Drug use during COVID-19

Utilization of drugs with reports on potential efficacy or harm on COVID-19 before, during, and after the first pandemic wave

Course and potential influencing factors

Master thesis for the degree of *Master of Science in Epidemiology (MSc)*

by Salka Enners (Matriculation number: 226719)

Charité – Universitätsmedizin Berlin, Berlin School of Public Health

salka.enners@charite.de

Date of submission: September 29, 2021

1st Supervisor: Prof. Dr. Martin Schulz

German Institute for Drug Use Evaluation

m.schulz@abda.de

2nd supervisor: Dr. Toivo Glatz

Institute for Public Health, Charité - Universitätsmedizin Berlin

toivo.glatz@charite.de

DAPI

Deutsches Arzneiprüfungsinstitut e.V.

BSPH

BERLIN SCHOOL OF PUBLIC HEALTH

Table of Content

List of Tables

List of Figures

List of Abbreviations

ABDA, ABDA − Bundesvereinigung Deutscher Apothekerverbände e. V. (Federal Union of German Associations of Pharmacists)

ACE2, angiotensin-converting enzyme 2

ACEi, angiotensin-converting enzyme inhibitor

AMK, Arzneimittelkommission der Deutschen Apotheker (Drug Commission of German Pharmacists)

ARB, angiotensin receptor blocker

ATC, Anatomical Therapeutic Chemical

BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)

COVID-19, coronavirus disease 2019

DAPI, Deutsches Arzneiprüfungsinstitut e.V (German Institute for Drug Use Evaluation)

DID, defined daily doses per 1,000 SHI-insured persons per day

EMA, European Medicines Agency

EVD, Ebola virus disease

HIV, human immunodeficiency virus

ISAC, International Society of Antimicrobial Chemotherapy

JAMA, Journal of the American Medical Association

NEJM, New England Journal of Medicine

OTC, over-the-counter (non-prescription drugs)

PHI, private health insurance

RAASi, renin–angiotensin–aldosterone system inhibitor

RAS, renin–angiotensin system

RCT, randomized controlled trials

RKI, Robert-Koch-Institut

SARS-CoV-2, severe acute respiratory coronavirus 2

SHI, statutory health insurance (funds)

SLE, systemic lupus erythematosus

WHO, World Health Organisation

Publication in Pharmacoepidemiology and Drug Safety

The main findings of this master thesis have been published as an original article in *Pharmacoepidemiology and Drug Safety* (impact factor 2020: 2.890). The original manuscript can be found in the appendix.

The original idea of this drug utilization study was presented by Prof. Dr. rer. nat. Martin Schulz and further conceptualized by Salka Enners as first and corresponding author and the co-authors Dr. rer. nat. Gabriele Gradl, Marita Kieble (MSc Epi), Prof. Dr. med. Michael Böhm, Prof. Dr. med. Ulrich Laufs, as well as Prof. Dr. Martin Schulz as senior author and supervisor.

The methodology was developed by Salka Enners, Gabriele Gradl and Marita Kieble in close consultation with Martin Schulz. The data analysis, as well as visualization was implemented by Salka Enners and quality-controlled by Gabriele Gradl and Marita Kieble.

The original draft was written by Salka Enners and reviewed and edited by Salka Enners and Martin Schulz, supported by all co-authors. The finalized manuscript was submitted by Salka Enners; all authors have read and agreed to the published version of the manuscript.

Title: Utilization of drugs with reports on potential efficacy or harm on COVID-19 before, during, and after the first pandemic wave

Authors: Salka Enners, Gabriele Gradl, Marita Kieble, Michael Böhm, Ulrich Laufs, Martin Schulz

First published: 09 July 2021 in Pharmacoepidemiology and Drug Safety

https://doi.org/10.1002/pds.5324

Eidesstattliche Erklärung

Hiermit erkläre ich, dass diese Masterarbeit von mir selbstständig verfasst wurde und keine anderen als die angegebenen Hilfsmittel benutzt wurden.

Berlin, 29.09.2021

Abstract

Introduction

Conflicting information and speculation on potential benefits of drugs as well as reports on hypothetical harm of commonly used drugs in coronavirus disease 2019 (COVID-19) treatment have challenged clinicians and healthcare systems. The aim of this drug utilization study is to analyse the change in ambulatory drug utilization before, during, and after the first wave of the pandemic in 2020 and to discuss potential influencing factors.

Methods

The study explores dispensing data of nearly 19,000 pharmacies at the expense of the statutory health insurance funds covering 88% of Germany's population. Drug utilization was analysed as number of packages dispensed per week from January to June 2020 and as percentage change compared to 2019. For ibuprofen and paracetamol, monthly dispensing data from privately insured patients and self-medication utilization were included.

Results

Utilization of hydroxychloroquine increased by +110% during March 2020 and then slightly decreased until the week of April 13–19. Renin–angiotensin–aldosterone system inhibitors as well as simvastatin and atorvastatin increased, +78% and +74%, respectively, and subsequently decreased below 2019 levels. After initial slight increase, utilization of azithromycin and all systemic antibiotics decreased continuously from March 2–8 until June to levels considerably lower compared to 2019 (June 22–28: azithromycin: −55%, all systemic antibiotics: −27%). Pneumococcal vaccines utilization initially increased +373%, followed by a sharp decrease due to drug shortages. Subsequently, utilizations increased again (+294%). Paracetamol utilization showed an initial increase of +111% in March 2020, mainly caused by an increase of over-the-counter dispensings. Ibuprofen dispensings also increased in March 2020, though less significant (+19%). From April onwards, a decrease in utilization for ibuprofen and paracetamol was observed.

Conclusions

The data suggest that, apart from the pandemic itself, dissemination of misinformation and unsound speculations as well as supply shortages influenced drug prescribing, utilization, and purchasing behaviour. The findings can inform post-pandemic policy to prevent unfounded over- and underprescribing, off-label use, as well as drug shortages during a public health crisis.

Zusammenfassung

Einleitung

Spekulationen und Informationen über eine potentielle Wirksamkeit von Arzneimitteln sowie widersprüchliche Berichte zu Arzneimitteln bezüglich ihres Risikos bei COVID-19 begleiteten die erste Pandemiewelle und stellten Mediziner, Pharmazeuten und das Gesundheitssystem vor Herausforderungen. Ziel dieser Untersuchung ist die Veränderung der Abgaben dieser öffentlich viel diskutierten Arzneimittel vor, während und nach der ersten Pandemiewelle in Deutschland zu analysieren und potentielle Einflussfaktoren zu diskutieren.

Methode

Die Studie untersucht Abgabedaten von annährend 19.000 Apotheken zu Lasten der gesetzlichen Krankenversicherung, repräsentativ für ca. 88 % der deutschen Bevölkerung. Die Abgaben der Arzneimittel wurden als abgegebene Packungen pro Woche von Januar bis Juni 2020 und als prozentuale Veränderung im Vergleich zu den Abgabedaten des Vorjahres analysiert. Für Ibuprofen und Paracetamol wurden zusätzlich monatliche Abrechnungsdaten der privaten Krankenversicherung sowie Abgabedaten der Selbstmedikation mit einbezogen.

Ergebnisse

Die Abgaben von Hydroxychloroquin stiegen im März um bis zu +110 %, anschließend waren sie bis zur Woche April 13-19 leicht rückläufig. Die Abgaben von Inhibitoren des Renin-Angiotensin-Aldosteron Systems, sowie von Simvastatin und Atorvastatin erhöhten sich um +78 % bzw. +74 %. Anschließend fielen sie auf Werte unterhalb des Vorjahresniveaus. Azithromycin, sowie die Gesamtheit der systemischen Antibiotika wurden in der Woche März 2-8 nach initialem leichtem Anstieg kontinuierlich weniger abgegeben und verblieben unter Vorjahresniveau (Juni 22−28: Azithromycin: -55 %, alle systemischen Antibiotika: -27 %). Die Absätze der Pneumokokken-Impfstoffe stiegen initial um +373 % an. Anschließend sanken die Absätze aufgrund von Lieferengpässen stark ab, stiegen dann erneut um +294 % an. Der Absatz von Paracetamol stieg im März 2020 initial um +111 % an, überwiegend im Rahmen der Selbstmedikation. Auch für Ibuprofen konnte ein Absatzanstieg beobachtet werden,

wenn auch weniger stark ausgeprägt (+19 %). Ab April wurde sowohl für Paracetamol als auch Ibuprofen ein Absatzrückgang gegenüber 2019 beobachtet.

Diskussion

Die Daten deuten darauf hin, dass abgesehen von den generellen Einflüssen der Pandemie auf den Absatzverlauf sowie Liefer- und Versorgungsengpässe, die Verbreitung von (Fehl-)Informationen und unfundierten Spekulationen einen Einfluss auf die Verschreibung, die Abgabe und den Kauf von Arzneimitteln hatten. Diese Ergebnisse können die Gesundheitspolitik darin unterstützen, Maßnahmen zu entwickeln, die Über- oder Unterversorgungen, Off-Label-Gebrauch sowie Lieferengpässen in zukünftigen (pandemischen) Krisen entgegenwirken.

1 Introduction

1.1 Coronavirus disease 2019 pandemic

On December 31, 2019 the outbreak of a novel coronavirus known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected in Wuhan, China. The disease it causes is called coronavirus disease 2019 (COVID-19).[1] Within weeks, it spread to multiple countries (more than 190 as per August 2021). The pandemic has affected approximately 214 million people worldwide and has claimed more than 4.46 million lives all around the world (as per August 2021).[2,3] The disease expresses itself from milder symptoms such as loss of taste or smell, sore throat and coughing to more severe symptoms, like fever, shortness of breath as well as pneumonia, which could possibly require artificial ventilation and intensive care and could end fatally. The severity of symptoms can vary massively between individuals. Particularly elderly, individuals with significant comorbidities, a weakened or suppressed immune system are affected markedly.[4,5,2]

On March 11, 2020 the World Health Organisation (WHO) officially declared COVID-19 a pandemic.[6] The first confirmed cases of COVID-19 emerged in Germany in January 2020. Between January and June 2020, there have been around 194,300 confirmed cases and 8,900 deaths verified by the Robert-Koch-Institute (RKI).[7] The virus is transmitted by human-to-human interaction.[2] Therefore, effective public health measures for the prevention of further spreading of COVID-19 include measures of hygiene, such as the wearing of facemasks, frequent hand washing, as well as social distancing.[5,8]

As the disease emerged to be a substantial risk to public health, strict regulations and restrictions on public interactions and social interactions were issued on March 22, 2020 by the Federal and State Governments of Germany to contain the further spread of COVID-19. First relaxations of these restrictions came into effect on April 20, 2020 after incidence rates and case numbers substantially decreased[7] due to the success of the above-mentioned measures in public and social life.
Furthermore, to protect people, especially the vulnerable, from potentially developing severe pulmonary symptoms, the Federal Health Minister of Germany, Jens Spahn,

issued a recommendation on March 9, 2020 for people over 60 years to get vaccinated against pneumococci to prevent a “superinfection” of pneumococci and COVID-19 in patients.[9]

1.2 „Infodemic“– Spreading of (mis-)information concerning COVID-19

While the public health measures were effective in controlling the spreading of the corona virus, they drastically interfered with everyday life and were accompanied by the dissemination of information and speculation concerning possible treatment options for the disease.[10] These (mis-)information spread quickly in non-scientific media and on social networks and emerged to be a major influence on public health.

A media analysis identified 2,311 reports of rumors, stigma, and conspiracy theories in 25 languages from 87 countries. 19% of the claims were related to treatment and cure.[11] For example, false claims that consumption of disinfectants and alcohols could prevent and treat COVID-19 were associated with 5,876 hospitalizations and 800 deaths from methanol poisoning in Iran between February 23 and May 2, 2020.[12] Another study examined the possible association between COVID-19 cleaning recommendations and the rising number of chemical exposures in 2020. It reports a sharp increase of the daily number of calls to 55 poison centers (45,550 calls in total) in the United States for exposure to cleaners (28,158) and disinfectants (17,392) in early 2020 and showed an overall increase of 20% and 16% in comparison to January to March 2019 and 2018, respectively.[13]

1.2.1 Challenges within the publishing process in times of crisis

As political decisions and public health measurements are often based on and supported by results and findings of scientific publications, it is essential to provide evidence-based new research as quickly as possible. To submit and publish a manuscript quickly in pandemic times may have been prioritised over thoroughness and quality, which may have led to or sustained the spread of conflicting (mis-)informations and therefore potentially wrong conclusions on treatment options.[14]

The high need for information on this novel virus led to a rush of research papers addressing the COVID-19 disease, which has stressed and challenged the scientific

publication system.[15] According to Elizabeth Loder, editor at *The BMJ* (previously *British Medical Journal*), more than 600 research manuscripts have been submitted per month to *The BMJ* during COVID-19. This is more than double the number of manuscripts usually submitted pre-pandemic.[15] It is a big challenge for scientific journals to handle the increase in submissions and to find suitable reviewers who are able to review the submissions properly. The number of submissions the journals are able to review, and edit is limited to a certain number of staff and resources per issue and the thorough and formal evaluation process is being highly challenged. The increase in submissions can become overwhelming, especially for smaller journals with few resources.[14,16,17]

Irving Steinberg, associate professor of clinical pharmacy and paediatrics at the University of Southern California states that, though speed is an important factor when publishing, especially in times of crisis such as the COVID-19 pandemic, it can also be a “risky endeavour”. He elaborates, that the risk of the results of scientific research being uncertain, or even unfounded, increases the faster the research is being published. Ensuring correct interpretation and implementation becomes harder when time is limited – and, again, the burden and the distress of the current pandemic influences the situation negatively.[18]

1.2.2 Publication of preprints

The backlog from weeks up to months within the publishing process may have led to reviewers accelerating peer review for quick publication,[19,20] resulting in reduced accuracy due being overworked and highly strained.

