been observed in one patient treated with favipiravir in a pooled analysis of phase III clinical trials (Study 312 and Study JP313).[16] The report in VigiBase suggests that the suspected neutropenic episode occurred on the first of three days of treatment and abated after eight upon discontinuation. The patient was not taking any medicinal product known to induce neutropenia. As concerns hyperuricaemia, this adverse event was highlighted in clinical trials.[16] The only report of loss of consciousness occurred in a patient in her fifties and the event manifested after one day of treatment; other than the serious nature of the report, no further information is available. Hyponatraemia was reported in a patient in their seventies (unknown sex) who was treated with hydroxychloroquine, dexamethasone, enoxaparin and pantoprazole, but no additional data are available. Finally, the remaining adverse events (constipation, upper abdominal pain) were non-serious and resolved; again, the main limiting factor is the lack of medical history and clinical evolution of the symptoms.

Non-Solidarity drugs shared more than 100 times into VigiBase

Hydroxychloroquine

There were 128 new reports for hydroxychloroquine during this reviewing period, adding up to a cumulative total of 2528 reports. The new reports included 56 men, 43 women and 29 with unknown sex. The new reports originated from the European Region (N=93), Region of the Americas (N=15), Eastern Mediterranean Region (N=11), Western Pacific Region (N=7) and South-East Asia Region (N=2). In the new reports the median age was 58 years. For the new reports hydroxychloroquine was the single suspected drug in 48 reports. Related cumulative counts are found in table Table B and an overview of the cumulative reporting demography is shown Figure 20. A cumulative overview of other COVID19 drugs co-administered with the drug, or drug group, is available in table Table .

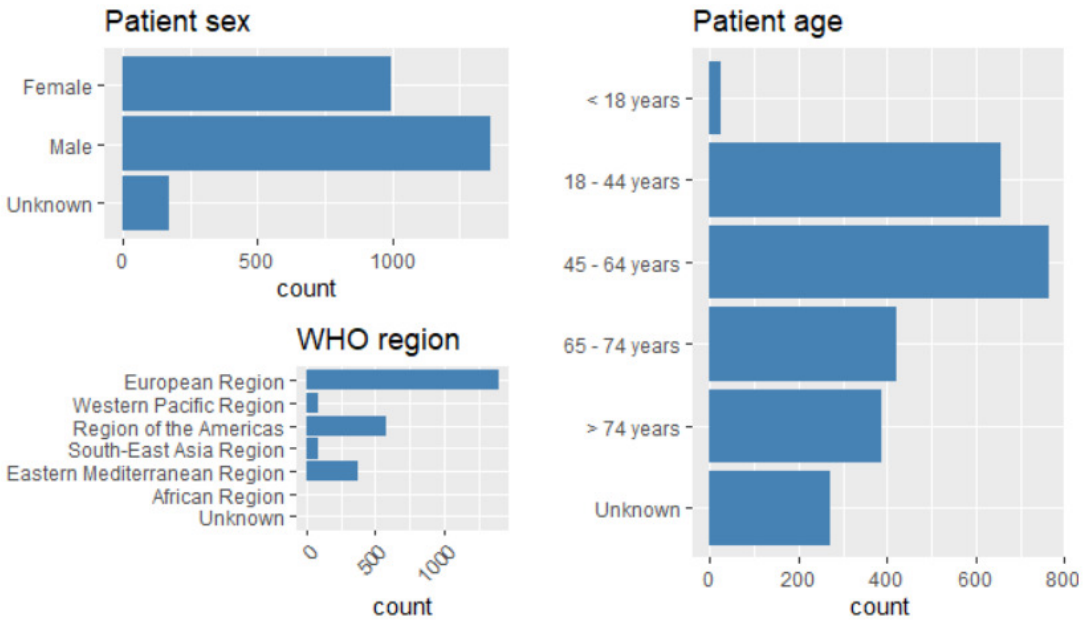

Figure 20. Demography of VigiBase reports received cumulatively so far on hydroxychloroquine as suspected or interacting drug.

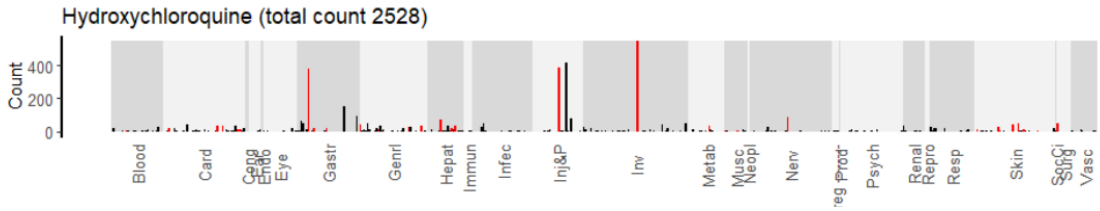

Figure 21. Cumulative report counts for hydroxychloroquine in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

PT	Reports (Total)	%
Electrocardiogram QT prolonged	547 (2528)	21.6
Off label use	417 (2528)	16.5
Intentional product use issue	384 (2528)	15.2
Diarrhoea	381 (2528)	15.1
Nausea	151 (2528)	6.0

PT	Reports	IC025_COVID
Electrocardiogram QT prolonged	547	1.0
Hypoglycaemia	35	0.9
Pre-existing condition improved	31	0.9
Long QT syndrome	33	0.8
COVID-19 treatment	49	0.7
Hepatitis	70	0.7

PT	Reports	IC025_VigiBase
Maculopathy	264	6.6
COVID-19 treatment	49	6.0
Retinopathy	264	5.8
Electrocardiogram QT prolonged	768	4.4
Acute generalised exanthematous pustulosis	157	4.0
Long QT syndrome	45	4.0

Figure 22 Hydroxychloroquine. Left subtable: Top 5 reported Preferred Terms (PT). Reports (Total) shows the cumulative number of reports in the COVID-19-dataset with both the drug and PT and the total count with drug respectively. Middle subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on COVID-19-reports. Reports-column shows the cumulative number of reports with the drug and PT in the COVID-19-dataset. Right subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on VigiBase (ie not limited to use in COVID-19). Reports-column shows the cumulative number of reports with the drug and PT in VigiBase. An IC025-value above 0 indicates that the observed value is disproportionately high compared to the expected count. Ties might result in more than 5 PTs.

