Identification of putative drugs against viral respiratory infections by the pharmacovigilance analysis tool OpenVigil 2

Ruwen Böhm[1*], Claudia Bulin[1], Vicki Waetzig[1], Ingolf Cascorbi[1], Hans-Joachim Klein[2], Thomas Herdegen[1]

[1] Institute of Experimental and Clinical Pharmacology, University Medical Center Schleswig-Holstein (UKSH), Kiel, Germany
[2] Department of Computer Science, Kiel University, Germany
[*] corresponding author: ruwen.boehm@pharmakologie.uni-kiel.de

Running head: OpenVigil identifies putative antivirals

Keywords:
pharmacovigilance, drug repurposing, drugs repositioning, influenza, coronavirus, COVID-19

Counts:
Title: 120/150 characters
Running head: 40/40 characters
Abstract: 158/250 words
Manuscript: 3077/4000 words
Figures: 5
Tables: 2

What is already known about this subject:

- There are several pharmacovigilance tools to scan for adverse events (AEs) associated with a drug.
- Disproportionality analyses of drugs in pharmacovigilance data focussing on drug-AE-combinations ***more*** frequently observed than expected reveal ***adverse drug reactions***.
- COVID-19 could possibly be treated or ameliorated by using drugs targeting peptidases crucial for viral entry, the viral RNA replicase and cytokines released in some patients.

What this study adds:

- OpenVigil 2 can be automated to reversely scan FDA pharmacovigilance data (FAERS) for drugs associated with an adverse event, catching both over- and underproportionality.
- Disproportionality analyses of diseases (coded as AE) in pharmacovigilance data focussing on AE-drug combinations ***less*** frequently observed than expected reveal ***candidate drugs***.
- Using our approach, at least 82 candidate drugs against viral respiratory diseases could be identified.
- Kinase inhibitors like erlotinib emerge as new threapeutical concept.
- (Hydroxy-)Chloroquine appears as a risk factor for viral respiratory diseases in our data.

Abstract

Aim: Pharmacovigilance data are primarily used to identify adverse drug reactions. However, scanning for associations of drugs and adverse events that occur less frequently than expected provides hypotheses for drug repurposing, i.e. a known drug could be therapeutically beneficial for a new indication like the coronavirus disease (COVID-19).

Methods: Drugs associated with viral respiratory tract infections and/or influenza were extracted from the U.S. FAERS pharmacovigilance data using OpenVigil2.1-MedDRA17, filtered for significant inverse associations ($p_{unadj}<0.05$), checked for plausibility, and categorised by their WHO Anatomical Therapeutic Chemical (ATC) classification code.

Results: ATC clustering of 82 candidate drugs revealed anti-diabetics, neuropharmacologic sigma-receptor agonists, peptidase inhibitors, kinase inhibitors and anti-androgens. Chloroquine appears as a statistically significant risk factor for viral diseases supporting actual knowledge.

Conclusion: OpenVigil 2 delivers new hypotheses for drug repurposing, theoretically for all indications. There is affirmative data for some of our results; the remaining proposed candidate drugs without already known antiviral mechanism of action should stimulate further exploration.

Introduction

The new coronavirus disease "COVID-19" prompts for pharmacologic treatments. Currently, drugs originally developed for *retroviridae* like HIV (lopinavir/ritonavir) and *filovidiridae* like ebola (remdesivir) are recommended[1]. Yet, there are more druggable targets[2]. Since conventional drug development pipelines are highly time-consuming, various *in silico* procedures are applied to accelerate the identification of potential candidate drugs[3].

Pharmacovigilance data consist of spontaneously gathered reports of adverse events (AEs). Since the late 1960es it is used to detect new adverse drug reactions (ADRs) of existing and of new medicinal products on the market by national drug regulating authorities. Answering a call for freely available pharmacovigilance analysis tools[4], several open-accessible web-based search engines are now available[5]. Our software OpenVigil 2 (openvigil.sf.net) is being used to detect ADRs by employing various statistical and computational designs and approaches, e.g. testing an *a-priori* defined study design or annotating results of pharmacovigilance queries with data from additional databases for a combined prediction model[6,7]. Conversely, the pharmacovigilance data can also be used to identify new therapeutic uses[8].

Data of viral respiratory infections resembling COVID-19 (e.g. respiratory tract infections or influenza) and their sequelae (e.g. elevated d-dimers or anosmia) are available within the FDA Adverse Event Reporting System (FAERS). AEs are coded using terms in the Medical Dictionary for Regulatory Activities (MedDRA) which is also integral part of the OpenVigil 2 software. We thus used OpenVigil2.1-MedDRA17 to scan FAERS data for inverse signals of AE high-level term (HLT) keywords related to the symptoms and pathogenesis of COVID-19 and similar viral diseases (i.e. RNA-viruses, Fig. 1) and their symptoms (i.e. respiratory manifestations) to detect already marketed drugs that could be repurposed for treatment of these viral infections. To our best knowledge, this pioneering drug discovery approach has not been applied to viral diseases before.

Methods

Signals

All pharmacovigilance calculations are done on a 2x2 contingency table of event and drug and measurements of disproportionality, e.g. the Reporting Odds Ratio (ROR) can be calculated (Fig. 2). If the 95%-confidence interval of the ROR does not cross the value 1, a statistically significant disproportionality, i.e. the deviation of observed and expected ratios, is assumed. Such a disproportionality is called a "signal". This can be indicative for an ADR. Each signal needs to be post-processed, e.g. checked for confounding and plausibility.