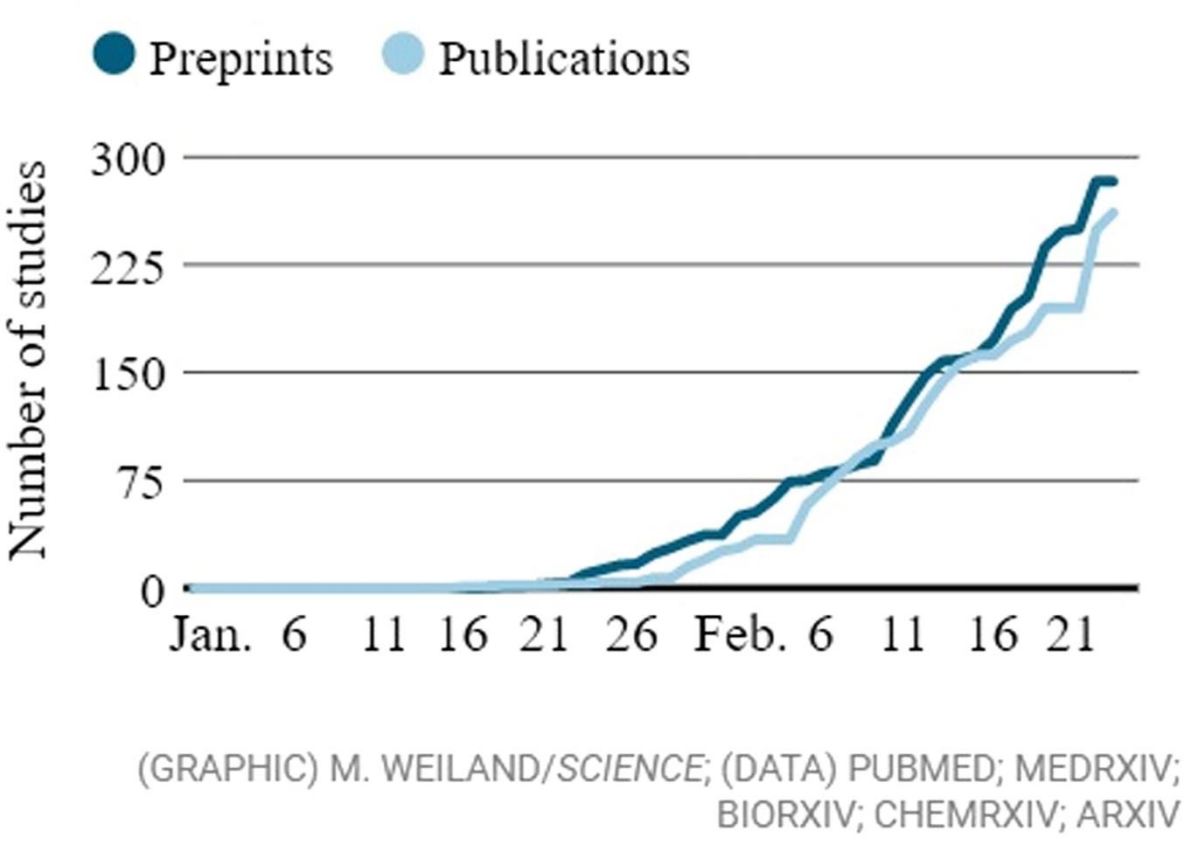
In addition to this, as researchers are eager to publish their research as quickly as possible, they publish their findings as pre-prints without scientific peer review. In turn, this may have resulted in preprints being published, indicating certain drugs to be suitable as treatment against COVID-19, and other drugs to be avoided in patients with COVID-19, which’s initial assumptions might not hold true upon closer inspection, yet influenced decisions on treatment options.

Though preprints make research accessible significantly sooner and releases findings into the public domain to be discussed earlier, they might still contain false claims or methodical errors.[21] Nevertheless, as the findings are of great public interest, they are

likely to get picked up by non-scientific media.[17] This may cause rapid spreading of findings and its potentially uncertain conclusions, which might not hold up to scientific standards. Kurth et al. state, that these public discussions lead to “confusion and [give] a false sense of confidence in unverified findings”.[14]

An investigations by Johansson et al. in 2018 of publication of manuscripts of previous pandemics such as the Zika epidemic from 2015 to 2016 and the Ebola virus disease (EVD) from 2014 to 2016, showed that the preprints can, in fact, speed up the dissemination of data and scientific findings.[22] More than 100 days have usually passed between the upload of a manuscript to a preprint server and the publication in a scientific journal. Less than 5% of the examined manuscripts regarding those two previous pandemics were uploaded as a preprint prior to publication. An article published in *Science Magazine* states, that during the COVID-19 pandemic, the use of preprint servers for sharing findings was higher than in any previous pandemic outbreaks. In parallel with preprints, the number of published papers is increasing rapidly as well since beginning of the pandemic (Figure 1).[20]

Figure 1 Number of COVID-19 related preprints and publications, January and February 2020



Within the first four months since the first emerged COVID-19 cases, over 16,000 papers regarding COVID-19 have been published, 6,000 of those were published on preprint servers. An analysis by Fraser et al. of around 14,800 preprints published between January to April 2020 on the preprint servers bioRxiv and medRxiv showed that COVID-19 preprints are substantially shorter than non-COVID-19 preprints at around half the length and with less tables, figures and references. COVID-19 preprints are accessed and distributed at least 15 times more than non-COVID-19 preprints. COVID-19 preprints were also downloaded almost 30 times more than non-COVID-19 preprints and had 200 times higher odds of being featured in news articles by non-scientific media.[17] The *New England Journal of Medicine (NEJM)*, a well-known and high-impact scientific journal, published one COVID-19 paper within 48 hours of submission.[20] Fraser et al. furthermore discovered that COVID-19 preprints were published in peer-reviewed journals 26 days faster than non-COVID-19 preprints on average. Usually, an average of 166 days past from first upload on a preprint server to registration of a Digital Object Identifier for a journal article.

1.2.3 Effect of (mis-)information on drug utilizations and patients

Many publications, including preprints regarding pharmaceutical drugs discussed study findings on potential health benefits for the treatment or prevention of COVID-19, or potential negative influence on the severity of COVID-19. Thus, the spread of partially unconfirmed (mis-)information, published precipitated or prematurely may have concluded in wrong, potentially harmful decisions on patients' medication. It may have caused more confusion as well as distrust and further challenged clinicians and the healthcare system.

For publicly discussed pharmaceutical drugs with potential health benefits, the consequently sharp and sudden increased interest and hence, the resulting rise of demand in utilizations could have resulted in drug shortages. The European Medicines Agency (EMA), in agreement with the medicine regulatory authorities of the European Union Member States, defines drug shortages as "when [the] supply (of a medicinal product for human or veterinary use) does not meet [the] demand at a national level".[23] Challenged medication supply chains due to restrictions in international trading channels as well as reduced manufacturing (i.e. in Wuhan, China) may have intensified the issue of drug shortages.[24]

Certain patient groups, such as those with chronical illnesses or weakened immune systems may have been especially affected by the implemented public health actions, as well as the drug shortages, which were possibly caused by the pandemic. Physician appointments became less accessible, routine health screening were missed and patients were asked to reduce visits to the community pharmacies only to the absolute necessary. As some chronic diseases, as well as certain pharmaceutical drugs are immunosuppressing, these concerned patients are especially vulnerable towards the infection with the SARS-CoV 2 virus.[24,25]

For the average person it is difficult to differentiate between evidence-based and scientifically proven facts versus speculations. However, this can lead to fatal decisions as well as loss of patients' trust in the healthcare system as well as individuals' adherence to medication intake. The patients' and physicians' desperation and fear of an uncertain future living with a virus without an effective treatment, as no vaccine available in 2020, was harrowing and certainly led to irrational and fearful decisions. Willingness to try medicine was high,[26] even with no proven benefit and potentially high chance of side effects. Also, politicization of finding treatment option as and pressure on officials to give answers and solutions to the public was high.[25,27,28]

1.3 Publicly discussed drugs with efficacy or harm on COVID-19

Several drugs, which are approved for other indications, have been tested for treatment or prevention of COVID-19 and might have been used off-label although reliable scientific evidence was insufficient. Consequently, a number of patients may have been exposed to hazardous effects of these drugs without a proven benefit. Other drugs were publicly discussed to increase the risk for a critical outcome of COVID-19 and therefore might have been avoided or discontinued. These hyptheses are currently without proven scientific evidence.[29-31]

1.3.1 Drugs with potential benefits

Hydroxychloroquine, a drug approved for malaria prophylaxis and treatment as well as treatment of rheumatoid arthritis and systemic lupus erythematosus (SLE), is a potent in vitro inhibitor of most coronaviruses since it inhibits pH-dependent steps in the virus replication as well as exertion of immunomodulatory effects. In vitro and in vivo experiments confirmed these mechanisms. It was therefore discussed to also be

potent against SARS-CoV-2, given the high genetic similarity.[10] The results of a small open-label French Study[32] on the supposedly high effectiveness of hydroxychloroquine in combination with azithromycin were interpreted prematurely as true and spread enthusiasm, even though the study results were misleading and had major methodological issues.[33] The former US president Donald Trump even promoted the drug as a potential treatment and authorized the purchase of hydroxychloroquine by the US government to be used on patients with COVID-19.[34]
Misinformation on hydroxychloroquine may have provoked or sustained pre-emptive stockpiling of packages, which ultimately might only have been used short-term for (prophylactic) use, if any. Further, stock shifting from outpatient to clinic supply could have provoked or worsened drug shortages. However, several subsequent clinical trials could not prove beneficial effects of this drug.[35-37]

Simvastatin and atorvastatin, HMG-CoA reductase inhibitors, have been proposed as an adjunct therapy for COVID-19 because of their anti-inflammatory effect[38] by the reduction of C-reactive protein and low-density lipoprotein cholesterol concentrations. Studies show a lower risk of all-cause mortality in in-hospital patients being treated with a statin therapy, compared to patients without a statin therapy.[39] However, simvastatin and atorvastatin also upregulate angiotensin-converting enzyme 2 (ACE2) expressions and therefore may increase the risk of SARS-CoV-2 entering the cell.[40] Experts advise continuation of guideline-based simvastatin and atorvastatin therapy in patients with cardiovascular diseases or diabetes but do not recommend routine intake for COVID-19 patients without cardiac injuries.[41]

The human immunodeficiency virus (HIV) therapeutics lopinavir and ritonavir's protease inhibiting abilities were also discussed to be effective against SARS-CoV-2. Several randomised trials could not prove significant clinical benefits or reduction of viral load and reported severe adverse events in patients.[42,43]

1.3.2 Drugs potentially increasing critical outcome of COVID-19

An increased risk for critical outcomes of COVID-19, defined as death or admission to an intensive care unit possibly requiring artificial ventilation, has mainly been discussed for drugs blocking the renin-angiotensin-aldosterone system (RAASi), including widely used angiotensin-converting-enzyme inhibitors (ACEi) and angiotensin receptor

blockers (ARB), due to the interaction between the SARS-CoV-2 virus with the renin-angiotensin-aldosterone system,[44] and based on studies investigating the correlation of hypertension, treatment with RAASi and developing severe COVID-19 disease progression. Although there was initial evidence for a significant difference in the severity of disease in a group in Wuhan,[45] the data were invalidated by several other studies which concluded that data is insufficient to recommend discontinuation of RAASi medication.[44,46] Another drug under debate was ibuprofen which, based on a recommendation by the WHO on March 17, 2020,[47] should not be used by people who show symptoms of COVID-19, but replaced by paracetamol. Both analgesics and antipyretics, available without prescription (as over-the-counter (OTC)-drugs) were therefore also included in the study.

Like COVID-19, pneumococci infections can lead to severe pneumonia as well as sepsis and can potentially require artificial ventilation of intensive care patients.[48] Therefore, they are a substantial additional risk factor for a critical outcome of COVID-19. Currently, all pneumococcal vaccines, which are indicated for adults are listed with restricted availability by the Paul-Ehrlich-Institute, the German Federal Agency for sera and vaccines. Therefore, to secure the vaccine availability for patients with weakened immune systems as well as for elderly over 60 years, the Standing Committee on Immunisation of Germany (Ständige Impfkommission, short STIKO) has adjusted the recommendations by the Federal Health Minister Jens Spahn, accordingly.[49]

1.4 Research question

The conflicting information on potential benefits of drugs as well as possibly speculative reports on hypothetical harm of commonly used drugs in COVID-19 treatment have challenged clinicians and healthcare systems providing evidence-based treatment options and therefore the best possible patient care. Data on how the prescription and self-medication dispensings of these publicly discussed drugs have been influenced by (mis-)information and thereupon have changed in the course of the pandemic are limited but potentially helpful. In future public health crises, it could help scientists and politicians to correctly interpret and implement findings into public health measures and recommendations, unbiased from misinformation and speculations. It can further be

helpful for patients and the public as well as to critically scrutinize information spread in (non-scientific) media.

To investigate ambulatory utilization of drugs with conflicting information regarding risks and benefits helps to understand the impact of the public spreading of (mis-)information on prescription behaviour by doctors and purchasing behaviour by the public in pharmacies. This could help to formulate practical advice for future public health crises on how to deal with the fast and massive spread of (non evidence-based) information. In addition, impending supply bottlenecks could be predicted and potentially prevented.

Ultimately, the research goal of this thesis is to provide empirical evidence if, and if so how, utilizations of drugs were affected by the public spreading of (mis-)information. For this, a descriptive drug utilization study was performed, analysing the change in ambulatory utilization of drugs with published reports regarding potential efficacy or harm on COVID-19 patients before, during and after the first pandemic wave in Germany. This study further aims to discuss other potential influencing factors on the course of utilizations.