Chloroquine

There were two new reports for chloroquine during this reviewing period, adding up to a cumulative total of 434 reports. For privacy reasons, we do not provide further details on the two new cases. Related cumulative counts are found in Table B and an overview of the cumulative reporting demography is shown in Figure 23. A cumulative overview of other COVID-19 drugs co-administered with the drug, or drug group, is available in table Table .

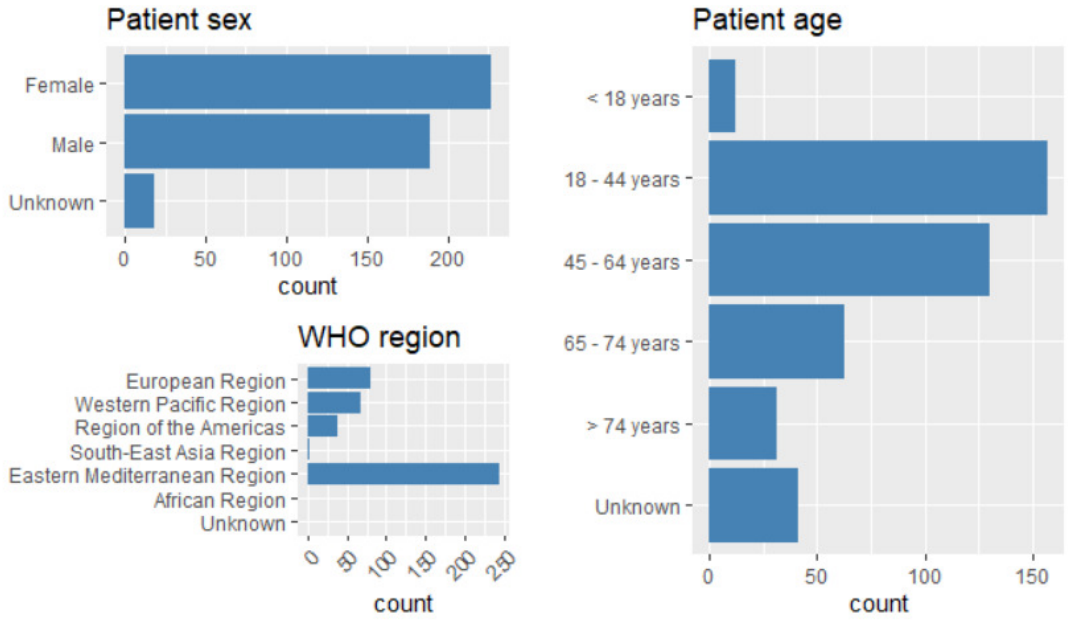

Figure 23. Demographics of VigiBase reports received cumulatively so far for chloroquine as suspected or interacting drug.

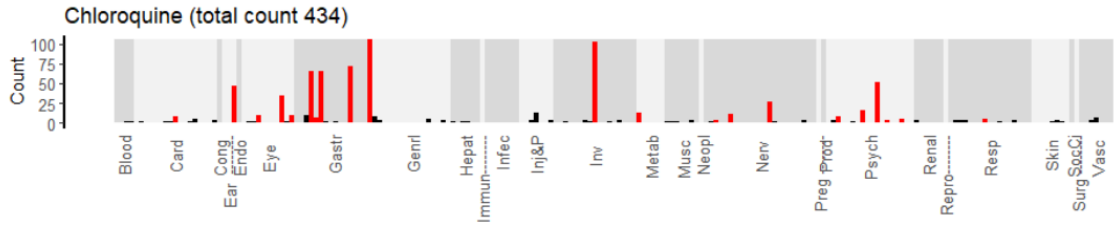

Figure 24. Cumulative report counts for chloroquine in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

PT	Reports (Total)	%
Vomiting	105 (434)	24.2
Electrocardiogram QT prolonged	102 (434)	23.5
Nausea	71 (434)	16.4
Abdominal pain upper	66 (434)	15.2
Diarrhoea	66 (434)	15.2

PT	Reports	IC025_COVID
Vertigo	47	3.1
Insomnia	52	3.0
Vision blurred	35	2.7
Vomiting	105	2.3
Abdominal pain upper	66	2.1
Hallucination	16	2.1

PT	Reports	IC025_VigiBase
Haemolytic anaemia	352	6.1
Electrocardiogram QT prolonged	140	3.9
Balance disorder	303	3.7
Decreased appetite	669	3.1
Abdominal pain upper	486	3.0

Figure 25.

Chloroquine. Left subtable: Top 5 reported Preferred Terms (PT). Reports (Total) shows the cumulative number of reports in the COVID-19-dataset with both the drug and PT and the total count with drug respectively. Middle subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on COVID-19-reports. Reports-column shows the

cumulative number of reports with the drug and PT in the COVID-19-dataset. Right subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on VigiBase (ie not limited to use in COVID-19). Reports-column shows the cumulative number of reports with the drug and PT in VigiBase. An IC025-value above 0 indicates that the observed value is disproportionately high compared to the expected count. Ties might result in more than 5 PTs.

Azithromycin

There were 82 new reports for azithromycin during this reviewing period, adding up to a cumulative total of 1528 reports. The new reports included 40 men, 38 women and 4 with unknown sex. The new reports originated from the region of the Americas (N=45), Eastern Mediterranean Region (N=17), European Region (N=17) and South-East Asia Region (N=3). In the new reports the median age was 45 years. For the new reports, azithromycin was the single suspected drug in 21 reports. Related cumulative counts are found in Table B and an overview of the cumulative reporting demography is shown in Figure 26. A cumulative overview of other COVID19 drugs co-administered with the drug, or drug group, is available in Table .