Inverse signals

The traditional signal concept, i.e. a drug and an AE are more frequently observed than expected, can also be turned around to focus on less frequently observed than expected combinations of drugs and AEs[8,9]. These inverse signals generate hypotheses for yet unknown new usages of drugs which are already available on the market, an approach called "drug repurposing" or "drug repositioning".

Cleaning of adverse events

Before analyzing pharmacovigilance data, entries to drugs and AEs need to be cleaned and semantically enriched. Concerning AEs, the FDA applies lowest-level terms (LLTs) of the Medical Dictionary for Regulatory Activities (MedDRA) for each condition reported. The MedDRA taxonomy offers hierarchies like high-level terms (HLTs) and other groupings, thus providing the power to cluster similar cases and analyze them together. MedDRA version 17 has been incorporated into OpenVigil 2 and searches can be performed on every level of the MedDRA hierarchy.

Cleaning of drugs and semantic enrichment

However, the data field containing the information on the drug used is not cleaned and may contain both names of medicinal products (here called "brandnames") and names of active substances ("drugnames"). OpenVigil 2 uses drugbank.ca and drugs@FDA to clean the data, associate each record with brandnames or drugnames and annotate WHO Anatomic Therapeutic Chemical (ATC) classification codes and molecular substructures where available. Reports are not imported if data of a single entry for drug usage cannot be unanimously resolved (e.g. non-parseable, unclear or contradictory). Approximately, 60% of all available FDA case reports could be completely imported in OpenVigil 2 under this condition. OpenVigil 2 is therefore a tool for complete case analysis; unlike the openFDA API (used by OpenVigilFDA) which provides available case analyses. In this openFDA database approx. 73% of reports were at best partially cleaned. Analyses in both tools will lead to different measurements of disproportionality (e.g. ROR), since it is unclear whether the approx. 35-40% of not fully understandable reports can be considered background or might contain cases with the drug to be analyzed. We consider complete case analysis thus superior for certain usages that require a low beta error, e.g. drug repurposing.

An installation of OpenVigil-2.1-MedDRA17 containing 6,719,410 case-reports from FDA FAERS data from 2004Q1 to 2019Q4 was used for data extraction. Compared to 11,171,211 cases in openFDA (accessed via OpenVigilFDA at 2019-12-14), we thus estimate a successful cleaning and import rate of 60.1%.

Choice of MedDRA terms for diseases caused by *coronaviridae* or similar viruses

Coronaviridae provoke Severe Acute Respiratory Syndrome (SARS) or Middle Eastern Respiratory Syndrome (MERS). COVID-19 caused by the current pandemic SARS-CoV-2 manifests with both an upper and sometimes a potentially deadly, highly inflammatory lower respiratory tract infection.

The family of *coronaviridae* belongs to the phylum of single-stranded plus-orientated RNA viruses (ss(+)RNA) (Fig. 1), like *flaviviridae* or *caliciviridae*. SARS-CoV-2 is often compared to influenza concerning the air-borne way of transmission and its mortality. However, Influenza A (family

orthomyxoviridae), belongs to the phylum of ss(-)RNA which also encompasses the ebola virus (*filovidiridae*).

Pharmacogivilance offers data of cases with viral infections, e.g. all the viral families mentioned above are available as AE in the OpenVigil 2 database. In addition, the respiratory manifestation of these viruses are also included in OpenVigil 2, e.g. coded as several types of respiratory tract infections.

The MedDRA version 17 preferred terms (PTs) "coronavirus test positive" (22 cases), "corona virus infection" (67 cases), "viral pneumonia" (620 cases), "fibrin D dimer increased" (848 cases), "severe acute respiratory syndrome" (34 cases), "middle east respiratory syndrome" (0 cases) and the high-level terms (HLTs) "olfactory nerve disorders" (5,046 cases), "astroviral infections" (4 cases), "caliciviral infections" (386 cases), "flaviviral infections" (801 cases), "parainfluenzae viral infections" (296 cases), "viral lower respiratory tract infections" (2,189 cases), "viral upper respiratory tract infections" (31049 cases) and "influenza viral infections" (27,988 cases) were identified as suitable query keywords. Due to the paucity of cases, only the latter three search terms were analyzed.

Search strategy

Two separate searches were performed: A first search focusing on influenza infections in order to find drugs suitable against general air-borne viral infections, and a second one, focusing on the respiratory inflammatory manifestations (HLT viral lower/upper respiratory tract infection (logically connected with "OR"), were done. Sequelae of COVID-19 like increased fibrin D-dimers or anosmia were not analyzed since our filtering criteria were not fullfilled.

Filtering confounders and clustering by ATC classification

Results were sorted for ascending upper bounds of the 95% confidence interval of the ROR. Only drug-AE combinations with values less than 1 and at least 30 reported cases were considered.

Rows referring to brandnames, each being a subset of the corresponding drugname, were removed. Drugs were categorised by their ATC classification code. At time of extraction it became evident that estrogen- and progesterone-hormones should be excluded due to confounding by the underlying condition (healthy women

of child bearing potential). Indeed, the signals were no longer present when the same extraction was done for case reports of patients 50 years or older.

Drugs which were considered confounded by the underlying disease or condition (i.e. hormonal contraceptives) or which were considered clinically unfeasible (i.e. cytotoxics) were removed.

The two resulting lists, each containing the 70 most statistically significant candidates, shared 58 candidates (71%); thus both lists were combined and the 82 candidate drugs were analyzed together.