It can be hypothesized that the spreading of (mis-)information, as well as other influencing factors led to an increase in utilization of potentially beneficial drugs, such as hydroxychloroquine and the macrolide antibiotic azithromycin. Furthermore it can be presumed, that a decrease followed in the utilization of drugs for which the increase of the risk to develop severe COVID-19 was discussed, for example for RAASi, including ACEi and ARB as well as ibuprofen. One could also hypothesize an increase in use of paracetamol as replacement for ibuprofen as well as an increase in vaccines.

2 Materials and methods

2.1 Literature research

The relevant pharmaceutical drugs included in this drug utilization study were determined by analysing the two documents "Behandlung von SARS-CoV-2/ COVID-19 – Potenzielle Wirkstoffe (Treatment of SARS-CoV-2/COVID-19 – potential pharmaceutical ingredients)"[50] by the Arzneimittelkommission der Deutschen Apotheker (Drug Commission of German Pharmacists, AMK) (as of March 31, 2020) and "Off-Label Medikamente gegen COVID-19 (Off-label pharmaceutical ingredients against COVID-19)"[51] by the *Gelbe Liste Pharmindex (Yellow List)*. The *Gelbe Liste Pharmindex* is a leading directory for medical drugs and pharmaceutical ingredients, offering current news and databases for physicians and pharmacists.[52] The document by the Gelbe Liste includes pharmaceutical drugs aimed at the viral replication cycle (antiviral medicines) as well as pharmaceutical drugs to control and alleviate COVID-19 symptoms. The list of the AMK includes pharmaceutical drugs as potential treatment options against COVID-19 from already published clinical trials as well as planned clinical trials, which were identified by ClinicalTrial.gov and a systematic review on therapeutics on COVID-19.[53]

The publications "Prescription Fill Patterns for Commonly Used Drugs During the COVID-19 Pandemic in the United States" published in the *Journal of the American Medical Association (JAMA)* by Vaduganathan et al.[54] and "The Impact of the COVID-19 "Infodemic" on Drug-Utilization Behaviors: Implications for Pharmacovigilance"[10] by Tuccori et al. published in *Drug Safety* also served as a basis for the analyses.

The references of the above-mentioned documents and publications were searched for further suitable literature. The literature research was carried out with strong consultation from Prof. Dr. Martin Schulz as an expert on drug utilization, who also provided further useful literature, which was used as reference.

2.2 Inclusion criteria

As the impact of (mis-)information on the public and on prescription behaviour by (resident) physicians is the main focus of the analysis, ambulatory/out-patient data is of interest. Therefore, orally applied drugs registered in Germany and dispensed at public pharmacies in Germany were included. Furthermore, pneumococcal vaccines were also included, though being applied intramuscular as the Federal Minister of Health of Germany specifically mentioned these in a public health measure to protect the elderly from a superinfection with pneumococci and COVID-19.
Excluded were drugs, which are presumably exclusively relevant to clinical use, such as drugs that need a parenteral application by medical staff.

2.3 Reference drugs

For an overview of the general course of utilizations in 2020, and for comparison on the included study drugs, reference drugs with a similar range of indication as the study drugs were determined. This helps to see if the changes in the course of utilization were most likely influenced by the mentions in the COVID-19 context or by other potential influencing factors.
Not only singular active ingredients but also the total number of dispensings of all prescribed drugs were analysed as a reference to show the general course of utilizations during a year influenced by a pandemic. Further, dispensings of all prescribed drugs can show whether the total utilization of all pharmaceutical drugs differed in 2020 in comparison to 2019; or if utilizations were just temporarily shifted due to interventions in daily life.
Therefore, dispensings for all prescribed drugs, all systematic antibiotics, and the most frequently used substances in the classes of penicillins (amoxicillin), cephalosporins (cefuroxime) and quinolones (ciprofloxacin) were analysed as reference, alongside the study drugs hydroxychloroquine, azithromycin, lopinavir-ritonavir, pneumococcal vaccines, paracetamol, simvastatine and atorvastatin, as well as RAASi and ibuprofen.

2.4 Data base

The change in utilizations from January to June was analysed by using seconday healthcara data, such as available in the database of the German Institute for Drug Use Evaluation (Deutsches Arzneiprüfungsinstitut e.V., DAPI). The database containes anonymous dispensing data, which was dispensed at community pharmacies in Germany at the expense of the statutory health insurance (SHI) funds.

The DAPI is a non-profit organisation active in the areas of pharmacoeconomics and pharmacoepidemiology. It is engaged in the appraisal of medicines and drug supply; its objectives are to perform and to support science and research and to support public health.[55]

The DAPI receives anonymized claims data on a monthly basis since 2000 from six major data processing centers (the so called “Rechenzentren”) in Germany since 2000. Community pharmacies transmit prescriptions to data processing centers for billing purposes. The anonymized prescription data is then fed into the DAPI data warehouse and linked with information from the ABDATA database (by the Avoxa - Mediengruppe Deutscher Apotheker GmbH[56]) via the product code (PZN, "Pharmazentralnummer"), a unique identifier for medicinal products.
The DAPI data warehouse contains consolidate prescription data about selected details of the insured person, on the prescribed product’s unified product code, the date of prescription, the number of prescribed packages per item as well as details on the prescribed products, such as, but not limited to, name, active ingredient(s), strength, pharmaceutical form, route of administration, package size, price, and pharmaceutical company.[55] Allocation of active ingredients was based on the official version of the Anatomical Therapeutic Chemical (ATC) classification system published by the German Institute of Medical Documentation.[57] The analysis data was retrieved from the DAPI data base by using Structured Query Language, the data base programming language.

All claims data from a representative sample of more than 80% (until June 2019) and more than 95% (from July 2019 onwards) of the community pharmacies are available in the DAPI data warehouse. The data were extrapolated by DAPI to 100% of the

population insured by the SHI covering 88% of Germany's population i.e., approximately 73.3 million people. Extrapolation is done by regional factors to mediate variations in the coverage across the different German regions. Until June 2019, regional factors were calculated by dividing the number of community pharmacies by the number of pharmacies covered by the DAPI database in the respective region. From July 2019 onwards, regional factors were calculated by dividing the number of dispensed packages reported by a federal information system about SHI-covered prescriptions known as GAmSi (GKV-Arzneimittel-Schnellinformation)[58] by dispensed packages in the DAPI database in the respective region. As the claims data in the data warehouse only comprises dispensings by community pharmacies at the expense of the statutory health insurance, prescriptions for privately insured patients (about 9% of the German population[59]) are not covered. Information about OTC drugs and drugs dispensed to patients during hospitalization are also not contained in the warehouse. Furthermore, data on the indication, treatment duration, or dosages as well as data on individual patients are not available.[60]

2.5 Utilization reporting parameters

The time course of utilization for hydroxychloroquine, RAASi, azithromycin, simvastatin and atorvastatin, pneumococcal vaccines, ibuprofen and lopinavir–ritonavir as well as for the reference drugs was analysed from January 2020 to June 2020. The observation period was divided into three periods:

A) from January 1, 2020 until the week of March 16–22; on March 22, nationwide restrictions on public and social life were implemented
B) from March 23–29 until April 13–19, 2020; during nationwide restrictions
C) from April 20 until the end of June 30, 2020; the period after first restrictions were lifted

By compartmentalizing the observation period, the effects of political implementations on public and social life can be connected to the influence of the spreading of (mis-)information on the course of drug utilizations.

Drug utilizations were investigated and are presented as dispensings analysed by number of packages dispensed per week (according to the ATC code level 5) as a suitable reporting parameter. For pneumococcal vaccines, utilizations were calculated as dispensed vaccine doses per week (by multiplying the number of dispensed packages with the contained doses per package). Weeks are written as the dates from Monday to Sunday of the weeks concerned.
The daily course of utilization was ruled out as a suitable reporting parameter, as it can fluctuate heavily and therefore be difficult to analyse and interpret. Instead, weekly utilization data was aggregated.

To have a comparison and to ascertain pre-pandemic utilizations, the utilizations of the analysed drugs were collected for the time period from January 1 to June 30, 2019 as reference value. The percentage change in number of utilized packages from January to June 2020 in comparison to 2019 was then evaluated.
Dispensing data from 2020 and 2019 were matched by weeks in consideration of public holidays to account for differences in week lengths between the two compared years. The weeks were matched taking into account the Christian public holidays of Easter and Pentecost. With Easter and Pentecost in 2020 falling a week earlier in the year, the calendar week numbers for 2020 were matched to the following calendar week number in 2019 (week number of 2020 +1). After this matching, the remaining weeks in 2019 and 2020, respectively, which still show different numbers of workdays (because of an unreligious, fixed public holiday), were aligned and adjusted by extrapolation.

The distribution of the package sizes per analysed drug from January to June 2020 compared to January to June 2019 was determined to rule out possible bias due to different amount of drugs per package in both evaluation periods. In practice, physicians usually prescribe one standard pack size N3 per quarter for the therapies of chronically ill patients (i.e., mostly 100 tablets), while the small package size N1 and medium package size N2 (10 to 20 tablets and most often 50 tablets, respectively) are usually prescribed for short term, acute therapies or therapy adjustments.
Furthermore, the data on dispensed packs of the study drugs with defined daily doses[61] per 1,000 SHI-insured persons per day (DID) was analysed to rule out differences between packages and DID as utilization parameters. The number of persons insured

by the SHI system was obtained from the Federal Ministry of Health.[62] As a possible indicator for stockpiling before restrictions on public and social life came into effect, the growth rate of prescription of the study drugs was investigated. The growth rate was calculated by comparing the percentage rate of prescriptions with more than one package per drug prescribed, as well as the percentage of prescriptions with over 100 dispensed units per prescription from March 2020 to the one from March 2019.

For all study drugs included, weekly utilizations at the expense of the statutory health insurance were included. Additionally, for ibuprofen and paracetamol, to fully cover all utilizations, monthly utilizations at the expense of the private health insurance (PHI) as well as OTC utilizations from the INSIGHT Health database[63] were included, in addition to the expenses to the SHI funds. This is because those drugs are widely used without a prescription and cand be interpreted as a proximate representation of patients' purchasing behaviour, potentially in connection with the WHO statement regarding ibuprofen. The INSIGHT Health database includes extrapolated data from a representative sample of over 4,500 community pharmacies. Data from this database was provided by the ABDA, the umbrella organisation of all pharmacists in Germany.

3 Results

3.1 Package size distribution and package dispensing in 2020 compared to 2019

There were no high percentage differences in proportions of package sizes in the analysed drugs in January to June 2020 compared to January to June 2019 (Table 1), neither for the study drugs nor for the reference drugs. When considering all prescription drugs, minimally more N3 packages were distributed (+3%) and minimally fewer N1 (-2.4%) and N2 (-0.6%) from January to June 2020. The total number of all distributed packages in the first half of 2019 and 2020 did not deviate much (+1.5% in 2019, packages dispensed in 1–6/2019: 327.2 million, packages dispensed in 1–6/2020: 322.3 million). All included study drugs as well as the reference drugs showed similar discrepancies in the differences of package size proportions.

For hydroxychloroquine, only N3 packages were distributed with -0.4% difference in proportions in January to June 2020 compared to January to June 2019. Though, in the first half of 2020, 16.0% more packages of hydroxychloroquine were dispensed compared to the first half of 2019.

The total amount of dispensed packages for all systematic antibiotics decreased by 19.9% from 17.4 million from January to June 2019 to 13.9 million from January to June 2020. This development can be observed in the analysed individual antibiotics azithromycin (-26.3% in 1–6/2020 compared to 1–6/2019), amoxicillin (-22.0%), cefuroxime (-26.1%) and ciprofloxacin (-28.1%) as well. For all analysed individual antibiotics as well as for all systematic antibiotics the difference in package size proportions between January to June 2019 and January to June 2020 was very little to none (from 1.9% to -1.8%).

Ibuprofen showed the highest differences in package size proportions of all study drugs (despite lopinavir–ritonavir, though number of dispensed packages were very low and therefore findings might be inconclusive) with -3.7% for N1 packages and +2.5% for N2 packages. In total, the dispensed packages for ibuprofen from January to June 2020 (11.9 million packages) were lower by 12.5% compared to January to June 2019 (13.6 million packages).

While the number of dispensed packages for RAASi as well as for simvastatin and atorvastatin increased by 3.6% each in January to June 2020 compared to January to June 2019 (RAASi: from 29.6 to 30.6 million packages; simvastatin and atorvastatin: from 10.1 to 10.4 million packages), the distribution in package size proportion was quite similar within the two compared time periods.