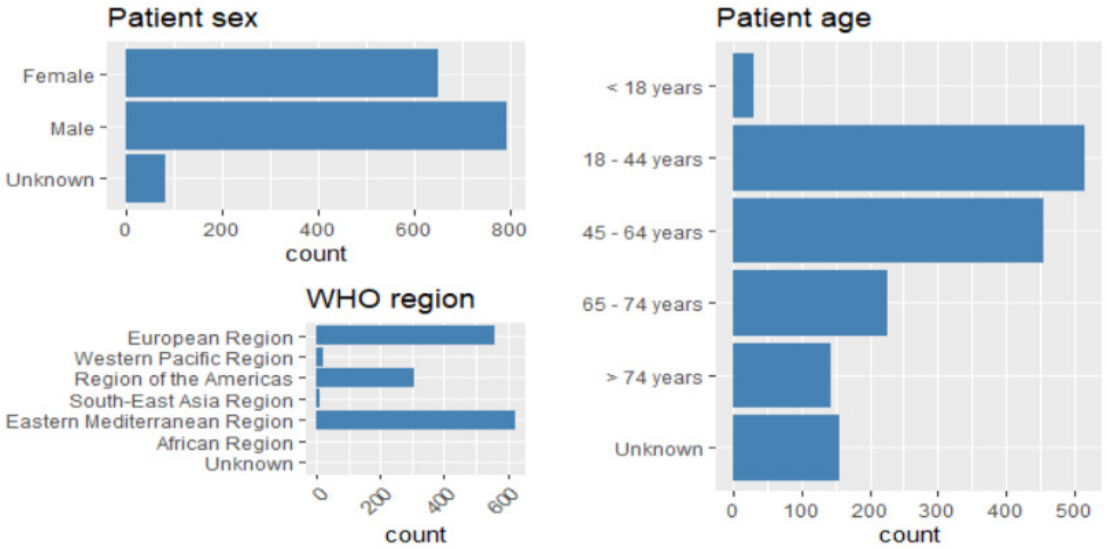

Figure 26. Demography of VigiBase reports received cumulatively so far on azithromycin as suspected or interacting drug.

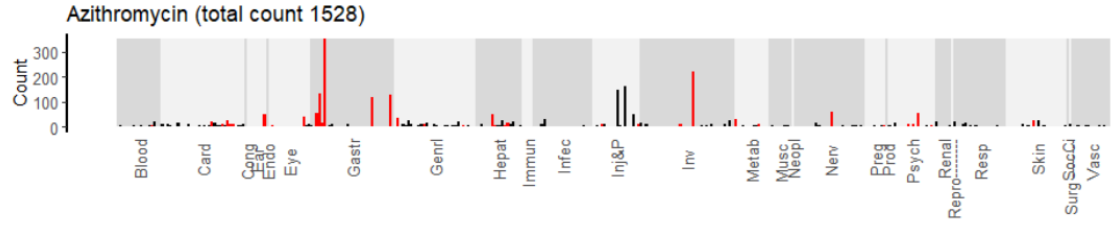

Figure 27. Cumulative report counts for azithromycin in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

PT	Reports (Total)	%
Diarrhoea	353 (1528)	23.1
Electrocardiogram QT prolonged	220 (1528)	14.4
Off label use	162 (1528)	10.6
Intentional product use issue	147 (1528)	9.6
Abdominal pain upper	134 (1528)	8.8

PT	Reports	IC025_COVID
Abdominal pain upper	134	1.5
Vertigo	51	1.5
Insomnia	56	1.4
Vision blurred	41	1.3
Diarrhoea	353	1.0

PT	Reports	IC025_VigiBase
COVID-19 treatment	12	3.3
Long QT syndrome	46	3.3
Electrocardiogram QT prolonged	648	3.2
Anosmia	309	3.1
Ear disorder	127	2.9
Torsade de pointes	159	2.9

Figure 28. Azithromycin. Left subtable: Top 5 reported Preferred Terms (PT). Reports (Total) shows the cumulative number of reports in the COVID-19-dataset with both the drug and PT and the total count with drug respectively. Middle subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on COVID-19-reports. Reports-column shows the cumulative number of reports with the drug and PT in the COVID-19-dataset. Right subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on VigiBase (ie not limited to use in COVID-19). Reports-column shows the cumulative number of reports with the drug and PT in VigiBase. An IC025-value above 0 indicates that the observed value is disproportionately high compared to the expected count. Ties might result in more than 5 PTs.

Lopinavir;ritonavir

There were 69 new reports for lopinavir;ritonavir during this reviewing period, adding up to a cumulative total of 872 reports. The new reports included 20 men, 15 women and 34 with unknown sex. The new reports originated from the European Region (N=66), Eastern Mediterranean Region (N=2) and Western Pacific Region (N=1). In the new reports the median age was 63 years. For the new reports lopinavir;ritonavir was the single suspected drug in 17 reports. Related cumulative counts are found in Table B and an overview of the cumulative reporting demography is shown in Figure 29. A cumulative overview of other COVID-19 drugs co-administered with the drug, or drug group, is available in Table .

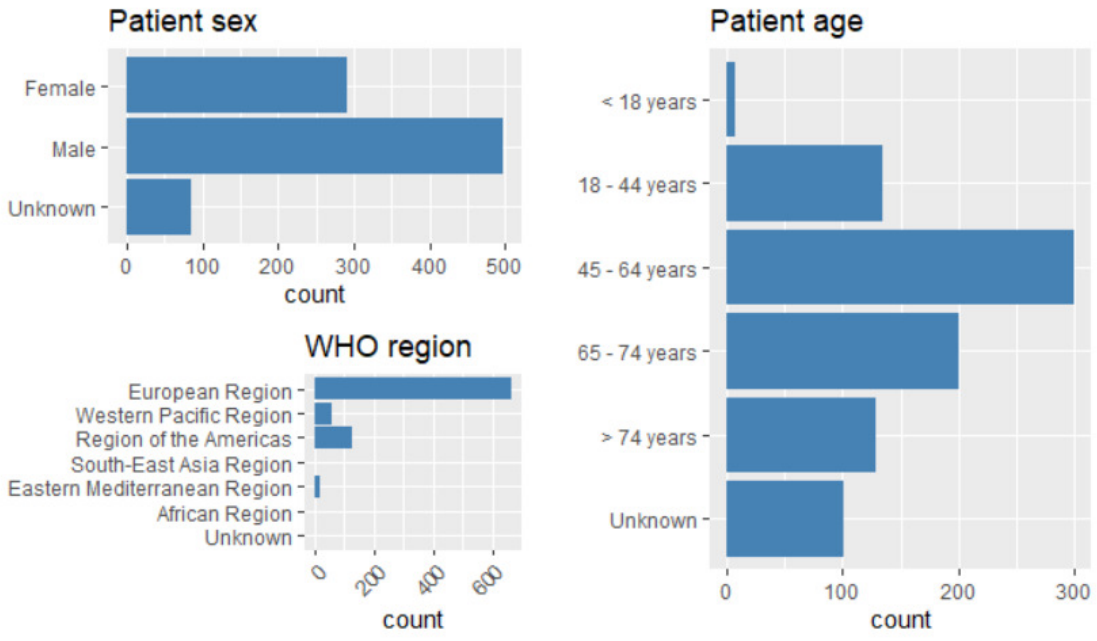

Figure 29. Demographics of VigiBase reports received cumulatively so far for lopinavir;ritonavir as suspected or interacting drug.