Results

We used OpenVigil 2 to extract signals of drugs that were inversely associated with AE indicative for either (i) viral infections (using HLT "influenza viral infection") or (ii) respiratory manifestations (HLT "viral lower respiratory tract infection" OR "viral upper respiratory tract infection"). Confounders like contraception and unsuitable drugs like cytotoxics were removed and WHO Anatomic Therapeutic Chemical (ATC) classification codes were annotated for semantic enrichment.

All data (raw and post-processed) are available in the supplemental tables 1 to 4. As an example, the five most statistically significant candidate drugs against viral respiratory infections are shown in Tab. 1.

All 82 candidate drugs were categorised according to their ATC classification code. The resulting clusters are given in Tab. 2 and Fig. 3.

Mechanisms of established antiviral or immunomodulatory activities and their references are presented in Tab. 2 and Fig. 4.

Post-processing of selected candidate drugs

Anti-diabetics

The anti-diabetic drugs rosiglitazone, pioglitazone and metformin were detected as potentially beneficial with rosiglitazone having the strongest signal in the whole dataset (see Tab. 1 and supplemental tables 1 and 3). All three drugs have previously been shown to impair viral replication (Fig. 4)[10–13]. Metformin increases interferon production[14]. Glitazones might either act via their anti-diabetic target, the peroxisome proliferator-activated receptor gamma (PPARγ), regulating T-cell activity[15], or by inhibiting viral transfer using solute carriers (SLC)[16]. This was recently hypothesized by another *in silico* drug repurposing approach, analyzing the interplay between the coronavirus–host interactome and pharmacogenomic drug targets[17]. A similar proteome-interactome-study also identifies the AMP-kinase activator metformin as candidate, possibly because of its mitochondria-impairing action, which affects viral replication[18].

Inhalation is considered an appropriate route of administration to target the lower respiratory tract. Inhalative metformin has previously been tested for its inhalative application against cancer[19].

Neuro-psychiatrics, sigma-receptor and replicase

The signals for antipsychotics (Tab. 3), antihistaminergic (here: loratadine) and GABA-ergic drugs (here: zolpidem) have previously been hypothesized as potentially anti-inflammatory in a study on inflammatory bowel disease using a similar drug repurposing approach[9].

Yet another *in silico* drug repurposing study based on data of the SARS-CoV-2 proteome detects the antipsychotic haloperidol (ROR 0.2, see supplemental material) as a candidate drug. Haloperidol binds to sigma-receptors which might interfere with the viral protein NSP6, a part of the viral replicase[18]. Binding of sigma-receptors is a common property of antipsychotics and also opioids. The latter might explain the abundance of opioid drugs in our findings.

Of note, the sigma-receptor agonist (hydroxy-)chloroquine was not found to be beneficial, but a risk factor in our data (supplemental tables 1 and 2: ROR ~1.8 (95%-CI 1.1-3.0) for HLTs viral upper/lower respiratory tract infection and influenza; also see Fig. 2 for AE PT „Pneumonia viral“: ROR 2.5 (95%-CI 1.1-5.6)). Recently, the RECOVERY trial group announced that there were no beneficial effects of hdroxychloroquine concerning mortality or stay duration but a trend towards higher mortality (hazard ratio 1.11)[20]. However, it appears important to stratify patients according to the dosages received. This is not readily possible with these data sources.

The antipsychotic aripiprazol, which has a quinolone moiety, was recently identified as a putative anti-influenza drug using a structured-based approach, since it is supposed to interfere with the viral RNA polymerase[21]. The same might hold true for gyrase inhibiting antibiotics like levofloxacin and ciprofloxacin (proposed candidate drugs), which have a central quinolone-moiety. However, since the RNA replicase of *coronaviridae* is fundamentally different from all other viruses, it appears very unlikely that these inhibitors work with SARS-CoV-2[22].

The candidate drug valproic acid, which is known to inhibit the human histone deacetylase 2 (HDAC2), is proposed to interfere with the coronavirus non-structural protein 5 (NSP5), which is part of the coronavirus replicase[18].

We identified several antidepressants as putative candidate drugs. The selective serotonin reuptake inhibitor (SSRI)-type antidepressant paroxetine is a candidate drug predicted by proteome analysis[17].

Peptidase inhibitors

Coronaviridae causing MERS and SARS enter cells by binding to certain exopeptidases like angiotensin-converting-enzyme 2 (ACE2) and dipeptidylpeptidase-4 (DPP4)[23]. Apparently, SARS-CoV-2 is primarily dependent on type II transmembrane serine protease 2 (TMPRSS2) and ACE2[2,24].

It has been hypothesized that patients treated with ACE-inhibitors (ACEi) might be at greater risk for severe COVID-19, since ACEi compensatory increase the expression of ACE2[25]. Two studies based on in-patient data denied the influence of ACEi and sartans on COVID-19[26,27]. OpenVigil detected the ACEi ramipril and the AT1-receptor antagonists olmesartan and irbesartan as candidate drugs. Irbesartan is also a possible anti-COVID-19 candidate drug predicted by proteome analysis[17].

ACE2 is increased in patients with diabetes mellitus or vascular diseases[28]. This finding might explain both the higher susceptibility of these patients for SARS-CoV-2, as well as the occurrence of anti-diabetics and antihypertensives among our candidate drugs.

Heparins like enoxaparin and oxazolidinones like rivaroxaban and other inhibitors of factor Xa were detected as signals. Factor Xa is a serine protease that cleaves the coronavirus spike-protein, so the virus can enter the cells[29]. Factor Xa is also needed by other viruses for the cleavage of certain viral proteins[30,31]. In addition to this special anti-viral mechanism, all inhibitors of coagulation were hypothesized to be beneficial against the thrombotic events occurring in COVID-19.