TABLE 1 Distribution of package sizes of drugs from January to June 2020 compared to January to June 2019

Drug	Package Size	Packages dispensed in 1–6/2019 [in thousand]	Packages dispensed in 1–6/2020 [in thousand]	Proportion among all package sizes in 1–6/2019	Proportion among all package sizes in 1–6/2020	Difference of proportions between 1–6/2020 and 1–6/2019
All prescription drugs	N1	65,257.8	56,323.3	19.9%	17.5%	-2.4%
	N2	61,996.9	59,065.5	18.9%	18.3%	-0.6%
	N3	188,141.7	195,120.3	57.5%	60.5%	3.0%
	Other	11,807.7	11,768.3	3.6%	3.7%	0.1%
	All package sizes	327,204.1	322,277.4	100.0%	100.0%	0.0%
Hydroxychloroquine	N3	131.3	151.5	97.0%	96.6%	-0.4%
	Other	4.1	5.4	3.0%	3.4%	0.4%
	All package sizes	135.3	156.9	100.0%	100.0%	0.0%
RAAS inhibitors	N1	490.8	418.3	1.7%	1.4%	-0.3%
	N2	960.7	1,009.3	3.2%	3.3%	0.1%
	N3	28,029.0	29,066.1	94.8%	94.9%	0.1%
	Other	86.0	147.7	0.3%	0.5%	0.2%
	All package sizes	29,566.6	30,641.4	100.0%	100.0%	0.0%
Simvastatin/ atorvastatin	N1	122.0	113.4	1.2%	1.1%	-0.1%
	N2	258.5	226.0	2.6%	2.2%	-0.4%
	N3	9,673.7	10,075.5	96.2%	96.7%	0.5%
	Other	0.0	0.0	0.0%	0.0%	0.0%
	All package sizes	10,054.2	10,414.9	100.0%	100.0%	0.0%
Lopinavir - ritonavir	N1	0.3	0.3	9.6%	10.9%	1.3%
	N2	1.2	0.8	37.7%	32.0%	-5.7%
	N3	1.7	1.4	52.2%	54.6%	2.4%
	Other	0.0	0.1	0.6%	2.5%	1.9%
	All package sizes	3.2	2.6	100.0%	100.0%	0.0%
Systemic antibiotics	N1	9,717.0	7,674.0	55.9%	55.1%	-0.8%
	N2	5,713.3	4,679.2	32.9%	33.6%	0.7%
	N3	1,191.7	958.7	6.9%	6.9%	0.0%
	Other	759.3	617.7	4.4%	4.4%	0.0%
	All package sizes	17,381.3	13,929.5	100.0%	100.0%	0.0%
Azithromycin	N1	1,066.7	766.8	73.9%	72.1%	-1.8%
	N2	365.5	289.6	25.3%	27.2%	1.9%
	N3	10.3	7.1	0.7%	0.7%	0.0%
	Other	0.0	0.0	0.0%	0.0%	0.0%
	All package sizes	1,442.5	1,063.5	100.0%	100.0%	0.0%
Amoxicillin	N1	1,205.5	949.7	36.7%	37.1%	0.4%
	N2	1,787.5	1,380.1	54.5%	53.9%	-0.6%
	N3	282.7	225.2	8.6%	8.8%	0.2%

Drug	Package Size	Packages dispensed in 1–6/2019 [in thousand]	Packages dispensed in 1–6/2020 [in thousand]	Proportion among all package sizes in 1–6/2019	Proportion among all package sizes in 1–6/2020	Difference of proportions between 1–6/2020 and 1–6/2019
	Other	5.2	3.1	0.2%	0.1%	-0.1%
	All package sizes	3,280.9	2,558.1	100.0%	100.0%	0.0%
Cefuroxime	N1	1,634.0	1,202.0	80.2%	79.9%	-0.3%
	N2	270.1	189.6	13.3%	12.6%	-0.7%
	N3	1.2	1.0	0.1%	0.1%	0.0%
	Other	131.3	111.5	6.4%	7.4%	1.0%
	All package sizes	2,036.5	1,504.1	100.0%	100.0%	0.0%
Ciprofloxacin	N1	676.9	481.1	70.5%	69.8%	-0.7%
	N2	241.4	175.2	25.2%	25.4%	0.2%
	N3	26.8	22.1	2.8%	3.2%	0.4%
	Other	14.5	11.0	1.5%	1.6%	0.1%
	All package sizes	959.6	689.4	100.0%	100.0%	0.0%
Ibuprofen	N1	7,554.4	6,162.9	55.7%	52.0%	-3.7%
	N2	3,727.3	3,554.6	27.5%	30.0%	2.5%
	N3	1,926.5	1,844.0	14.2%	15.6%	1.4%
	Other	344.0	296.9	2.5%	2.5%	0.0%
	All package sizes	13,552.2	11,858.4	100.0%	100.0%	0.0%
Paracetamol	N1	1,631.5	1,407.0	79.4%	77.2%	-2.2%
	N2	290.8	281.0	14.2%	15.4%	1.2%
	N3	98.7	101.9	4.8%	5.6%	0.8%
	Other	33.7	32.0	1.6%	1.8%	0.2%
	All package sizes	2,054.7	1,821.8	100.0%	100.0%	0.0%

Abbreviations: N1, N2, N3, norm size package small (N1 i.e., 10 to 20 tablets), medium (N2 i.e., 50 tablets), and large (N3 i.e., 100 tablets); RAAS, renin-angiotensin-aldosterone system.

3.2 Defined daily doses per 1 000 statutory health insurance-insured persons

There were no high percentage differences in the weekly time courses between the defined daily doses per 1 000 SHI-insured persons (DID) and utilizations expressed as packages (Table 2). All observed differences over all study drugs were between -0.53% and +1.49%, and thus very small.

3.3 Growth rate of prescriptions, March 2020 compared to March 2019

The growth rate of prescription was analysed as a possible indicator of stockpiling and calculated by comparing prescription rates from March 2020 to March 2019.

An increase in the growth rate of prescriptions, measured by prescriptions with more than one hundred dispensed units per prescription was considerable for paracetamol (+35.8%), RAASi (+32.0%), ibuprofen (+30.9%), simvastatin/ atorvastatin (+10.4%) and hydroxychloroquine (+5.7%). Azithromycin showed a very low number of prescriptions with over one hundred dispensed units and is therefore not an indicative growth rate. Lopinavir-ritonavir showed a small change in the growth rates (+0.4%) (Table 3a).

The growth rate of prescriptions, measured by prescriptions with more than one package per prescription, increased for ibuprofen (+119.8%), azithromycin (+69.1%), RAASi (+32.0%), paracetamol (+17.9%), simvastatin/ atorvastatin (+7.9%) and hydroxychloroquine (+7.3%). Lopinavir-ritonavir showed a low number of prescriptions, on which more than one package per prescription was dispensed. Therefore, the growth rate for lopinavir-ritonavir is not indicative (Table 3b).

TABLE 2 Weekly dispensed drugs before (Period A), during (Period B), and after (Period C) the first COVID-19 pandemic wave and relative change from 2019, expressed as DID

Drug	January 6 - 12	…	February 24 - March 1	March 2 - 8	March 9 - 15	March 16 - 22	March 23 - 29	March 30 - April 5	April 6 - 12	April 13 - 19	April 20 - 26	April 27 - May 3	May 4 - 10	…	June 22 - 28
	Period A						Period B				Period C				
Hydroxychloroquine															
Change from 2019, %	-0.1%		0.3%	0.2%	0.4%	1.1%	0.4%	0.1%	0.1%	0.2%	0.0%	0.1%	0.0%		-0.1%
DID dispensed	0.32		0.35	0.41	0.42	0.62	0.46	0.39	0.31	0.27	0.36	0.30	0.34		0.32
RAAS inhibitors															
Change from 2019, %	0.07%		0.14%	0.24%	0.34%	0.81%	-0.08%	-0.11%	-0.11%	0.00%	-0.16%	-0.10%	-0.07%		-0.19%
DID dispensed	424.66		363.71	464.36	462.62	588.81	365.66	359.40	288.68	266.04	363.98	300.43	356.27		350.74
Simvastatin/ atorvastatin															
Change from 2019, %	0.08%		0.13%	0.20%	0.30%	0.80%	-0.09%	-0.08%	-0.08%	0.03%	-0.14%	-0.08%	-0.05%		-0.19%
DID dispensed	103.98		87.24	110.71	110.41	140.08	89.30	90.03	72.31	66.76	90.40	74.14	88.85		85.81
Lopinavir - ritonavir															
Change from 2019, %	-0.19%		-0.24%	-0.20%	0.25%	0.50%	-0.17%	-0.20%	-0.10%	-0.23%	-0.36%	0.06%	-0.31%		-0.43%
DID dispensed	0.01		0.01	0.01	0.01	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.01		0.01
Systemic antibiotics															
Change from 2019, %	-0.01%		0.00%	0.00%	0.07%	0.01%	-0.26%	-0.36%	-0.39%	-0.37%	-0.44%	-0.30%	-0.37%		-0.23%
DID dispensed	13.01		12.80	13.82	13.56	12.36	9.19	7.76	6.34	5.54	6.71	6.09	6.72		7.83
Azithromycin															
Change from 2019, %	0.03%		0.04%	0.04%	0.11%	0.01%	-0.28%	-0.43%	-0.48%	-0.46%	-0.53%	-0.40%	-0.49%		-0.32%
DID dispensed	0.73		0.71	0.79	0.74	0.64	0.47	0.35	0.23	0.17	0.20	0.16	0.17		0.16
Amoxicillin															
Change from 2019, %	0.03%		0.04%	0.04%	0.11%	0.01%	-0.28%	-0.43%	-0.48%	-0.46%	-0.53%	-0.40%	-0.49%		-0.32%
DID dispensed	2.93		3.01	3.21	3.10	2.72	1.89	1.49	1.17	1.01	1.15	1.04	1.10		1.26
Cefuroxime															

Drug	January 6 - 12	…	February 24 - March 1	March 2 - 8	March 9 - 15	March 16 - 22	March 23 - 29	March 30 - April 5	April 6 - 12	April 13 - 19	April 20 - 26	April 27 - May 3	May 4 - 10	…	June 22 - 28
Change from 2019, %	0.01%		-0.05%	-0.03%	0.05%	0.01%	-0.27%	-0.39%	-0.43%	-0.46%	-0.50%	-0.38%	-0.45%		-0.37%
DID dispensed	2.12		2.00	2.15	2.07	1.90	1.39	1.14	0.92	0.79	0.93	0.83	0.90		0.97
Ciprofloxacin															
Change from 2019, %	-0.39%		-0.34%	-0.35%	-0.29%	-0.28%	-0.38%	-0.30%	-0.12%	-0.05%	-0.18%	-0.03%	-0.08%		-0.12%
DID dispensed	0.34		0.32	0.34	0.35	0.35	0.30	0.29	0.25	0.23	0.28	0.25	0.29		0.28
Pneumococcal vaccines															
Change from 2019, %	-0.16%		0.82%	0.96%	3.70%	2.66%	2.20%	1.35%	0.54%	0.22%	0.10%	1.49%	2.93%		0.41%
DID dispensed	0.14		0.18	0.24	0.59	0.69	0.44	0.31	0.15	0.11	0.16	0.30	0.60		0.18

Abbreviations: DID, defined daily doses per 1000 statutory health insurance-insured persons per day; RAAS, renin-angiotensin-aldosterone system

TABLE 3 Growth rate of prescriptions of the study drugs (reference drugs excluded), March 2020 in comparison to March 2019

A. Prescriptions with over 100 dispensed units (tablets, pills, capsules, …) per prescription

Study Drug	Number of prescriptions with > 100 dispensed units in March 2019	Number of prescriptions with > 100 dispensed units in March 2020	Number of all prescriptions in March 2019	Number of all prescriptions in March 2020	Rate [%] of prescriptions with > 100 dispensed units from all prescriptions in March 2019	Rate [%] of prescriptions with > 100 dispensed units from all prescriptions in March 2020	Growth rate of prescriptions with > 100 dispensed units (March 2020 vs March 2019)
Hydroxychloroquine	1,070	2,098	17,303	32,111	6.18	6.53	5.66
RAAS inhibitors	87,045	161,646	3,753,527	6,132,985	4.55	5.24	31.95
Simvastatin/ atorvastatin	2,485	4,386	1,306,605	2,090,335	0.19	0.21	10.36
Lopinavir - ritonavir	354	442	370	460	95.68	96.09	0.43
Azithromycin	8	8	220,401	254,798	0.00	0.00	-13.89
Ibuprofen	1,011	1,642	1,923,217	2,386,906	0.05	0.07	30.86
Paracetamol	192	350	289,465	388,557	0.07	0.09	35.75

B. Prescriptions with more than one package per prescription

Study Drug	Number of prescriptions with > 1 dispensed packages in March 2019	Number of prescriptions with> 1 dispensed packages in March 202020	Number of all prescriptions in March 2019	Number of all prescriptions in March 2020	Rate [%] of prescriptions with > 1 dispensed packages from all prescriptions in March 2019	Rate [%] of prescriptions with> 1 dispensed packages from all prescriptions in March 2020	Growth rate of prescriptions with > 1 dispensed packages (March 2020 vs March 2019)
Hydroxychloroquine	1,073	2,137	17,303	32,111	6.20	6.66	7.32
RAAS inhibitors	87,045	161,646	3,753,527	6,132,985	4.55	5.24	31.95
Simvastatin/ atorvastatin	2,623	4,526	1,306,605	2,090,335	0.20	0.22	7.87
Lopinavir - ritonavir	38	37	370	460	10.27	8.04	-21.68
Azithromycin	2,843	5,559	220,401	254,798	1.29	2.18	69.14
Ibuprofen	4,667	12,731	1,923,217	2,386,906	0.24	0.53	119.83
Paracetamol	6,035	9,551	289,465	388,557	2.08	2.46	17.90

3.4 Course of utilizations

3.4.1 All prescription drugs

Until the week of February 17–23, 2020 utilization of all prescription drugs remained more or less at 2019 levels, with only a slight increase (+2.0%). During the remaining of period A before implementations on public and social life, utilization increased continuously in comparison with 2019, from +7.8% in week February 24–March 1 with 12.9 million packages over +18.8% in week March 9–15 with 15.3 million packages and finally peaked at 17.6 million packages per week (+42.9%) from March 16–22.

Subsequently, utilizations decreased below the level of 2019 during period B, during nationwide restrictions. Utilizations decreased by -18.1% during week March 30–April 5 to 12.1 million packages to 9.0 million packages per week during week April 13–19 (-7.4% compared to 2019 utilizations) compared to the respective weeks of 2019.

At the beginning of period C after first restrictions were lifted, utilizations increased slightly to 12.1 million packages dispensed per week, still a -18.0% reduction compared to 2019 levels, though differences in utilizations in 2020 slowly rose back to 2019 values after that. Utilizations first reached 2019 levels in week June 15–22 with 13.1 million packages dispensed per week (+2.8% compared to 2019).

3.4.2 Hydroxychloroquine

At the beginning of period A, utilizations of hydroxychloroquine remained at a similar level compared to 2019 with 5,572 (-4.9%) to 5,809 (+6.4%) dispensed packages between the weeks of January 6–12 and February 17–23, 2020, respectively. However, the total number of utilizations was low. Utilizations started rising from February 24 – March 1 with +32.2% compared to 2019 and 6,123 packages dispensed and further increased to +109.9% and 10,726 packages utilized per week at the end of period A.