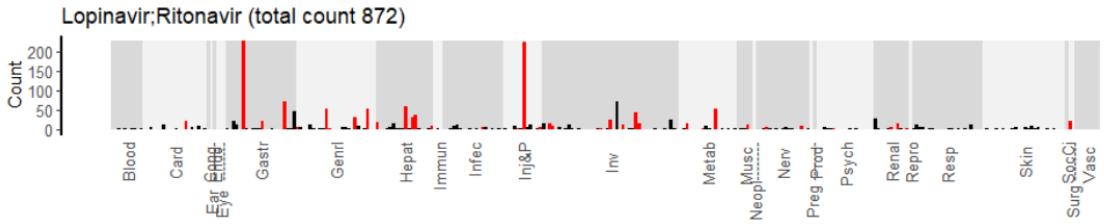

Figure 30. Cumulative report counts for lopinavir;ritonavir in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

PT	Reports (Total)	%
Diarrhoea	228 (872)	26.1
Off label use	224 (872)	25.7
Nausea	71 (872)	8.1
Electrocardiogram QT prolonged	70 (872)	8.0
Hepatocellular injury	59 (872)	6.8

PT	Reports	IC025_COVID
Hypertriglyceridaemia	52	2.4
Pre-existing condition improved	31	2.3
Therapeutic response unexpected	53	2.3
Drug level increased	26	2.0
Immunosuppressant drug level increased	14	1.9

PT	Reports	IC025_VigiBase
Hypertriglyceridaemia	304	6.0
COVID-19 treatment	23	4.8
Hypercholesterolaemia	137	4.1
Anticoagulation drug level increased	16	4.0
Live birth	42	3.9

Figure 31. Lopinavir;Ritonavir. Left subtable: Top 5 reported Preferred Terms (PT). Reports (Total) shows the cumulative number of reports in the COVID-19-dataset with both the drug and PT and the total count with drug respectively. Middle subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on COVID-19-reports. Reports-column shows the cumulative number of reports with the drug and PT in the COVID-19-dataset. Right subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on VigiBase (ie not limited to use in COVID-19). Reports-column shows the cumulative number of reports with the drug and PT in VigiBase. An IC025-value above 0 indicates that the observed value is disproportionately high compared to the expected count. Ties might result in more than 5 PTs.

Tocilizumab

There were 49 new reports for tocilizumab during this reviewing period, adding up to a cumulative total of 596 reports. The new reports included 21 men, six women and 22 with unknown sex. The new reports originated from the South-East Asia Region (N=26), European Region (N=12), Western Pacific Region (N=9) and African Region (N=2). In the new reports the median age was 60 years. For the new reports, tocilizumab was the single suspected drug in 42 reports. Related cumulative counts are found in Table B and an overview of the cumulative reporting demography is shown in Figure 32 A cumulative overview of other COVID19 drugs co-administered with the drug, or drug group, is available in Table .

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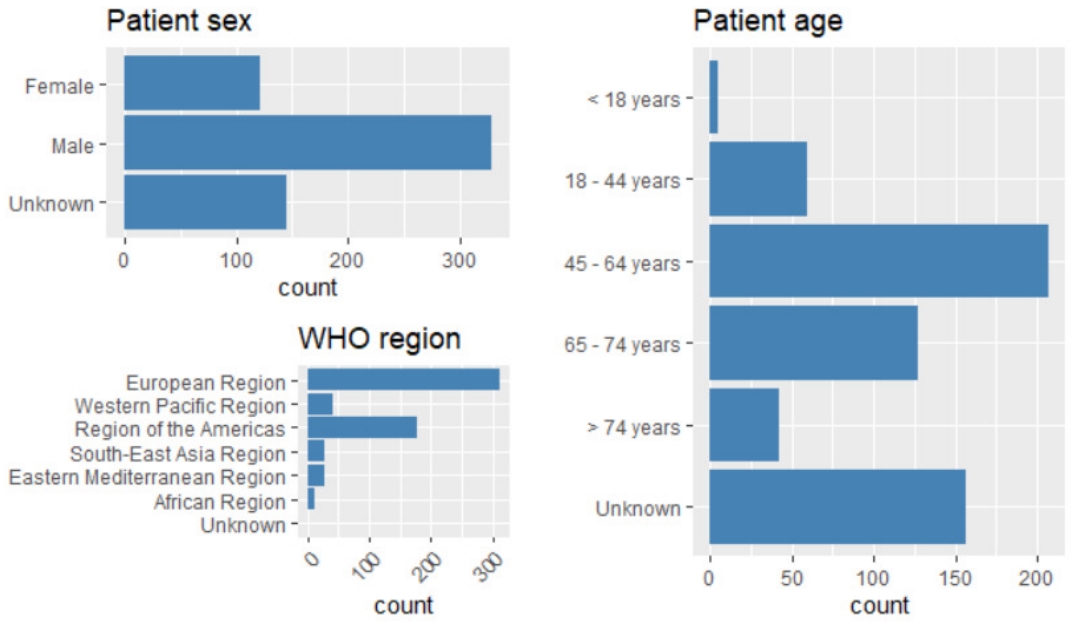

Figure 32. Demographics of VigiBase reports received cumulatively so far for tocilizumab as suspected or interacting drug.