Sitagliptin, a DPP4-inhibitor, was previously tested against SARS and MERS. The negative results might reflect the different binding sites of virus and drug[32]. Furthermore, DPP4 appears not to be a relevant exopeptidase for SARS-CoV-2.

Kinase inhibitors

Inhibition of intracellular kinases that regulate cell viability and immune reactions appears as new concept for treatment of COVID-19: Our candidate drug erlotinib has previously been proposed to treat dengue fever, possibly by inhibition of intracellular kinases that regulate trafficking of viruses[33]. Imatinib (a further

candidate drug listed in the supplemental material) could inhibit the fusion of coronaviruses with the cell, maybe due to a putative Abelson-TMPRSS2-pathway[24] or by interfering with actin dynamics needed for cell-virus-fusion[34].

Anti-androgens

Male gender is a major risk factor[35,36]. Androgens enhance the expression of TMPRSS2[35] and - at least in rats - ACE2[37]. We have identified three anti-androgenic drugs, i.e. leuprolide, enzalutamide and arbiraterone as potentially beneficial.

Various

Niacin (nicotinic acid) and its derivatives are implicated in boosting anti-viral defenses[38,39]. There is a clinical trial just now commencing at Kiel University Medical Center Schleswig-Holstein to test nicotinamide against mild to moderate COVID-19 (German Clinical Trials Registry no. DRKS00021214).

We detected proton pump inhibitors (PPIs) like (es-)omeprazole. Indeed, there is an intrinsic antiviral effect of these drugs. However, PPIs were not effective against *flaviviridae*[40], which are similar to *coronaviridae*. In addition, the antiviral effect will probably be countered by the increased susceptibility to bacteria and viruses due to the effect of PPIs on gastric pH and the gastrointestinal antimicrobial barrier, subsequently. The gastrointestinal tract is a possible route for MERS-CoV infections[41], so using PPIs against SARS-CoV-2 appears not feasible.

The various antibodies that turned up as candidate drugs are probably confounded by the very special situation of the patients (e.g. hospitalized treatment and thus less risk of airborne infections). However, since some of the antibodies modulate inflammatory pathways, we have not removed them from the set of candidate drugs.

For some candidate drugs no affirmative data could be found in the literature. This absence of evidence must not be misinterpreted as an evidence of absence of any mechanism. Contrarily, this should stimulate research to elucidate these disproportionality signals.

Discussion

All reports in OpenVigil 2 are biased by technical limitations as explained later on and by the nature of spontaneous reporting: The reports represent only a small proportion of the real-world situation (so called "open-world-problem"). The healthy part of the population is not known and thus all calculations of observed/expected disproportionality are performed against the background of all other drugs and all other events. AE are expected to be underreported by 1:1.1 to 1:100, dependent on their seriousness and whether an ADR was already well known and presented in scientific or lay media. Eventually, the data on SARS-CoV-2 will become available, albeit in a biased way: E.g. reporting of AEs of the anti-influenza-drug oseltamivir spiked during 2009 (A/H1N1, "swine flu"), 2016 (A/H5N8, "avian flu") and 2018 (A/H3N2) (Fig. 5). This selective reporting over time introduces bias into the data, with possibly a similar or even greater relevance than the (disputed) Weber effect[42]. The new MedDRA version 23 contains various terms related to COVID-19.

The ATC system has important weaknesses: A substance can have more than one ATC classification code, depending on the route of application and the intended indication. Level 3 and 4 are diffusely mixing therapeutic, chemical and pharmacologic categories. Thus, group sizes are arbitrary. Subgroups containing the letter "X" contain substances with different mechanisms of action and/or chemical structures. Building a multi-dimensional space based on affinities of substances to different targets and detecting cluster appears to be a superior method to the arbitrary ATC classification system.

From a statistical point of view, an adjustment of p-values of each of the >5000 statistical tests performed during data extraction should be made. At WHO or FDA or similar institutions, this is not done for their routine research, i.e. quickly detecting new ADRs. Each test is treated as an independent test and thus no adjustment was performed.

The data do not allow to distinguish whether a candidate drug can prevent or ameliorate the condition. Furthermore, the effect size is not known. Some case reports feature data on drug dosage, treatment duration, AE severity or outcome (e.g. "dead") but mostly this information is not available. Thus, the potential benefit cannot be estimated solely based on pharmacovigilance data. Especially, no dosage recommendations can be derived.

Especially in viral diseases like COVID-19, the different treatment goals, i.e. post-exposition or pre-exposition prophylaxis, treatment of mildly or severely ill patients, curative or palliative need to be distinguished and suitable drugs for each need to be identified.

Drug repurposing using pharmacovigilance data is a rather new application. We have currently limited knowledge how to translate results to bedside and which pitfalls like confounding to avoid.
This is especially true when using an established drug in a new way of application, i.e. targetting directly the inflammatory tissue by inhalation. With exception maybe for metformin and interferon which are being used inhalatively, the safety of these applications need to be proven in clinical trials.

Outlook

OpenVigil

Upstream of the OpenVigil application, we aim to improve the drugname cleaning procedure; possibly by adding more drug dictionaries. Downstream, interactions with other databases are needed to further explore the signals and (in)validate them, e.g. by cross-checking with published datasets like clinicaltrials.gov or by using pharmacogenomic approaches like CMap[43], IUPHAR pharmacodynamic data[7], or proteome-interactome predictions[18,44]. Besides developing new antiviral strategies, this approach can be used for other diseases[8].