With the beginning of period B, utilizations decreased from 7,956 packages per week (with still +38.7% compared to the respective week in 2019) during the week of March 23–29 to 4,732 packages per week at the end of period B in week April 13–19, while remaining at +22.1% dispensed packages per week compared to 2019 (Table 4, Figure 2a).

In period C, utilizations remained above the levels of 2019 with +3.5% (6,349 packages during April 20–26) and +10.7% (5,309 packages during April 27–May 3). Utilizations first dropped below 2019 levels within the week of June 1–7. At the end of period C, hydroxychloroquine evened out around 2019 levels.

3.4.3 Renin-angiotensin-aldosterone system inhibitors (RAASi)

During January 6–12, the beginning of the observation period, 1.36 million packages of RAASi were dispensed (+5.8% above this week's 2019-levels). Until week February 17–23, utilization remained at these levels compared to 2019 (+5%). From week 2–8, utilizations started to increase to 1.5 million packages dispensed per week (+21.6%) and increased continuously until the end of period A to 1.88 million packages dispensed per week with +77.9% compared to 2019 levels. Subsequently, utilizations decreased with the beginning of period B and remained below the level of 2019 (Table 4, Figure 2a) throughout with 1.19 million packages dispensed in the week March 23–29 (-8.8%) and 935,700 packages in the week April 6–12 (-11.5% compared to 2019 levels). During period C, utilizations first reached similar prior-year levels during week June 8–14 with 1.06 million dispensed packages (+0.8%).

3.4.4 Statins, lopinavir–ritonavir

Simvastatin and atorvastatin, similar to RAASi and all prescription drugs, showed comparable weekly utilizations at the beginning of period A and throughout with 467,600 dispensed packages in the week January 6–12 (+5.7%) to 494,600 packages in the week March 2–8 (+17.6%) to finally peaking at 623,000 packages per week (+74%) from March 16–22. Utilizations then dropped to 398,800 (-11.2%) at the beginning of period B in week March 23–29 and to 405,500 packages (-15%) at the beginning of period C in week April 20–26. Utilization approximated to 2019 values until the end of the observation period (Table 4, Figure 2a).

The amount of ambulatory dispensed packages of lopinavir–ritonavir was very low (approximately 102 packages per week) and did not show any differences between 2020 and 2019 (Table 4).

3.4.5 Antibiotics

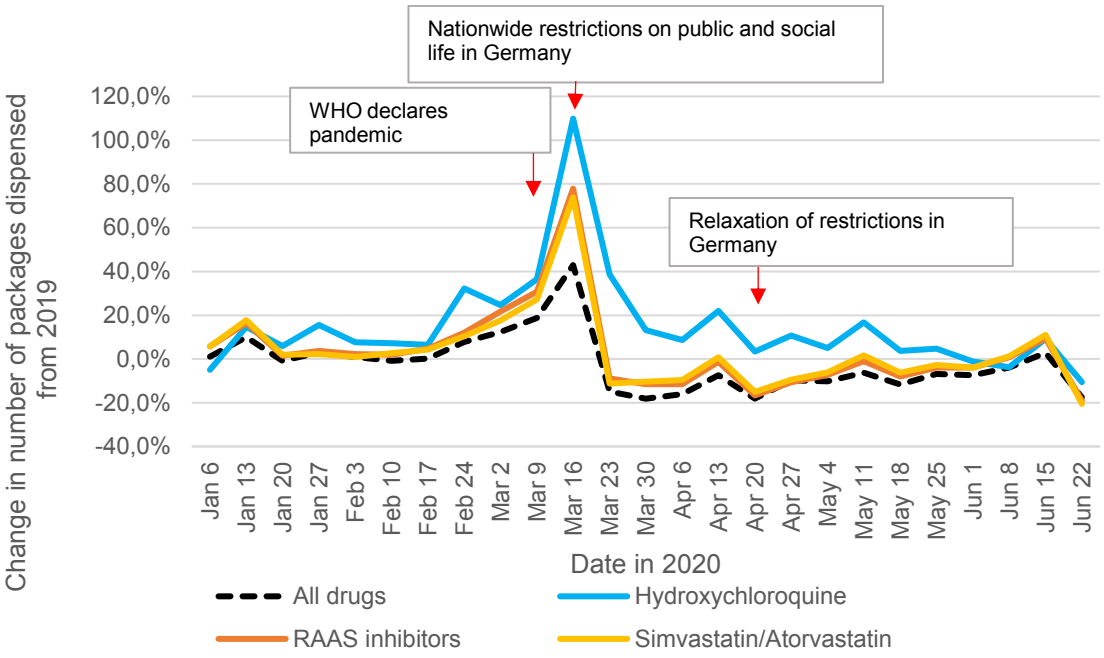
During period A, azithromycin utilizations slightly increased to 77,400 packages (+9%) in the week March 2–8 and 72,000 packages (+16%) in the week March 9–15. Amoxicillin use increased to 159,700 packages (+6%) and 154,200 packages (+11%) in the weeks of March 2–8 and March 9–15 (Table 4, Figure 2b). After implementation

of restrictions, dispensing levels of all analysed antibiotics decreased to values substantially lower than in 2019. All systemic antibiotics dropped from 780,700 packages during week March 2–8 -37%, azithromycin -58%, amoxicillin -48%, and cefuroxime -47%, at the end of period B in week April 13–19. Ciprofloxacin use, which was markedly reduced in the first quarter of 2020 compared to 2019 (-37%), returned to slightly below 2019 levels during period C (average: -6%) (Table 4).

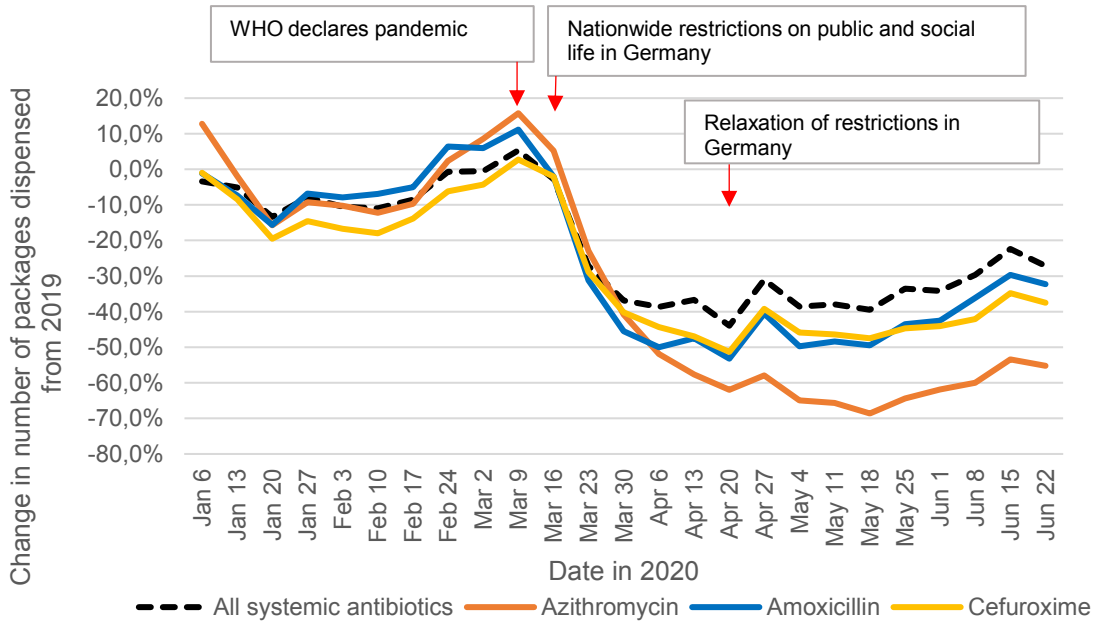
FIGURE 2 Dispensings of prescription drugs before, during, and after the first COVID-19 pandemic wave. Relative change in weekly dispensings in 2020, compared to 2019.

Each date on the x-axis refers to the first day of the week.

A. All prescription drugs, hydroxychloroquine, RAAS inhibitors, and simvastatin/ atorvastatin



B. All systemic antibiotics, azithromycin, amoxicillin, and cefuroxime



Abbreviations: RAAS, renin-angiotensin-aldosterone system; WHO, World Health Organisation.

3.4.6 Pneumococcal vaccines

In the course of period A until the week of February 17–23, utilization of pneumococcal vaccines hovered around 2019 levels with an average of 73,200 doses per week. Utilizations then substantially increased to 302,700 doses (+373%) and peaked at 350,500 doses (+268%) at the end of period A. After decreasing back to 58,400 doses, still +23% compared to 2019, utilization increased again to 306,000 doses (+294%) during week May 4–10, then decreased again (Table 4, Figure 3).

FIGURE 3 Dispensings of pneumococcal vaccine doses before, during, and after the first COVID-19 pandemic wave. Relative change in weekly dispensings in 2020, compared to 2019.

Each date on the x-axis refers to the first day of the week.

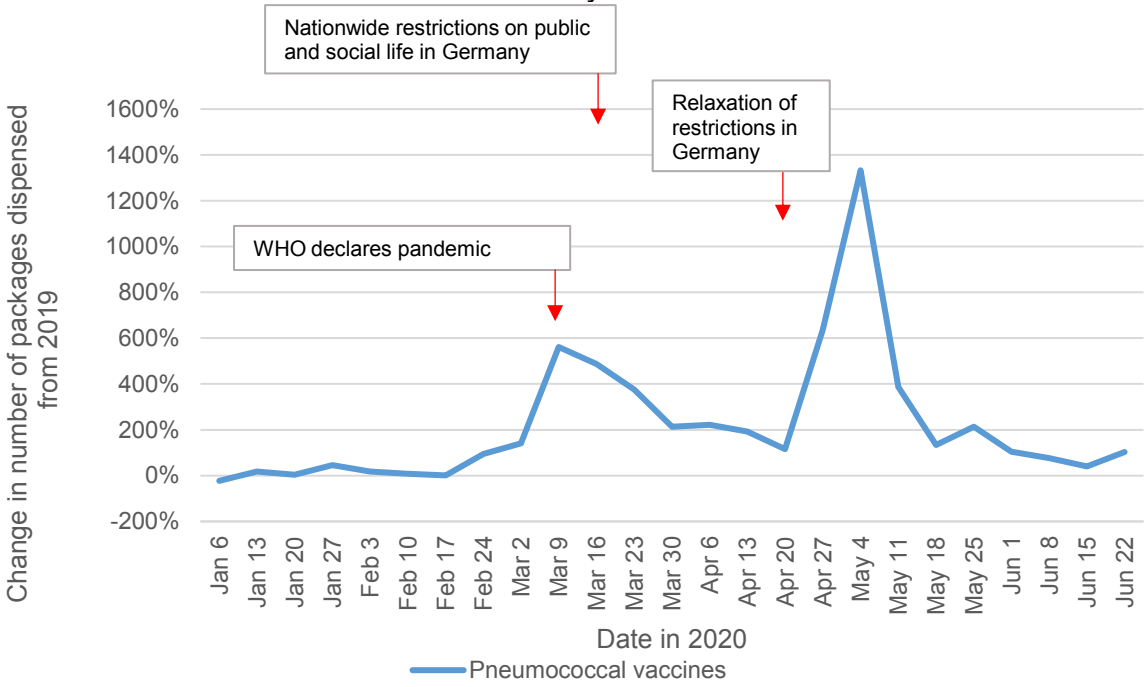


TABLE 4 Weekly dispensed drug packages before (Period A), during (Period B), and after (Period C) the first COVID-19 pandemic wave and relative change from 2019

Drug	January 6 - 12	…	February 24 - March 1	March 2 - 8	March 9 - 15	March 16 - 22	March 23 - 29	March 30 - April 5	April 6 - 12	April 13 - 19	April 20 - 26	April 27 - May 3	May 4 - 10	…	June 22 - 28
	Period A						Period B				Period C				
All prescription drugs															
Change from 2019, %	1.0%		7.8%	12.3%	18.8%	42.9%	-14.9%	-18.1%	-16.1%	-7.4%	-18.0%	-9.7%	-10.3%		-17.6%
Packages dispensed	14,331,957		12,878,475	15,360,267	15,297,938	17,612,702	12,062,613	11,734,236	9,737,995	8,992,123	12,093,385	10,205,599	11,897,790		11,647,779
Hydroxychloroquine															
Change from 2019, %	-4.9%		32.2%	24.7%	36.5%	109.9%	38.7%	13.2%	8.7%	22.1%	3.5%	10.7%	5.1%		-10.6%
Packages dispensed	5,572		6,123	7,036	7,344	10,726	7,956	6,710	5,365	4,732	6,349	5,309	6,206		5,592
RAAS inhibitors															
Change from 2019, %	5.8%		12.0%	21.6%	30.7%	77.9%	-8.8%	-11.5%	-11.5%	-1.3%	-16.6%	-10.7%	-7.2%		-19.0%
Packages dispensed	1,364,377		1,168,590	1,489,546	1,480,982	1,888,470	1,185,012	1,160,730	935,786	858,281	1,172,412	966,063	1,149,883		1,121,710
Simvastatin/ atorvastatin															
Change from 2019, %	5.7%		10.5%	17.6%	27.3%	73.9%	-11.2%	-10.3%	-9.6%	0.7%	-15.0%	-9.4%	-6.1%		-20.5%
Packages dispensed	467,600		390,065	494,644	493,013	622,989	398,868	402,012	324,179	298,297	405,450	330,941	397,744		382,767
Lopinavir - ritonavir															
Change from 2019, %	-22.9%		-19.0%	-25.5%	16.0%	43.0%	-9.4%	-25.5%	-22.2%	-15.7%	-29.9%	2.2%	-36.1%		-38.8%
Packages dispensed	121		124	108	116	143	125	108	98	75	101	79	99		85
Systemic antibiotics															
Change from 2019, %	-3.4%		-0.7%	-0.5%	5.3%	-2.8%	-27.2%	-36.8%	-38.7%	-36.7%	-44.0%	-31.1%	-38.6%		-27.2%
Packages dispensed	729,275		728,055	780,733	763,758	680,693	510,407	432,291	357,195	312,653	372,403	335,860	367,660		402,300
Azithromycin															
Change from 2019, %	12.8%		2.3%	8.5%	15.8%	5.2%	-22.9%	-40.8%	-51.9%	-57.6%	-62.0%	-58.0%	-65.0%		-55.3%
Packages dispensed	71,201		70,190	77,382	72,002	61,218	44,758	32,630	21,577	16,165	18,411	14,725	15,312		14,830