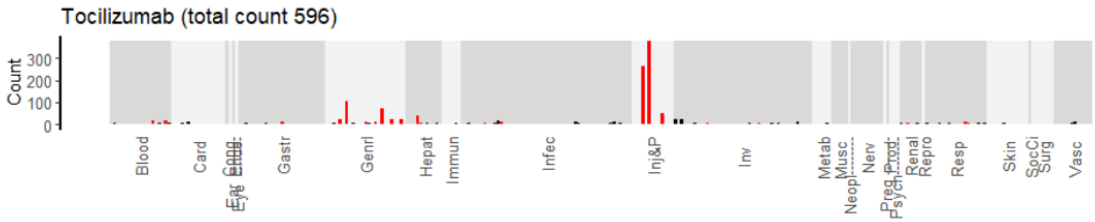

Figure 33. Cumulative report counts for tocilizumab in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

PT	Reports (Total)	%
Off label use	380 (596)	63.8
Intentional product use issue	264 (596)	44.3
Death	104 (596)	17.4
No adverse event	72 (596)	12.1
Product use in unapproved indication	51 (596)	8.6

PT	Reports	IC025_COVID
Hypofibrinogenaemia	15	2.3
Pre-existing condition improved	23	2.3
No adverse event	72	2.2
Death	104	1.9
Intentional product use issue	264	1.9
Off label use	380	1.9

PT	Reports	IC025_VigiBase
Diverticular perforation	126	5.0
Rheumatoid arthritis	3646	5.0
Hypofibrinogenaemia	44	4.9
Gastrointestinal perforation	136	4.2
Treatment failure	1125	4.2

Figure 34. Tocilizumab. Left subtable: Top 5 reported Preferred Terms (PT). Reports (Total) shows the cumulative number of reports in the COVID-19-dataset with both the drug and PT and the total count with drug respectively. Middle subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on COVID-19-reports. Reports-column shows the

cumulative number of reports with the drug and PT in the COVID-19-dataset. Right subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on VigiBase (ie not limited to use in COVID-19). Reports-column shows the cumulative number of reports with the drug and PT in VigiBase. An IC025-value above 0 indicates that the observed value is disproportionately high compared to the expected count. Ties might result in more than 5 PTs.

Oseltamivir

There were three new reports for oseltamivir during this reviewing period, adding up to a cumulative total of 178 reports. For privacy reasons, we do not provide further details on the new reports. Related cumulative counts are found in table C and an overview of the cumulative reporting demography is shown in Figure 35 A cumulative overview of other COVID19 drugs co-administered with the drug, or drug group, is available in Table .

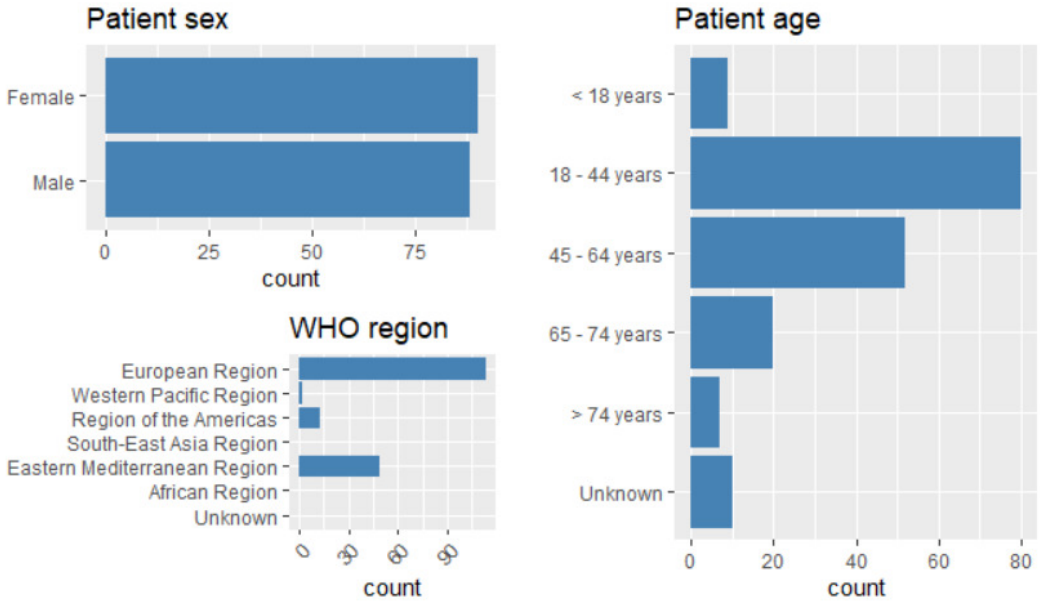

Figure 35. Demographics of VigiBase reports received cumulatively so far for oseltamivir as suspected or interacting drug.

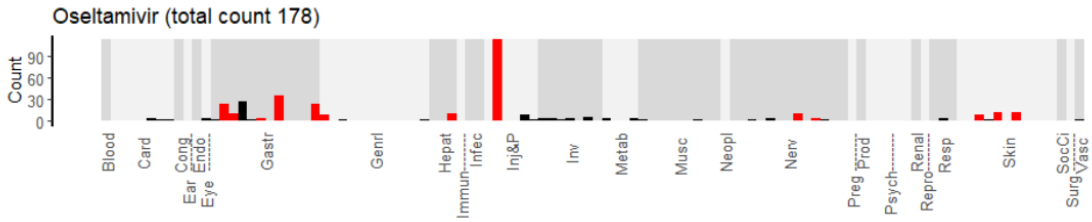

Figure 36. Cumulative report counts for oseltamivir in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

PT	Reports (Total)	%
Intentional product use issue	113 (178)	63.5
Nausea	35 (178)	19.7
Diarrhoea	27 (178)	15.2
Vomiting	24 (178)	13.5
Abdominal pain	23 (178)	12.9

PT	Reports	IC025_COVID
Intentional product use issue	113	2.3
Hepatotoxicity	11	2.1
Abdominal pain	23	1.8
Pruritus	12	1.6
Nausea	35	1.3

PT	Reports	IC025_VigiBase
Pathogen resistance	98	4.8
Hallucination	768	3.4
Vomiting	3409	2.3
Intentional product use issue	128	2.1
Anosmia	46	1.8

Figure 37. Oseltamivir. Left subtable: Top 5 reported Preferred Terms (PT). Reports (Total) shows the cumulative number of reports in the COVID-19-dataset with both the drug and PT and the total count with drug respectively. Middle subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on COVID-19-reports. Reports-column shows the cumulative number of reports with the drug and PT in the COVID-19-dataset. Right subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on VigiBase (ie not limited to use in COVID-19). Reports-column shows the cumulative number of reports with the drug and PT in VigiBase. An IC025-value above 0 indicates that the observed value is disproportionately high compared to the expected count. Ties might result in more than 5 PTs

Sarilumab

There was one new report for sarilumab during this reviewing period, adding up to a cumulative total of 159 reports. For privacy reasons, we do not provide further details on this one new report.case series. Related cumulative counts are found in table C and an overview of the cumulative reporting demography is shown in Figure 38. A cumulative overview of other COVID19 drugs co-administered with the drug, or drug group, is available in Table .