COVID-19

We have identified a plethora of candidate drugs. Some could already be validated by two large SARS-CoV-2-proteome-host-interactome studies and by manual literature research. Yet preclinical and clinical trials to evaluate these hypotheses are necessary. Candidate drugs, which were not explainable by our research, should stimulate further research. The raw data and the results presented here might guide and thus accelerate these trials with "educated guesses".

Acknowledgements

We thank all contributors to OpenVigil 2, especially (in alphabetical order) Babak Alizadeh, Christian Eggeling, Leocadie von Hehn, Daniela Heidebrecht, Thomas Müller, Tsvetelin Polomski, Sören Zieger.

Conflict of interest

None.

Funding information

No external funding.

Data availability

All data are included in the supplemental material.

Code availability

OpenVigil 2 can be downloaded as executable and source from https://openvigil.sf.net under the GNU General Public License v2.

Contributions

HJK developed OpenVigil 2. RB performed the data extraction. CB cleaned and annotated the data. VW and TH post-processed the signals. IC gave conceptional advice.

All authors contributed to writing the manuscript.

References

1. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther*. 2020;14(1):58-60. doi:10.5582/ddt.2020.01012
2. Prajapat M, Sarma P, Shekhar N, et al. Drug targets for corona virus: A systematic review. *Indian J Pharmacol*. 2020;52(1):56-65. doi:10.4103/ijp.IJP_115_20
3. Shah B, Modi P, Sagar SR. In silico studies on therapeutic agents for COVID-19: Drug repurposing approach. *Life Sci*. 2020;252:117652. doi:10.1016/j.lfs.2020.117652
4. Making a difference. *Nat Biotechnol*. 2009;27(4):297. doi:10.1038/nbt0409-297
5. Böhm R, von Hehn L, Herdegen T, et al. OpenVigil FDA – Inspection of U.S. American Adverse Drug Events Pharmacovigilance Data and Novel Clinical Applications. Yang J-M, ed. *PLoS One*. 2016;11(6):e0157753. doi:10.1371/journal.pone.0157753
6. Lehrer S, Rheinstein PH. Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Reduce Suicidal Ideation and Depression. *Discov Med*. Published online 2019.
7. Siafis S, Papazisis G. Detecting a potential safety signal of antidepressants and type 2 diabetes: a pharmacovigilance-pharmacodynamic study. *Br J Clin Pharmacol*. 2018;84(10):2405-2414. doi:10.1111/bcp.13699
8. Böhm R, Bulin C, Tropmann-Frick M, Klein HJ, Herdegen T. Large-scale drug repositioning by inverse safety signals using the OpenVigil 2 pharmacovigilance data analysis tool. In: *Naunyn-Schmiedebergs Archives of Pharmacology*. Vol 392. ; 2019:S53--S53.
9. Hosomi K, Fujimoto M, Ushio K, Mao L, Kato J, Takada M. An integrative approach using real-world data to identify alternative therapeutic uses of existing drugs. Yang J-M, ed. *PLoS One*. 2018;13(10):e0204648. doi:10.1371/journal.pone.0204648
10. Potula R, Ramirez SH, Knipe B, et al. Peroxisome proliferator-activated receptor-γ activation suppresses HIV-1 replication in an animal model of encephalitis. *AIDS*. 2008;22(13):1539-1549. doi:10.1097/QAD.0b013e3283081e08

11. Wakui Y, Inoue J, Ueno Y, et al. Inhibitory effect on hepatitis B virus in vitro by a peroxisome proliferator-activated receptor-γ ligand, rosiglitazone. *Biochem Biophys Res Commun*. 2010;396(2):508-514. doi:10.1016/j.bbrc.2010.04.128

12. Xun YH, Zhang YJ, Pan QC, et al. Metformin inhibits hepatitis B virus protein production and replication in human hepatoma cells. *J Viral Hepat*. 2014;21(8):597-603. doi:10.1111/jvh.12187

13. Omeragic A, Kara-Yacoubian N, Kelschenbach J, et al. Peroxisome Proliferator-Activated Receptor-gamma agonists exhibit anti-inflammatory and antiviral effects in an EcoHIV mouse model. *Sci Rep*. 2019;9(1):1-12. doi:10.1038/s41598-019-45878-6

14. Tsai WL, Chang TH, Sun WC, et al. Metformin activates type I interferon signaling against HCV via activation of adenosine monophosphate-activated protein kinase. *Oncotarget*. 2017;8(54):91928-91937. doi:10.18632/oncotarget.20248

15. Bernier A, Cleret-Buhot A, Zhang Y, et al. Transcriptional profiling reveals molecular signatures associated with HIV permissiveness in th1th17 cells and identifies peroxisome proliferator-activated receptor gamma as an intrinsic negative regulator of viral replication. *Retrovirology*. 2013;10(1). doi:10.1186/1742-4690-10-160

16. Donkers JM, Zehnder B, Van Westen GJP, et al. Reduced hepatitis B and D viral entry using clinically applied drugs as novel inhibitors of the bile acid transporter NTCP. *Sci Rep*. 2017;7(1):1-13. doi:10.1038/s41598-017-15338-0

17. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov*. 2020;6(1):1-18. doi:10.1038/s41421-020-0153-3

18. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature*. Published online April 30, 2020:1-13. doi:10.1038/s41586-020-2286-9