Amoxicillin															
Change from 2019, %	-1.2%		6.4%	5.9%	11.2%	-2.1%	-31.2%	-45.6%	-50.0%	-47.5%	-53.2%	-40.5%	-49.7%		-32.3%
Packages dispensed	138,658		151,755	159,660	154,216	132,104	90,030	70,135	55,803	48,302	55,306	50,344	53,725		62,032
Cefuroxime															
Change from 2019, %	-1.0%		-6.2%	-4.3%	2.7%	-2.0%	-28.9%	-40.2%	-44.4%	-46.9%	-51.3%	-39.2%	-45.9%		-37.5%
Packages dispensed	86,579		82,401	88,705	85,265	76,863	56,811	46,659	37,784	32,172	38,047	34,004	36,656		39,486
Ciprofloxacin															
Change from 2019, %	-40.9%		-35.3%	-35.7%	-31.5%	-31.6%	-40.8%	-30.9%	-9.6%	-1.8%	-17.2%	-2.0%	-6.1%		-10.0%
Packages dispensed	29,813		28,164	30,384	30,610	29,575	26,027	25,232	22,754	20,896	25,370	22,830	26,098		25,172
Pneumococcal vaccines															
Change from 2019, %	-15.4%		82.8%	96.9%	372.7%	267.7%	222.0%	136.2%	55.2%	22.6%	10.9%	150.5%	294.3%		42.0%
Doses dispensed	73,360		89,782	123,009	302,715	350,483	225,863	159,752	74,573	58,438	80,619	151,863	306,057		90,209

Abbreviation: RAAS, renin-angiotensin-aldosterone system.

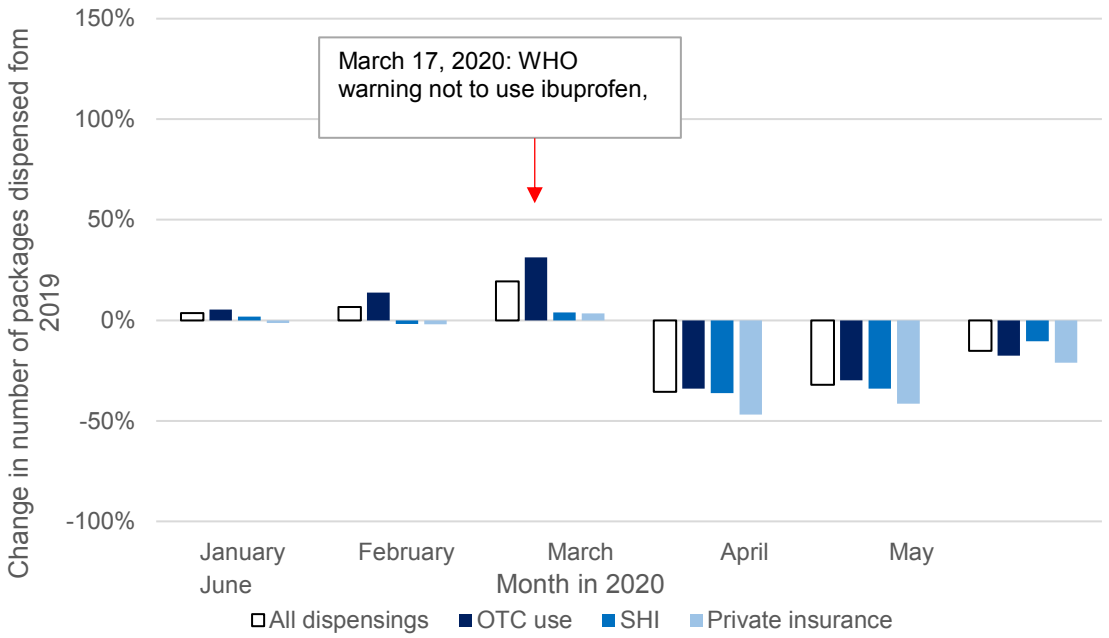
3.4.7 Ibuprofen and paracetamol

For ibuprofen and paracetamol, utilizations included SHI-, PHI-, and OTC dispensings. While the utilizations per month increased moderately for ibuprofen to 7.47 million packages in March 2020 with +19% compared to 2019, all paracetamol utilizations showed a huge increase with +111% to 8.04 million packages. These increases were mainly caused by the increase of OTC dispensings: +31% for ibuprofen with 4.66 million packages and +127% for paracetamol with 7.28 million packages.

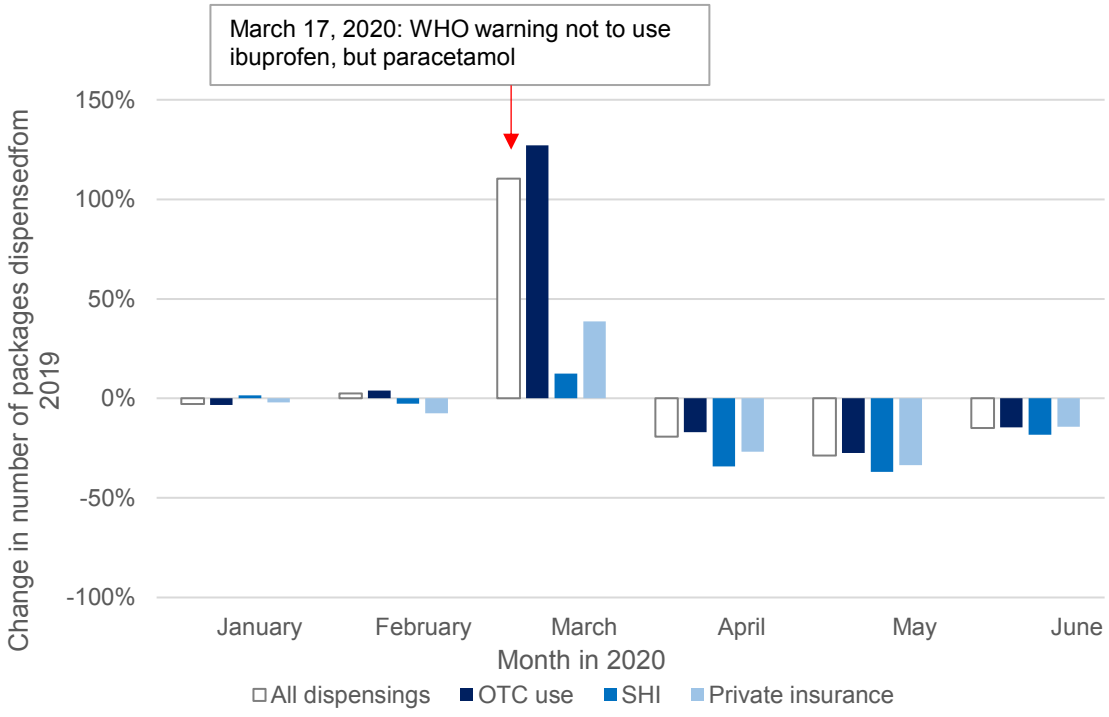
In April 2020, all utilized packages for both drugs decreased markedly in comparison to 2019; ibuprofen: 3.73 million, -36%; paracetamol: 2.64 million, -19%, and slowly recovered by June with 4.37 million dispensed packages for ibuprofen (-15%) and 2.29 million (-15%) for paracetamol. Decreases were evenly distributed among OTC dispensings as well as SHI- and PHI prescriptions (Table 5, Figure 4).

FIGURE 4 Dispensings of ibuprofen and paracetamol before, during, and after the first COVID-19 pandemic wave. Relative change in monthly dispensings January to June 2020, compared to 2019.

A. Ibuprofen



B. Paracetamol



Abbreviations: OTC, over-the-counter (drug); SHI, statutory health insurance.

TABLE 5 Monthly dispensings of ibuprofen and paracetamol from January to June 2020

A. Ibuprofen

Ibuprofen	January	February	March	April	May	June
OTC	3,597,354	4,022,403	4,657,881	2,188,182	2,272,510	2,521,809
SHI	2,530,391	2,506,373	2,440,847	1,370,304	1,431,638	1,641,885
PHI	379,558	403,379	373,825	168,396	176,477	202,889
Total	6,507,303	6,932,155	7,472,553	3,726,882	3,880,625	4,366,583

B. Paracetamol

Paracetamol	January	February	March	April	May	June
OTC	3,298,893	3,607,558	7,280,035	2,298,097	1,871,681	1,957,676
SHI	400,980	413,921	410,980	200,989	191,492	211,746
PHI	261,388	275,553	344,126	142,123	117,067	124,222
Total	3,961,261	4,297,032	8,035,141	2,641,209	2,180,240	2,293,644

Abbreviations: OTC, over-the-counter (drug); PHI, private health insurance; SHI, statutory health insurance.

4 Discussion

4.1 Drug utilization overall

The aim of the study was to investigate the course of utilizations during the first pandemic wave and examine potential influencing factors on the utilization course.

All in all, the study demonstrates that drug prescribing, purchasing, utilization, and utilization behaviour was significantly altered, particularly during the first weeks of the COVID-19 pandemic in early 2020, possibly influenced by misinformation and speculation about potential treatment efficacy as well as hypothetical concerns about harmfulness of commonly used drugs.[11,39,64,4,65,32,66] Further potential influencing factors on the course of utilizations can be, amongst others, stockpiling, as well as the interruption of production and supply chains, and political implementations on public and social life. The following paragraph will discuss the main study finding, discuss potential influencing factors and explore possible explanations on the course of the utilizations.

4.1.1 Stockpiling

As mentioned above, several factors could have potentially affected the course of utilization, besides the dissemination of conflicting information and speculation concerning the study drugs. The observed peak of drug utilization of all prescription drugs at the end of period A i.e., March 16–22 indicates stockpiling and was most likely caused by the anticipated intensification of nationwide restrictions on public life and social interactions and, hence, concerns with regard to continuous drug supply. With a growing fear of imminent social restrictions and disruptions of supply chains, stockpiling became a general phenomenon of the pandemic as it was also observed for goods and essential products, such as toilet paper and groceries, during the first wave of the pandemic.[67]

The total time course for utilization data of all prescription drugs in 2020 supports the hypothesis of initial stockpiling. However, the data reveal that the number of all packages dispensed from January to June 2020 differed from 2019 by only -2%, showing that the initial increase was compensated by a subsequent decrease.

Utilization data of RAASi, hydroxychloroquine, as well as simvastatin and atorvastatin show a similar course to all prescribed drugs, again indicating initial stockpiling and having no signs of under-prescribing within those drug groups.

Since prescription only drugs (with the exception of ibuprofen and paracetamol) were analysed, the peak in dispensed packages at the end of period A stems from an increase in prescribed packages. It may be assumed that patients prematurely contacted their prescribers to issue new prescriptions before actually needing to (since already receiving a N3 package within this quarter) to issue new prescriptions with the intention of stockpiling. Also, physicians may have prescribed multiple packages with the intention to decrease the necessity for contact in the near future and potentially reducing patients fear of drug supply shortages. The latter is supported by the investigations of the growth rate of the prescriptions of the study drugs in March 2020 compared to March 2019. Theoretically, the number of patients in need for i.e. hydroxychloroquine for rheumatoid arthritis could have increased in the observations period and therefore could confound this study. Though looking at the total course of utilization, this seems unlikely to be the cause of change in utilization, since these were very abrupt and the changes in the overall course of utilizations can be aligned with the implementations on public and social life.

Reduced physician visits[68,69] and, subsequently, pharmacies under conditions of social interaction restriction correlate with the subsequent decrease of dispensings for all analysed drugs and therefore can be interpreted as one possible reason on the subsequent decrease of utilization, among other possible reasons such as drug shortages or the sufficient patients' supply due to previous stockpiling.