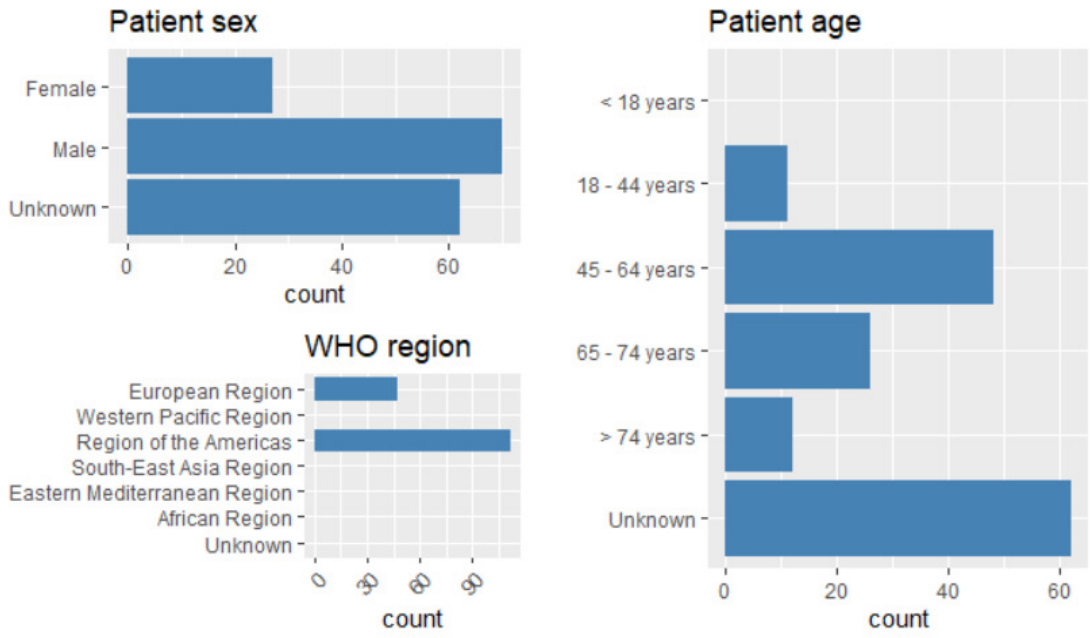

Figure 38 Demographics of VigiBase reports received cumulatively so far for sarilumab as suspected or interacting drug.

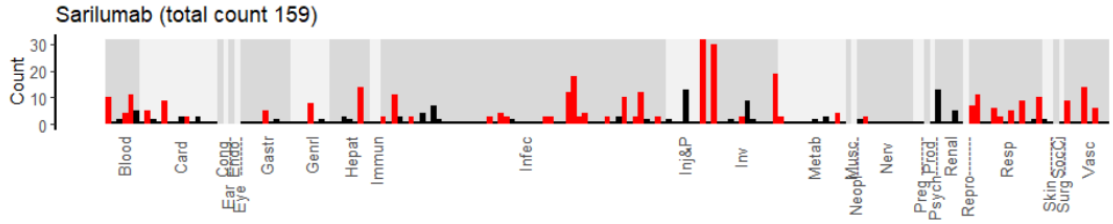

Figure 39. Cumulative report counts for sarilumab in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

PT	Reports (Total)	%
Alanine aminotransferase increased	32 (159)	20.1
Aspartate aminotransferase increased	30 (159)	18.9
Transaminases increased	19 (159)	11.9
Pneumonia bacterial	18 (159)	11.3
Hepatocellular injury	14 (159)	8.8
Hypotension	14 (159)	8.8

PT	Reports	IC025_COVID
Pneumonia bacterial	18	3.2
Staphylococcal infection	12	2.9
Bacteraemia	11	2.7
Deep vein thrombosis	9	2.5
Neutropenia	11	2.0

PT	Reports	IC025_VigiBase
Pneumonia bacterial	19	3.4
COVID-19	10	2.4
Neutropenia	161	2.3
Bacteraemia	13	2.2
Transaminases increased	34	2.1

Figure 40. Sarilumab. Left subtable: Top 5 reported Preferred Terms (PT). Reports (Total) shows the cumulative number of reports in the COVID-19-dataset with both the drug and PT and the total count with drug respectively. Middle subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on COVID-19-reports. Reports-column shows the cumulative number of reports with the drug and PT in the COVID-19-dataset. Right subtable: Top 5 PTs sorting by IC025 when the observed and expected count is based on VigiBase (ie not limited to use in COVID-19). Reports-column shows the cumulative number of reports with the drug and PT in VigiBase. An IC025-value above 0 indicates that the observed value is disproportionately high compared to the expected count. Ties might result in more than 5 PTs.

Drugs for use in COVID-19 reported less than 100 times into VigiBase

Drugs identified as being used in a COVID-19 indication and reported less than 100 times into VigiBase are presented as “other” Table C, D.

Disclaimer

Data in the reports are not complete and only a subset of the reports in the analysis unfortunately contained narratives precluding quality causality assessment. 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 automated deduplication method was used. Any signals detected from the monitoring will be communicated separately. Details of the methodology including the disproportionality analyses are available upon request.

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Appendix

Table A. Number of reports (summary)

Drug group	N_old	N_new	N_total
Azithromycin	1446	82	1528
Chloroquine	432	2	434
Hydroxychloroquine	2400	128	2528
Lopinavir;Ritonavir	803	69	872
Remdesivir	1975	43	2018
Tocilizumab	547	49	596
Heparin group substances	195	11	206
Oseltamivir	175	3	178
Sarilumab	158	1	159
Glucocorticoids group	217	34	251
Ivermectin	65	66	131
Favipiravir	81	22	103
Other drugs	496	37	533
Unique reports	6701	391	7092

Table A. N_old display reports described in previous reports, which included reports received to VigiBase no later than the 17th of August. N_new includes reports received to VigiBase no later than the 6th of September. Other drugs are selected from medical expertise from the set of corona virus indicated drugs reported to VigiBase, see Table 3. Counts include suspected or interacting drugs. As one report may contain several drugs, rows are not mutually exclusive.