19. Osama H, Sayed OM, Hussein RRS, Abdelrahim M, A. Elberry A. Design, optimization, characterization, and in vivo evaluation of sterosomes as a carrier of metformin for treatment of lung cancer. *J Liposome Res*. 2020;30(2):150-162. doi:10.1080/08982104.2019.1610434

20. No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19 — RECOVERY Trial. Accessed June 8, 2020. https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-

2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19

21. Watanabe K, Ishikawa T, Otaki H, et al. Structure-based drug discovery for combating influenza virus by targeting the PA-PB1 interaction. *Sci Rep*. 2017;7(1):1-12. doi:10.1038/s41598-017-10021-w

22. Ziebuhr J. The coronavirus replicase. *Curr Top Microbiol Immunol*. 2005;287:57-94. doi:10.1007/3-540-26765-4_3

23. Raj VS, Mou H, Smits SL, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature*. 2013;495(7440):251-254. doi:10.1038/nature12005

24. Coleman CM, Sisk JM, Mingo RM, Nelson EA, White JM, Frieman MB. Abelson Kinase Inhibitors Are Potent Inhibitors of Severe Acute Respiratory Syndrome Coronavirus and Middle East Respiratory Syndrome Coronavirus Fusion. *J Virol*. 2016;90(19):8924-8933. doi:10.1128/jvi.01429-16

25. Sanchis-Gomar F, Lavie CJ, Perez-Quilis C, Henry BM, Lippi G. Angiotensin-Converting Enzyme 2 and Antihypertensives (Angiotensin Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors) in Coronavirus Disease 2019. *Mayo Clin Proc*. Published online April 4, 2020. doi:10.1016/j.mayocp.2020.03.026

26. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin–Angiotensin–Aldosterone System Inhibitors and Risk of Covid-19. *N Engl J Med*. Published online May 1, 2020:NEJMoa2008975. doi:10.1056/NEJMoa2008975

27. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19. *N Engl J Med*. Published online May 1, 2020. doi:10.1056/nejmoa2006923

28. Soro-Paavonen A, Gordin D, Forsblom C, et al. Circulating ACE2 activity is increased in patients with type 1 diabetes and vascular complications. *J Hypertens*. 2012;30(2):375-383. doi:10.1097/HJH.0b013e32834f04b6

29. Du L, Kao RY, Zhou Y, et al. Cleavage of spike protein of SARS coronavirus by protease factor Xa is associated with viral infectivity. *Biochem Biophys Res Commun*. 2007;359(1):174-179. doi:10.1016/j.bbrc.2007.05.092

30. Kanade GD, Pingale KD, Karpe YA. Activities of Thrombin and Factor Xa Are Essential for Replication of Hepatitis E Virus and Are Possibly Implicated in ORF1 Polyprotein Processing. *J Virol*. 2018;92(6). doi:10.1128/jvi.01853-17

31. Straus MR, Whittaker GR. A peptide-based approach to evaluate the adaptability of influenza A virus to humans based on its hemagglutinin proteolytic

cleavage site. Russell CJ, ed. *PLoS One*. 2017;12(3):e0174827. doi:10.1371/journal.pone.0174827

32. Wang N, Shi X, Jiang L, et al. Structure of MERS-CoV spike receptor-binding domain complexed with human receptor DPP4. *Cell Res*. 2013;23(8):986-993. doi:10.1038/cr.2013.92

33. Pu SY, Xiao F, Schor S, et al. Feasibility and biological rationale of repurposing sunitinib and erlotinib for dengue treatment. *Antiviral Res*. 2018;155:67-75. doi:10.1016/j.antiviral.2018.05.001

34. Sisk JM, Frieman MB, Machamer CE. Coronavirus S protein-induced fusion is blocked prior to hemifusion by Abl kinase inhibitors. *J Gen Virol*. 2018;99(5):619-630. doi:10.1099/jgv.0.001047

35. Pozzilli P, Lenzi A. Testosterone, a key hormone in the context of COVID-19 pandemic. *Metabolism*. 2020;108:154252. doi:10.1016/j.metabol.2020.154252

36. Salonia A, Corona G, Giwercman A, et al. SARS‐CoV‐2, Testosterone and frailty in males (PROTEGGIMI): A multidimensional research project. *Andrology*. Published online May 5, 2020:andr.12811. doi:10.1111/andr.12811

37. Dalpiaz PLM, Lamas AZ, Caliman IF, et al. Sex hormones promote opposite effects on ACE and ACE2 activity, hypertrophy and cardiac contractility in spontaneously hypertensive rats. *PLoS One*. 2015;10(5). doi:10.1371/journal.pone.0127515

38. Murray MF. Nicotinamide: An Oral Antimicrobial Agent with Activity against Both Mycobacterium tuberculosis and Human Immunodeficiency Virus . *Clin Infect Dis*. 2003;36(4):453-460. doi:10.1086/367544

39. Li WY, Ren JH, Tao NN, et al. The SIRT1 inhibitor, nicotinamide, inhibits hepatitis B virus replication in vitro and in vivo. *Arch Virol*. 2016;161(3):621-630. doi:10.1007/s00705-015-2712-8

40. Watanabe SM, Ehrlich LS, Strickland M, et al. Selective Targeting of Virus Replication by Proton Pump Inhibitors. *Sci Rep*. 2020;10(1):1-15. doi:10.1038/s41598-020-60544-y

41. Zhou J, Li C, Zhao G, et al. Human intestinal tract serves as an alternative infection route for Middle East respiratory syndrome coronavirus. *Sci Adv*. 2017;3(11):eaao4966. doi:10.1126/sciadv.aao4966

42. Arora A, Jalali RK, Vohora D. Relevance of the Weber effect in contemporary pharmacovigilance of oncology drugs. *Ther Clin Risk Manag*. 2017;13:1195-1203. doi:10.2147/TCRM.S137144

43. Lamb J, Crawford ED, Peck D, et al. The connectivity map: Using gene-expression signatures to connect small molecules, genes, and disease. *Science (80-)*. 2006;313(5795):1929-1935. doi:10.1126/science.1132939

44. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov*. 2020;6(1):1-18.