4.1.2 Interruption of production and supply chains

Supply chains all over the world were challenged by the pandemic, hampering reliable drug supply. (Short term-) drug shortages may have effected utilizations during the observation period due to interruption of production of pharmaceuticals and supply chains because of rising COVID-19 cases. Especially since a lot of pharmaceutical active ingredients are produced and manufactured in the by COVID-19 particularly affected region Wuhan (Hubei, China), where public and working life was severely limited and nearly stopped completely.[70] According to the Federal Institute for Drugs and Medical Devices (BfArM), 19 registered pharmaceutical drugs were produced in

the region of Wuhan in February 2020. 17 out of these drugs were classified as supply-relevant by the BfArM.[71]

A commentary published by Choo et al.[72] stated, that the usual supply chains are inadequate in pandemic times. As a possible approach, ensuring the availability of important medications to the public in crisis times, this commentary suggests a rearrangement of regulatory procedures and processes. Accordingly, active pharmaceutical ingredients should be produced by multiple manufacturers, ideally in different locations so that dependencies are spread evenly, and possible short comings can be balanced out. For this purpose, the expansion of domestic manufactures as 'backup' manufacturing should be considered to be more independent of imports. Choo et al. further suggested stockpiling of critically important medications to be mobilized to hospitals in need. To establish the need, a centralized tracking system should be established on the basis of patient caseload. Rapid and equitable supply shifts can then be implemented to the places in direct need.[26]

4.1.3 Use of drugs with positive reports on COVID-19

On March 17, hence immediately before the start of period B, a small clinical trial on COVID-19 treatment showed a positive effect of hydroxychloroquine and additional an benefit when adding azithromycin.[32] This report by Gautret et al. received high attention after being published in the *International Journal of Antimicrobial Agents*, even though it had major methodological issues. Despite the open-label, non-randomized study design, it was criticized that no robust clinical evidence on efficacy of hydroxychloroquine (in combination with azithromycin) was provided, as clinical efficacy cannot alone be established by the clearance of viremia, which was the chosen surrogate parameter in this study. An inadequate composition of controls and different procedures for determination of viral load among the controls as well as the large number of lost to follow-up was also criticized. Furthermore, it was noted that the number of patients included into the study was small and their symptoms did not represent an average hospitalized COVID-19 patient.[33] Several subsequent clinical trials falsified beneficial effects of chloroquine/hydroxychloroquine in the context of COVID-19 and even raised major safety concerns.[73,74,1]

Moreover, the EMA[75] and the BfArM[76] have warned of serious side effects, including cardiac arrhythmias and cardiac arrest due to prolongation of the QT interval (time from

the beginning of the QRS complex to the end of the T wave in the electrocardiogram). In addition to myocardial effects, hydroxychloroquine may cause neuropsychiatric disorders. According to the warning, chloroquine/hydroxychloroquine is also known to affect the liver, cause neuronal damage that can lead to seizures, and hypoglycemia.[75,76]

The data show that the time-course in prescription fills for hydroxychloroquine corresponded to the WHO declaring a global pandemic on March 11.[6] The data were also in line with an analysis by Vaduganathan et al. in the United States, which showed a relative increase in hydroxychloroquine prescription fills by more than 200% during week March 14–21. The analysis further found overall 483,425 excess chloroquine/hydroxychloroquine fills during a 10-week period from February 16 to April 25, 2020 compared to February 17 to April 27, 2019.[54]

The touting of hydroxychloroquine as a potential treatment against COVID-19 resulted in chronically ill patients with rheumatic diseases or SLE having issues filling their prescriptions. Patients without access to their treatment drugs possibly face a worsening in their state of health, i.e. flare-ups of rheumatic attacks or potentially development of irreversible organ damage.[77] A survey published in November 2020 aimed to assess the impact of drug shortages during the COVID-19 pandemic and discovered, that 2.1% of patients in European regions receiving chloroquine/hydroxychloroquine and 6.8% in American regions were unable to fill their prescriptions at their community pharmacies due to supply-/ drug shortages. Patients in African (26.7%) and Southeast Asian regions (21.4%) were even more affected by drug shortages and inadequate drug supplies.[78,79]

The BfArM reported a supply shortage for hydroxychloroquine sulfate 200 mg tablets from April to August 2020.[80] This drug shortage may have contributed to the observed subsequent decline in dispensings and may have affected patients with SLE or rheumatoid arthritis. To counteract this limited availability of hydroxychloroquine for chronically ill patients, on April 4, the BfArM issued a “recommendation” that hydroxychloroquine should only be prescribed with an approved indication documented on the prescription and in a maximum supply of 100 tablets.[76]

Despite the proposed beneficial effect of co-treatment of hydroxychloroquine with azithromycin,[32,1] prescriptions of azithromycin rose only slightly and in contrast to the

sharp increase in those of hydroxychloroquine, suggesting that off-label co-treatment was not prevalent in ambulatory care.

The combination of lopinavir–ritonavir was mainly administered to hospitalized patients with an COVID-19 infection.[42,81] The analysed data confirm this finding with only approximately 102 packages per week dispensed in German ambulatory care. Several randomized trials did not find significant clinical benefits or a reduction of viral load in patients hospitalized for COVID-19 and gastrointestinal adverse effects were more common in the lopinavir–ritonavir group.[42,43]

4.1.4 Use of drugs with conflicting information regarding risks for COVID-19

The results indicate an inconsistent impact on utilization of drugs with conflicting information regarding risks for or critical outcomes of COVID-19.

The data does not suggest an insufficient supply of patients with RAASi or statins during or after the first pandemic wave. Pharmacological blockade of the RAAS[44] with ACEi or ARB as well as low-density cholesterol lowering with statins reduces morbidity and mortality in various cardiovascular diseases, therefore sufficient supply and continuous medication intake by patients throughout is important.[82]

It was shown that RAASi may lead to upregulation of ACE2 expression/activity, and that, therefore, use of ACEi or ARB might be associated with an increased risk for and severity of COVID-19 infection.[39,4] Various studies investigated the association of hypertension, treatment with RAASi and developing severe COVID-19 disease progression. Although there was initial evidence for a difference in the severity of disease in a cohort in Wuhan, China,[45] several other studies concluded that the data is insufficient to recommend discontinuation of RAASi.[44,46] Moreover, robust evidence is strongly encouraging patients to continue ACEi or ARB pharmacotherapy during the COVID-19 pandemic.[46,83,30] Indeed, there is evidence suggesting that these medications might be rather protective against serious lung complications in patients with COVID-19 infection.[83,84] It was shown that COVID-19 patients are not characterized by major changes in RAS activity in plasma including ACE2 activity.[85]

A study showed an association of lower risk of all-cause mortality in in-hospital COVID-19 patients being treated with statins, compared to patients without statin

therapy.[39] It may be speculated, that this observation in a retrospective cohort study might have been influenced by confounding. Experts advise continuation of guideline-based statin therapy, but do not recommend routine intake for COVID-19 patients[41,40] without risk factors for atherosclerotic cardiovascular diseases. The analysed data indicates for the two most frequently used statins, simvastatin and atorvastatin, a sufficient supply during and after the first pandemic wave indicating that patients continued statin therapy despite public speculations.[86]

A study in diabetic rats found upregulation of ACE2 by ibuprofen, however, lower ACE2-levels were documented in the diabetic compared to healthy rats.[87] Other in vitro studies suggested ibuprofen may even facilitate cleavage of ACE2 from the membrane, preventing membrane-dependent viral entry into the cell.[29,31] In a nationwide register-based cohort study, there was no significant association between ibuprofen prescription claims and severe COVID-19.[88] Recently, ibuprofen use in COVID-19 patients was shown not to be associated with worsening clinical outcomes, compared with paracetamol or no antipyretic.[89] Hence, there is no experimental and clinical data demonstrating appropriate evidence to avoid ibuprofen in COVID-19 patients.[90]

The analysed data shows that recommendations on the avoidance for ibuprofen had a marginal impact on utilization. Dispensings for SHI and PHI prescriptions as well as OTC-use increased moderately in March but decreased in April, indicating similar stockpiling of ibuprofen to paracetamol, although a lot less pronounced. Though unconfirmed, recommendations to avoid intake of ibuprofen[65] and to prefer paracetamol may have resulted in a disproportional purchase of paracetamol drug products, as strongly supported by the data for March. The utilizations of ibuprofen suggest that misinformation of ibuprofen only had a minor impact on patients and prescribers into choosing paracetamol over ibuprofen, with utilization of ibuprofen remaining higher than paracetamol utilization, except for OTC products in March and April.

The BfArM[76] reported several supply shortages of paracetamol since March 2020, partially estimated to last until March and June 2021.[80] In accordance with the Federal Ministry of Health, the Drug Commission of German Pharmacists in March 2020 asked pharmacists to dispense and physicians to prescribe paracetamol only if needed and

to limit the number of tablets to treat the actual course of a disease.[91] This highlights the weakness of the distribution system and its vulnerability to sudden (justified) peaks in demands during pandemics. [92]

4.1.5 Use of antibiotics

Prescription fills for all systemic antibiotics, amoxicillin, cefuroxime as well as for azithromycin declined substantially (between -37% and -58%).

The data for azithromycin was unexpected and in contrast to hydroxychloroquine. One would expect for azithromycin to show a parallel course of utilization to hydroxychloroquine, as these two drugs in combination were discussed to be effective against COVID-19. Currently, there is no evidence of a beneficial use or effectiveness of azithromycin (in combination with hydroxychloroquin) at any disease stage of COVID-19.[1,73,93,94] Of note, the antiviral effects of azithromycin remain questionable.[68]

The sharp fall in antibiotic prescriptions compared to 2019, and in particular, the decline in prescriptions for amoxicillin, azithromycin, and cefuroxime, suggests a corresponding decrease in the occurrence of respiratory tract infections, transmitted bacterially or virally. It is likely that this was due to the introduction of pandemic-related measures of hygiene, such as the wearing of face masks, frequent hand washing, and social distancing (the so called “AHA” rules in Germany: Distance (Abstand), Sanitation (Hygiene), Face Mask (Alltagsmasken)). This observation is consistent with the observations of a study from the Netherlands, where general practitioners have also prescribed fewer antibiotics for respiratory tract infections in the period of May to August 2020 compared to the same period in 2019.[95] It is also in accordance with a time-series study by Silva et al., which evaluated antibiotic dispensings in Portugal in consideration of the amount of physician appointments as well as the impact of the governmental public health measures to restrict public and social live. The results of this Portuguese study showed a significant decrease of antibiotic prescriptions as well as a decline in prescribed defined daily doses (DDD) of antibiotics per physician appointment for primary care between March and June 2020.[96]

The use of ciprofloxacin did not decrease considerably after the start of the pandemic, as in previous years. It may be assumed that this fluoroquinolone antibiotic was only used for severe infections of the lower respiratory tract and for complicated urinary

tract infections, but not for non-serious respiratory tract infections, in accordance with guidelines.[97,98] In addition, this decrease in infections and also the general introduction of strict regulations and restrictions on public life and social interactions could have resulted in a reduced frequency of contact to healthcare professionals (physicians and pharmacists) during this time.[99]

The weekly influenza report by the task force influenza (Influenza-Wochenbericht, Arbeitsgruppe Influenza) by the RKI calculates the estimated rate of Germany's inhabitants with newly emerging cases of acute respiratory diseases, the so called ARE-rate. A comparison of the ARE-rates of the last four influenza seasons shows an abrupt decline in the ARE-rate in 2020 and an ongoing, abnormal low ARE-rate throughout. According to the RKI, this course is most likely a consequence of the nationwide implemented social-distancing measures due to the corona pandemic.[100] This information supports the results and observations of this drug utilization study.

4.1.6 Use of pneumococcal vaccines

The use of pneumococcal vaccines peaked after a recommendation by the German Federal Minister of Health on March 9, 2020 followed by drug shortages and increased again after imports of vaccines from Japan on April 3, 2020 and England on April 28, 2020.[101,9,8] These findings demonstrate that an unexpected rise in use of vaccines e.g., pneumococcal can result in drug shortages, which are difficult to counteract as most vaccines have a long manufacturing time.

4.2 Publication and peer review process – problems & potential solutions

4.2.1 Preprint servers

Drug utilizations may have been influenced by published (mis-)information. The current publication and review process of scientific journals may have contributed to this, as it certainly has its weaknesses and limitations, which are highlighted when the system is particularly challenged. This is the case in the current pandemic times and potentially led to researchers prioritized uploading their findings on pre-print servers, and thus publishing possibly premature findings.[102,103,17,19]

Research being published on pre-print servers prior to being adequately peer-reviewed and published in a journal eventually, certainly does not automatically mean that the published findings are flawed or incorrect. Fraser et al. showed that 40% of the preprints submitted to preprint servers in January 2020 were published by the end of October 2020 with little changes made.[17,102] However, there might be an increased risk of unverified findings being discussed publicly instead of within the scientific peer-review process.[18] A preprint[104] published in January 2020 on bioRxiv about similarities in the genetic sequences of SARS-CoV-2 and HIV was heavily discussed (Top 4 'tweeted- about' COVID-19 preprint and Top 3 'commented-on' COVID-19 preprint according to Fraser et al.[17]) and its flaws were pointed out. The paper has since been withdrawn from the server and a paper classifying and clarifying the findings correctly was published shortly after.[105]

On the other hand, there is no guarantee that a peer-reviewed manuscript does not have its flaws and false claims when published.[20,106,32] A peer-reviewed Letter to the Editor published by the *NEJM* as well as the previously mentioned hydroxychloroquine trial by Gautret et al. published in the *International Journal of Antimicrobial Agents* were heavily discussed and critiqued after publication in the high-profile journals and findings were revoked but had already drawn a lot of attention from the media as well as governments and therefore possibly influenced decision making on treatment options. Furthermore, findings of two studies (conducted by the same lead author/ research group) published in *The Lancet* as well as in the *NEJM*, investigating hydroxychloroquine or RAASi as potential COVID-19 treatment options, were even retracted by the authors after publication as validation of data sources was not possible.[107,108]

With research being advocated for being more open, it is necessary to communicate the "preliminary nature of the information in preprints".[20] The results should not be "regarded as conclusive, guide clinical practice and health-related behaviour, or to be reported in news media as established information", as stated in a disclaimer on bioRxiv website.[21,103] Scientists as well as operators of pre-print servers can only urge non-scientific media to indicate this information and reference the preliminary findings and their interpretation. To further enhance their screening checks and publication procedure, BioRxiv and medRxiv have decided to no longer accept and upload

manuscripts “making predictions about treatment for COVID-19 solely on the basis of computational work”. Much of the speculative work, which was published previously was based on those computational models and those prediction models should be peer-reviewed properly, as stated by Richard Sever, a co-founder of BioRxiv as well as medRxiv.[19]

4.2.2 Speed and accuracy of the peer review process and possible solutions for improvement

Open access and quick release of urgently needed information may outweigh the disadvantages of releasing preliminary findings. *NEJM* Editor-in-Chief Ric Rubin states, that there needs to be a balance between rigor and speed and that “the best quality information available quickly is better than perfect information that can’t be accessed until it’s not helpful”.[20] Andreas Voss, President of the International Society of Antimicrobial Chemotherapy (ISAC) states, “it is important to help the scientific community by publishing new data fast, this cannot be at the cost of reducing scientific scrutiny and best practices”. The ISAC is the organisation behind the journal which published be above-mentioned, heavily discussed hydroxychloroquine trail by Gautret et al. and the statement was published as response to the critic.[109]