Table B. Reporting numbers per drug, sex, age and region (Solidarity trial)

		Azithromycin		Chloroquine		Hydroxychloroquine		Lopinavir;Ritonavir		Remdesivir	
		N	%	N	%	N	%	N	%	N	%
Report characteristics											
	Total N	1528	100	434	100	2528	100	872	100	2018	100
	Single Susp.	208	13.6	163	37.6	1004	39.7	311	35.7	1930	95.6
	Serious	646	42.3	136	31.3	1288	50.9	408	46.8	1545	76.6
	Fatal	73	4.8	12	2.8	148	5.9	52	6	439	21.8
Sex											
	Female	652	42.7	227	52.3	994	39.3	291	33.4	743	36.8
	Male	794	52	189	43.5	1365	54	497	57	1251	62
	Unknown	82	5.4	18	4.1	169	6.7	84	9.6	24	1.2
Age											
	Median (Q1-Q3)	50 (35-65)		50 (33-64)		57 (41-70)		61 (49-71)		61 (48-72)	
	< 18 years	29	1.9	12	2.8	27	1.1	7	0.8	35	1.7
	18 - 44 years	516	33.8	157	36.2	655	25.9	135	15.5	352	17.4
	45 - 64 years	456	29.8	130	30	765	30.3	300	34.4	698	34.6
	65 - 74 years	227	14.9	63	14.5	422	16.7	201	23.1	439	21.8
	> 74 years	144	9.4	31	7.1	388	15.3	128	14.7	391	19.4
	Unknown	156	10.2	41	9.4	271	10.7	101	11.6	103	5.1
WHO region											
	African Region	2	0.1	0	0	2	0.1	0	0	2	0.1
	Eastern Mediterranean Region	625	40.9	245	56.5	369	14.6	20	2.3	0	0
	European Region	560	36.6	80	18.4	1402	55.5	667	76.5	240	11.9
	Region of the Americas	308	20.2	38	8.8	583	23.1	127	14.6	1754	86.9
	South-East Asia Region	12	0.8	3	0.7	85	3.4	0	0	6	0.3
	Western Pacific Region	21	1.4	68	15.7	87	3.4	58	6.7	16	0.8
	Unknown	0	0	0	0	0	0	0	0	0	0

Table B. Reporting numbers from drugs included in the solidarity trial. Single susp. = Drug was reported as single suspected or interacting drug, Q1-Q3 = First to third quartile. Counts include suspected and interacting drugs. As one report may contain several drugs, columns are not mutually exclusive.

Last updated: September 22, 2020

Table C. Reporting numbers per drug, sex, age and region on non-Solidarity drugs

		Tocilizumab		Heparin group substances		Oseltamivir		Sarilumab		Glucocorticoids group		Ivermectin		Favipiravir		Other Drugs		Unique reports	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Report characteristics																			
	Total N	596	100	206	100	178	100	159	100	251	100	131	100	103	100	533	100	7092	100
	Single Susp.	413	69.3	56	27.2	33	18.5	139	87.4	64	25.5	77	58.8	51	49.5	314	58.9	4763	67.2
	Serious	446	74.8	162	78.6	52	29.2	151	95	177	70.5	7	5.3	32	31.1	324	60.8	4045	57
	Fatal	203	34.1	26	12.6	5	2.8	50	31.4	34	13.5	2	1.5	3	2.9	139	26.1	979	13.8
Sex																			
	Female	122	20.5	67	32.5	90	50.6	27	17	90	35.9	65	49.6	35	34	190	35.6	2665	37.6
	Male	329	55.2	132	64.1	88	49.4	70	44	143	57	64	48.9	68	66	298	55.9	3975	56
	Unknown	145	24.3	7	3.4			62	39	18	7.2	2	1.5			45	8.4	452	6.4
Age																			
	Median (Q1-Q3)	61 (50-68)		63 (49-71)		42 (32-57)		60 (50-69)		56 (40-66)		43 (33-56)		53 (39-63)		63 (51-73)		59 (44-70)	
	< 18 years	5	0.8	2	1	9	5.1	0	0	5	2	3	2.3	0	0	8	1.5	112	1.6
	18 - 44 years	59	9.9	33	16	80	44.9	11	6.9	61	24.3	64	48.9	33	32	58	10.9	1550	21.9
	45 - 64 years	207	34.7	69	33.5	52	29.2	48	30.2	96	38.2	44	33.6	41	39.8	183	34.3	2328	32.8
	65 - 74 years	127	21.3	56	27.2	20	11.2	26	16.4	51	20.3	13	9.9	14	13.6	121	22.7	1329	18.7
	> 74 years	42	7	28	13.6	7	3.9	12	7.5	15	6	4	3.1	9	8.7	88	16.5	1037	14.6
	Unknown	156	26.2	18	8.7	10	5.6	62	39	23	9.2	3	2.3	6	5.8	75	14.1	736	10.4
WHO region																			
	African Region	12	2	0	0	0	0	0	0	1	0.4	0	0	2	1.9	1	0.2	17	0.2
	Eastern Mediterranean Region	27	4.5	19	9.2	49	27.5	0	0	16	6.4	0	0	6	5.8	19	3.6	816	11.5
	European Region	313	52.5	118	57.3	114	64	47	29.6	92	36.7	2	1.5	93	90.3	286	53.7	2668	37.6
	Region of the Americas	177	29.7	63	30.6	13	7.3	112	70.4	140	55.8	129	98.5	0	0	133	25	3118	44
	South-East Asia Region	26	4.4	5	2.4	0	0	0	0	0	0	0	0	2	1.9	10	1.9	144	2
	Western Pacific Region	41	6.9	1	0.5	2	1.1	0	0	2	0.8	0	0	0	0	84	15.8	329	4.6
	Unknown	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table C. Reporting numbers from other drugs selected from medical expertise from the set of corona virus indicated drugs reported to VigiBase. The totals column represents all drugs included in this report, including those listed in solidarity drugs table. Single susp. = Drug was reported as single suspected or interacting drug, Q1-Q3 = First to third quartile. Counts include suspected and interacting drugs. As one report may contain several drugs, columns are not mutually exclusive.