45. Evans SJW, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf*. 2001;10(6):483-486. doi:10.1002/pds.677

Table legends

Table 1: 5 most statistically significant candidate drugs

Drugs associated with cases of MedDRA HLTs "viral lower respiratory tract infections" OR "viral upper respiratory tract infections" (see supplemental table 1) sorted for ascending upper bounds of the Reporting Odds Ratio (ROR), with brandnames, confounders and unsuitable drugs removed. Only the 5 most statistically significant results are shown. For full raw and curated data see supplemental tables 1 and 3.
drug: USAN of the active substance, ROR: Reporting Odds Ratio, RORlb: lower bound of the 95%-confidence interval of ROR, RORub: upper bound of the 95%-confidence interval of ROR, DE: number of cases (reports with drug used and event occurred)
For calculations see Fig. 2.

drug	ROR	RORlb	RORub	DE
rosiglitazone	0.076385	0.053706	0.10864	31
aripiprazole	0.209824	0.160644	0.274061	54
nicotine	0.209397	0.154128	0.284485	41
cinacalcet	0.246481	0.18674	0.325334	50
omeprazole	0.266241	0.193651	0.366043	38

Table 2: Candidate drugs grouped and ordered by ATC classification code

anatomical main group	therapeutic subgroup	therapeutic/ pharmacological subgroup	chemical/ therapeutic/ pharmacological subgroup	chemical substance	drug	proposed anti-viral or immuno-modulatory mechanism or action against SARS-CoV-2/COVID-19
A Alimentary tract and metabolism	A02	A02B	A02BC	A02BC01	omeprazole	PPIs impair our antiviral defense but have an independent anti-viral mechanism but probably not for SARS-CoV-2[40]
				A02BC02	pantoprazole	
				A02BC03	lansoprazole	
				A02BC05	esomeprazole	
	A10	A10B	A10BA	A10BA02	metformin	these anti-diabetics impair viral replication[10–13]
			A10BG	A10BG02	rosiglitazone	
				A10BG03	pioglitazone	
			A10BH	A10BH01	sitagliptin	negative results for SARS-CoV[32]
			A10BJ	A10BJ02	liraglutide	
	A11	A11H	A11HA	A11HA01	niacin	boosts anti-viral defense[38,39]
B Blood and blood forming organs	B01	B01A	B01AB	B01AB05	enoxaparin	Factor Xa cleaves the spike protein[29]
			B01AC	B01AC04	clopidogrel	
			B01AF	B01AF01	rivaroxaban	Factor Xa cleaves the spike protein[29]
				B01AF02	apixaban	
	B03	B03X	B03XA	B03XA02	darbepoetin alfa	
C Cardiovascular system	C01	C01B	C01BD	C01BD01	amiodarone	
	C02	C02A	C02AC	C02AC01	clonidine	
	C07	C07A	C07AB	C07AB03	atenolol	
				C07AB07	bisoprolol	
	C09	C09A	C09AA	C09AA05	ramipril	
		C09C	C09CA	C09CA04	irbesartan	proteome analysis[17]
				C09CA08	olmesartan	
	C10	C10A	C10AA	C10AA01	simvastatin	
				C10AA05	atorvastatin	

anatomical main group	therapeutic subgroup	therapeutic/ pharmacological subgroup	chemical/ therapeutic/ pharmacological subgroup	chemical substance	drug	proposed anti-viral or immuno-modulatory mechanism or action against SARS-CoV-2/COVID-19
			C10AX	C10AX09	ezetimibe	
D Dermatologicals	D10	D10A	D10AD	D10AD04	isotretinoin	
G Genito-urinary system and sex hormones	G03	G03B	G03BA	G03BA03	testosterone	maybe confounded by testosterone replacement therapy in hypogonadism
	G04	G04B	G04BD	G04BD08	solifenacin	
		G04C	G04CA	G04CA02	tamsulosin	
H Systemic hormonal preparations	H05	H05B	H05BX	H05BX01	cinacalcet	
J Antiinfectives for systemic use	J01	J01F	J01FA	J01FA09	clarithromycin	
		J01M	J01MA	J01MA02	ciprofloxacin	direct inhibition of RNA replicase of influenza but not corona[21]
				J01MA12	levofloxacin	
		J01X	J01XA	J01XA01	vancomycin	
	J05	J05A	J05AE	J05AE03	ritonavir	primarily used as ABCB1/CYP3A4/SLC-booster for several anti-viral drugs
			J05AF	J05AF05	lamivudine	
			J05AP	J05AP02	telaprevir	
L Antineoplastic and immunomodulating agents	L01	L01X	L01XC	L01XC02	rituximab	
				L01XC03	trastuzumab	
				L01XC07	bevacizumab	
				L01XC17	nivolumab	
			L01XE	L01XE03	erlotinib	inhibits TMPRSS2[24]
			L01XX	L01XX44	aflibercept	
	L02	L02B	L02AE	L02AE02	leuprolide	anti-androgenic treatment might be beneficial[35]
			L02BB	L02BB04	enzalutamide	
			L02BX	L02BX03	abiraterone	

anatomical main group	therapeutic subgroup	therapeutic/ pharmacological subgroup	chemical/ therapeutic/ pharmacological subgroup	chemical substance	drug	proposed anti-viral or immuno-modulatory mechanism or action against SARS-CoV-2/COVID-19
	L03	L03A	L03AA	L03AA13	pegfilgrastim	
M Musculo-skeletal system	M01	M01A	M01AB	M01AB05	diclofenac	
			M01AE	M01AE02	naproxen	
			M01AH	M01AH02	rofecoxib	
	M04	M04A	M04AA	M04AA01	allopurinol	
	M05	M05B	M05BX	M05BX04	denosumab	
N Nervous system	N02	N02A	N02AA	N02AA01	morphine	upon activation by an agonist, the sigma-receptor interferes with NSP6[18]
				N02AA05	oxycodone	
			N02AB	N02AB03	fentanyl	
			N02AC	N02AC52	methadone	
		N02A	N02AE	N02AE01	buprenorphine	
		N02B	N02BA	N02BA01	acetylsalicylic acid	
		N02C	N02CC	N02CC01	sumatriptan	
	N03	N03A	N03AB	N03AB02	phenytoin	
			N03AF	N03AF01	carbamazepine	
				N03AF02	oxcarbazepine	
			N03AG	N03AG01	valproic acid	might bind to NSP5[18]
			N03AX	N03AX09	lamotrigine	
				N03AX11	topiramate	
				N03AX14	levetiracetam	
	N05	N05A	N05AH	N05AH02	clozapine	
				N05AH03	olanzapine	
				N05AH04	quetiapine	
			N05AN	N05AN01	lithium	
			N05AX	N05AX08	risperidone	
				N05AX12	aripiprazole	direct inhibition of RNA replicase of influenza but not corona[21]

anatomical main group	therapeutic subgroup	therapeutic/ pharmacological subgroup	chemical/ therapeutic/ pharmacological subgroup	chemical substance	drug	proposed anti-viral or immuno-modulatory mechanism or action against SARS-CoV-2/COVID-19
		N05C	N05CF	N05CF02	zolpidem	GABAergic drugs might be antiinflammatory[9]
	N06	N06A	N06AX	N06AX11	mirtazapine	the SSRI paroxetine is a candidate drug identified by proteome analysis[17]
				N06AX12	bupropion	
		N06B	N06BA	N06BA04	methylphenidate	
			N06B	N06BA09	atomoxetine	
	N07	N07B	N07BA	N07BA01	nicotine	
				N07BA03	varenicline	
Respiratory system	R03	R03B	R03BB	R03BB04	tiotropium	
	R06	R06A	R06AX	R06AX13	loratadine	
				R06AX26	fexofenadine	

Figure legends

Figure 1: Virus taxonomy

Overview of the different virus phyla and families. Viruses belonging to the same phylum might share identical genes (e.g. proteases or replicases) and might thus be susceptible to the same anti-viral agents. Numbers in the center indicate the Baltimore virus classification.

Figure 2: 2x2 contigency table and signal concept

(A) The letters "D", "d", "E" and "e" refer to the datasets involved: Capital D: drug was used, lowercase d: this drug was not used but other drugs, Capital E: event occurred, lowercase e: this event did not occur but other events. For more complex contingency tables, indices can be used to refer to a certain drug or event by name or numbering. Intersections of the datasets can be made by combining letters, e.g., "DE" is the subpopulation where the drug was used and the event occurred while "de" is the subpopulation where neither this drug was administered, nor this AE occurred. To detect a disproportionality of observed and expected cases, the odds of experiencing the AE in the group of patients taking the drug (cell DE/De) can be compared to the odds of contracting this AE while not being exposed to this drug (dE/de), resulting in the Reporting Odds Ratio (ROR). A statistically significant disproportionality - a signal - can be assumed if DE>2, and the 95%-confidence interval of the ROR does not cross 1[45].
(B) Contingency table of the drugs "chloroquine" OR "hydroxychloroquine" x AE "Pneumonia viral" as an example for a signal of a putative adverse drug reaction (ADR).

Figure 3: Candidate drugs grouped by ATC classification levels

See Tab. 2 for ATC classification codes and classes.
Of note, this is a snapshot of only 82 drugs, detected in data from 2004 to 20019. Proportions and clusters will change with different data or a different grouping method (e.g. based on target structures). Cf. the weaknesses of the ATC classification system in the discussion section.

Figure 4: Selection of antiviral pathways of the candidate drugs identified with our pharmacovigilance-based approach

ACE: angiotensine converting enzyme; AMPK: AMP-activated proteinkinase; DPP: dipeptidylpeptidase; ER: endoplasmatic reticulum; Factor Xa: coagulation factor X activated; GA: Golgi apparatus; NSP: non-structural protein; PP1A/B: viral poly-proteins 1A/1B; TMPRSS2: transmembrane protease serine subtype 2; Question marks indicate structures relevant for other viruses than SARS-CoV-2.

Figure 5: AE reports for the anti-influenza drug oseltamivir over time in OpenVigil 2

All AE reports of oseltamivir in the U.S. FDA FAERS pharmacovigilance data from 2014Q1 to 2019Q4. The distinct spikes in the years 2010, 2016 and 2018 are due to increased drug usage because of serious influenza pandemics (cf. text)