Table D. Drugs reported with a COVID-19 indication, less than 100 times into VigiBase

Drug	N	%
Unique reports	533	100
Eculizumab	46	8.6
Ritonavir	46	8.6
Ruxolitinib	41	7.7
Anakinra	37	6.9
Plasma	32	6
Atazanavir	30	5.6
Darunavir	27	5.1
Hyperimmune plasma Covid-19	22	4.1
Baricitinib	21	3.9
Apixaban	20	3.8
Interferon beta-1b	19	3.6
Canakinumab	18	3.4
Rituximab	15	2.8
Epoprostenol	14	2.6
Lopinavir	13	2.4
Metamizole	13	2.4
Ribavirin	13	2.4
Ascorbic acid	12	2.3
Montelukast	12	2.3
Cobicistat;Darunavir	11	2.1
Immunoglobulin human normal	11	2.1
Zinc	11	2.1
Baloxavir marboxil	10	1.9
Alteplase	9	1.7
Colchicine	8	1.5
Colecalciferol	8	1.5
Itolizumab	8	1.5
Warfarin	8	1.5
Siltuximab	5	0.9

Table D. 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
Note that table D continues on the next page.

Aciclovir	4	0.8
Interferon beta	4	0.8
Interferon beta-1a	4	0.8
Investigational drug	4	0.8
Nitazoxanide	4	0.8
Valaciclovir	4	0.8
Apremilast	3	0.6
Interferon	3	0.6
Selinexor	3	0.6
Bromhexine	2	0.4
Ciclosporin	2	0.4
Cobicistat	2	0.4
Daclatasvir	2	0.4
Darunavir;Ritonavir	2	0.4
Infliximab	2	0.4

Table D continued. 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.

Table E. Co-medication frequencies

	Azithromycin	Chloroquine	Hydroxychloroquine	Lopinavir;Ritonavir	Remdesivir	Tocilizumab	Heparin group substances	Oseltamivir	Sarilumab	Glucocorticoids group	Favipiravir	Ivermectin
Total (S/I/C)	2256	461	2965	986	2036	765	1573	273	160	1066	131	154
Single suspected	849	183	1367	407	1943	556	1060	97	140	761	70	90
Azithromycin		274	1332	232	318	153	565	138	60	374	47	60
Chloroquine	274		9	33	4	15	44	6	2	14		1
Hydroxychloroquine	1332	9		517	82	231	593	220	80	308	79	22
Lopinavir;Ritonavir	232	33	517		21	94	186	18	1	92	3	13
Remdesivir	318	4	82	21		140	741	3	6	585	1	4
Tocilizumab	153	15	231	94	140		170	12	4	137	12	5
Heparin group substances	565	44	593	186	741	170		73	57	566	50	22
Oseltamivir	138	6	220	18	3	12	73			14	23	1
Sarilumab	60	2	80	1	6	4	57			47		1
Glucocorticoids group	374	14	308	92	585	137	566	14	47		8	24
Favipiravir	47		79	3	1	12	50	23		8		
Ivermectin	60	1	22	13	4	5	22	1	1	24		
Acalabrutinib	1				1		1					
Aciclovir	3		6	3	6	2	6			4		
Almitrine							1		1			
Alteplase	9		7		1	6	8	1	1	1		
Anakinra	20		22	2	7	8	10	1	4	22		
Apixaban	13	2	24	10	48	8	25	2	4	28		
Apremilast	2		2		1	1	3			1		
Ascorbic acid	156	15	120	15	147	29	190	22	8	135	19	2
Atazanavir			34	3			3	2		3		
Baloxavir marboxil								1				
Baricitinib	6		6	25	6	1	8			5		
Bromhexine	2	2	12		1	1	8	7		3		
Canakinumab			2		1		1			4		
Ciclosporin	1		7	2	2	1	1			5		
Cobicistat			2	1								
Cobicistat;Darunavir	10		21	10	1	5	7			3		1
Colchicine	7		15	3	6	5	11	1		10		
Colecalciferol	73	3	46	2	78	11	73	1	3	61	7	1
Darunavir	6	4	26	3	2	7	15			10	1	
Darunavir;Ritonavir			3									
Eculizumab	6		8	3	1	1	7			3		
Epoprostenol	17		5		31	11	30		2	22		
Ganciclovir	2			2		1		1		2		
Iloprost					1		2					
Immunoglobulin human normal	4		7	2	2	6	5		1	5		
Immunoglobulins nos			3	1		1	1	2				
Infliximab	1		1					1		1		
Interferon	2		4	1			1			1		
Interferon beta	4		4	5		1	1			3		
Interferon beta-1a			1	4			3					
Interferon beta-1b	16	2	30	30		6	10	2		7		
Investigational drug					1					1		
Lopinavir	5		18	1		2	5			4		
Maraviroc					2					2		
Metamizole	33	2	48	17	15	6	42	8		15	2	
Montelukast	12		3	3	24	2	19			19	1	
Nitazoxanide	5		1	5			1	2		6		1
Peginterferon alfa-2a	1		1								2	
Plasma	4	1	6		7	5	8		4	6		
Ribavirin	16		10	51	2	3	4	1	1	2		
Ritonavir	11		69	6	1	5	18	2		14	2	
Rituximab	4		6	1	1	8		1		11		
Ruxolitinib	5	1	17	8	2	4	18	1		11		1
Selinexor	2				5		5			2		
Siltuximab			1	1			1					
Tofacitinib										1		
Umifenovir				1				1				
Valaciclovir	1		3	1	3		6		1			
Warfarin	6		9	3	10	3	9	4	1	10		
Zinc	120	8	77	7	136	22	150	7	7	119	5	1
Other	1173	110	1403	535	1248	303	1395	159	122	896	91	43

Table E. 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.

Table F. Abbreviations used for SOCs

SOC_ABBREV	SOC
Blood	Blood and lymphatic system disorders
Card	Cardiac disorders
Cong	Congenital, familial and genetic disorders
Ear	Ear and labyrinth disorders
Endo	Endocrine disorders
Eye	Eye disorders
Gastr	Gastrointestinal disorders
Genrl	General disorders and administration site conditions
Hepat	Hepatobiliary disorders
Immun	Immune system disorders
Infec	Infections and infestations
Inj&P	Injury, poisoning and procedural complications
Inv	Investigations
Metab	Metabolism and nutrition disorders
Musc	Musculoskeletal and connective tissue disorders
Neopl	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Nerv	Nervous system disorders
Preg	Pregnancy, puerperium and perinatal conditions
Prod	Product issues
Psych	Psychiatric disorders
Renal	Renal and urinary disorders
Repro	Reproductive system and breast disorders
Resp	Respiratory, thoracic and mediastinal disorders
Skin	Skin and subcutaneous tissue disorders
SocCi	Social circumstances
Surg	Surgical and medical procedures
Vasc	Vascular disorders

Table F. Abbreviations used for SOCs displayed in the reaction overview bar charts.

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.