Despite everything, the peer review process remains of critical importance and is regarded as the standard procedure in scientific publishing, though possibly in need of innovation and restructuring. A paper by Tennant and Ross-Hellauer as well as an article by Kurth et al. suggest possible solutions, that ensure the preservation of quality, even in crisis times with little time and high pressure for new findings (though the possible solutions are also not free of hurdles and difficulties).[110] The proposed solutions include setting consensus standards for what constitutes peer review, providing data infrastructure supporting set standards as well as discussing the idea of an interactive/ collaborative review, in which the review is treated more like a public real-time discussion or conversation between the authors and reviewers, and the identities of all parties are known.[110,14]

4.3 Occurrence of (mis-)information, challenge of finding effective treatment

Apart from the challenges of publishing and adequately reviewing manuscripts, discovering effective treatments the quickest possible in the middle of an epidemic or pandemic of a novel virus, such as SARS-CoV-2 also remains difficult. With an epidemic such as the EVD outbreak in 2014 or a global pandemic such as the ongoing and rapidly spreading corona virus pandemic, it is very challenging, as well as potentially ethically controversial, to conduct proper (long-term) outcome trials such as randomized controlled trials (RCT) for finding efficient as well as safe treatments. This might have also influenced the arise and dissemination of (mis-)information concerning possible treatment and prevention options for COVID-19 and might have led to discrepancies in the published findings. It was noted by the Editor-in-Chief of *JAMA*, Howard Bauchner, that the quality of submissions showed an opposed course to the number of submitted manuscripts; while the quality of submissions decreased, the number of submissions substantially rose (+53%) in 2020 compared to 2019.[19]

4.3.1 Current study situation during COVID

As Andre Kalil, Professor at the Department of Internal Medicine at the University of Nebraska Medical Center states in an article in *JAMA*, most studies aiming to find a treatment during the first weeks of the COVID-19 pandemic wave, with few exceptions,[111] were single-group interventional clinical trials without proper concurrent control arms. Patients of a control arm usually received either a placebo or standard (usual) care, though at that point, for COVID-19 no specific effective treatment options were available besides supportive care.[112] In the absence of a control group, drawing definite conclusions regarding efficacy or safety is difficult, since the potential benefit or harm of any experimental drug cannot be assessed accurately. Define conclusions are desirable and can prevent confusion and misinformation.

Many of the studies conducted in the first pandemic wave examined drugs, which showed in vitro activity against different corona viruses such as SARS-CoV-2, but they were unable to provide clinical evidence for efficacy in humans.[112] Resorting to the off-label use of those drugs without proven benefit as a last line treatment erroneously assumes that a potential benefit predominates potential harm. Kalil states, that it is hard to discriminate if severely ill patients receiving drugs with unproven clinical

efficacy benefited or were harmed by those drugs since mostly, there was no adequate control group. Given this, it cannot automatically be assumed that if the patient died, they died from the severity of the disease, but if the person survived, they survived because of the given drug.[112]

Especially, since most patients who succumbed COVID-19 in the first pandemic wave were elderly and had cardiovascular comorbidities,[5] they could have been harmed by hydroxychloroquine or lopinavir-ritonavir, for example. These drugs can increase the risk of cardiac failures, so it cannot be clearly determined if death occurred due to the disease or due to side effects of the drugs used off-label, especially in the absence of a control group, hence, outside a RCT setting.[113,114]
Kalil claims that off-label use, single-group cohort studies may be less safe and will be unsuccessful in finding new treatment options and that "the rapid and simultaneous combination of supportive care and RCTs is the only way to find effective and safe treatments for COVID-19 and any other future outbreaks".[112] Given all this, results from a RCT design would be desirable. Well conducted RCTs can increase the confidence in the findings with small-to-moderate effects and decrease the risk of findings being confounded or effected by selection or observation bias, and thus prevent the spread of misleading information.[115]

In the progression on the first pandemic wave, the number of RCTs investigating COVID-19 treatment options increased. A systematic review/ network meta-analysis by Siemieniuk et al. was published in *The BMJ* at the end of July 2020 and analysed effects of treatments for COVID-19 from 113 RCTs in which patients with suspected, probable, or confirmed COVID-19 were randomized to drug treatment or standard care. The review showed that, neither hydroxychloroquine nor lopinavir-ritonavir nor azithromycin appeared to have clinically relevant benefits.[116]

Currently (September 1, 2021), there are over 4,000 studies listed at ClinicalTrials.gov, around 2,800 of which are interventional studies. From January to July, 2020 (the observation period of this study), 1,600 studies were listed with around 1,000 being interventional studies.[117] A search of PubMed.gov showed 1,006 results for clinical trials researching COVID-19 treatment options in 2020 and 2021, 566 of which were RCTs (Search term at pubmed.ncbi.nlm.nih.gov: ("COVID-19"[Mesh] OR

"SARS-CoV-2"[Mesh]) AND LitCTREATMENT [filter]).[118] The Cochrane COVID-19 Study Register currently lists over 14,000 studies for the treatment and management of COVID-19; around 9,300 observational studies and 4,500 interventional studies. Of the interventional studies, 3,400 were assigned the intervention randomly.[119]

4.4 Limitations

Since pseudonymized data were unavailable, there is no patient level information including prescription indications, other clinical or lab data and potential impact on patients' outcome. Whether intake of potentially beneficial drugs against COVID-19 is associated with an increase in unexpected or long-term adverse drug reactions remains to be seen. One can only speculate that an increase in utilization was connected to an off-label use for COVID-19 without more direct detailed information from patients or physicians on indication and prescribing behaviour. This information could be conducted by interviews or questionnaires.
The increase in pharmacy claims data in the data basis from July 2019 onwards could have introduced a potential bias, though detailed and extensive internal investigations by DAPI showed no difference in the utilization spectrum of newly introduced compared to previous pharmacy claims data.

It can only be speculated to what extend the quality of a manuscript published on preprint servers (hence, prior to peer review and publication in a scientific journal eventually) would have changed within the traditional, sufficient peer review process. Conflicting information and findings, which were later revised or softened were also published in traditional scientific, even high impact journals, passing through the traditional peer review although often an accelerated process.

Of course, further monitoring of the utilizations beyond the observation period of this study is desirable for future analyses.

5 Conclusions

Apart from the pandemic itself, the data suggests that dissemination of misinformation and unsound speculations as well as supply shortages influenced drug prescribing, utilization, and purchasing behaviour for analysed drugs with perceived benefit or harm on COVID-19. Premature publication of findings and the challenge of conducting suitable RCTs for finding effective treatment options may have contributed to the dissemination of (mis-)information.

These data may contribute to the prevention of unfounded over- and underprescribing and off-label use as well as drug shortages during a public health crisis.

References

1. Abella BS, Jolkovsky EL, Biney BT, et al. Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers: A Randomized Clinical Trial. *JAMA Intern Med*. 2021;181(2):195-202. doi:10.1001/jamainternmed.2020.6319
2. Ahn D-G, Shin H-J, Kim M-H, et al. Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID-19). *J Microbiol Biotechnol*. 2020;30(3):313-324. doi:10.4014/jmb.2003.03011
3. Radtke R. Statistiken und Zahlen zur Corona-Pandemie 2019-2021. Published August 26, 2021. Accessed August 31, 2021. https://de.statista.com/themen/6018/corona/
4. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *The Lancet Respiratory Medicine*. 2020;8(4):e21. doi:10.1016/S2213-2600(20)30116-8
5. Kluge H. *Erklärung – Ältere Menschen Sind Durch COVID-19 Am Stärksten Gefährdet, Doch Alle Müssen Handeln, Um Eine Ausbreitung in Der Bevölkerung Zu Verhindern*. 02.04.2021.
6. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed*. 2020;91(1):157-160. doi:10.23750/abm.v91i1.9397
7. Robert Koch Institut. COVID-19: Fallzahlen in Deutschland und weltweit: Fallzahlen in Deutschland. https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Fallzahlen.html
8. Robert Koch-Institut. COVID-19 und Impfen: FAQ. Published September 17, 2021. Accessed June 23, 2021. https://www.rki.de/SharedDocs/FAQ/COVID-Impfen/gesamt.html
9. Wallenfels M. Pneumokokken-Vakzine: Corona führt zu hoher Impfbereitschaft. *CME (Berl)*. 2020;17(9):29. doi:10.1007/s11298-020-8043-4
10. Tuccori M, Convertino I, Ferraro S, et al. The Impact of the COVID-19 "Infodemic" on Drug-Utilization Behaviors: Implications for Pharmacovigilance. *Drug Saf*. 2020;43(8):699-709. doi:10.1007/s40264-020-00965-w
11. Islam MS, Sarkar T, Khan SH, et al. COVID-19-Related Infodemic and Its Impact on Public Health: A Global Social Media Analysis. *Am J Trop Med Hyg*. 2020;103(4):1621-1629. doi:10.4269/ajtmh.20-0812
12. Hassanian-Moghaddam H, Zamani N, Kolahi A-A, McDonald R, Hovda KE. Double trouble: methanol outbreak in the wake of the COVID-19 pandemic in Iran-a cross-sectional assessment. *Crit Care*. 2020;24(1):402. doi:10.1186/s13054-020-03140-w
13. Chang A, Schnall AH, Law R, et al. Cleaning and Disinfectant Chemical Exposures and Temporal Associations with COVID-19 - National Poison Data System, United States, January 1, 2020-March 31, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(16):496-498. doi:10.15585/mmwr.mm6916e1
14. Kurth T, Piccininni M, Loder E, Rohmann J. A parallel pandemic: the crush of covid-19 publications tests the capacity of scientific publishing. Published May 26, 2020. Accessed June 22, 2021. https://blogs.bmj.com/bmj/2020/05/26/a-parallel-pandemic-the-crush-of-covid-19-publications-tests-the-capacity-of-scientific-publishing/
15. Woolston C. Coronavirus crowds out other research papers: Non-COVID researchers are 'collateral damage' as journals are forced to prioritize. Published June 5, 2020. Accessed June 22, 2021. https://www.natureindex.com/news-blog/coronavirus-pandemic-crowds-out-other-science-research-papers
16. Da Silva JAT. The preprint debate: What are the issues? *Med J Armed Forces India*. 2018;74(2):162-164. doi:10.1016/j.mjafi.2017.08.002
17. Fraser N, Brierley L, Dey G, et al. The evolving role of preprints in the dissemination of COVID-19 research and their impact on the science communication landscape. *PLoS Biol*. 2021;19(4):e3000959. doi:10.1371/journal.pbio.3000959

18. Steinberg I. Coronavirus research done too fast is testing publishing safeguards, bad science is getting through. Accessed July 29, 2021. https://theconversation.com/coronavirus-research-done-too-fast-is-testing-publishing-safeguards-bad-science-is-getting-through-134653
19. Kwon D. How swamped preprint servers are blocking bad coronavirus research. *Nature*. 2020;581(7807):130-131. doi:10.1038/d41586-020-01394-6
20. Kupferschmidt K. 'A completely new culture of doing research.' Coronavirus outbreak changes how scientists communicate. *Science*. 2020. doi:10.1126/science.abb4761
21. bioRxiv. What is an unrefereed preprint? Accessed June 22, 2021. https://www.biorxiv.org/content/what-unrefereed-preprint
22. Johansson MA, Reich NG, Meyers LA, Lipsitch M. Preprints: An underutilized mechanism to accelerate outbreak science. *PLoS Med*. 2018;15(4):e1002549. doi:10.1371/journal.pmed.1002549
23. European Medicines Agency. Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA): EMA/674304/2018. Accessed July 29, 2021. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-detection-notification-shortages-medicinal-products-marketing-authorisation-holders-mahs_en.pdf
24. Badreldin HA, Atallah B. Global drug shortages due to COVID-19: Impact on patient care and mitigation strategies. *Res Social Adm Pharm*. 2021;17(1):1946-1949. doi:10.1016/j.sapharm.2020.05.017
25. Kretchy IA, Asiedu-Danso M, Kretchy J-P. Medication management and adherence during the COVID-19 pandemic: Perspectives and experiences from low-and middle-income countries. *Res Social Adm Pharm*. 2021;17(1):2023-2026. doi:10.1016/j.sapharm.2020.04.007
26. Anderson S, Windscheffel J, Gunning K. Covid Media Misguidance: A Case Report Highlighting the Influence of Media on Patient Medication Decision Making. *Innov Pharm*. 2021;12(1):eCollection. doi:10.24926/iip.v12i1.3555
27. Bhaskar S, Tan J, Bogers MLAM, et al. At the Epicenter of COVID-19-the Tragic Failure of the Global Supply Chain for Medical Supplies. *Front Public Health*. 2020;8:562882. doi:10.3389/fpubh.2020.562882
28. Nam VH, Luu HN, Anh NTT, Nguyen T-A, Doan HQ. Household Stockpiling in Response to the Covid-19 Pandemic: Empirical Evidence from Vietnam. *Forum for Social Economics*. 2021:1-17. doi:10.1080/07360932.2021.1904431
29. Moore N, Carleton B, Blin P, Bosco-Levy P, Droz C. Does Ibuprofen Worsen COVID-19? *Drug Saf*. 2020;43(7):611-614. doi:10.1007/s40264-020-00953-0
30. Simone G de. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers. Published July 21, 2020. Accessed June 24, 2021. https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang
31. Smart L, Fawkes N, Goggin P, et al. A narrative review of the potential pharmacological influence and safety of ibuprofen on coronavirus disease 19 (COVID-19), ACE2, and the immune system: a dichotomy of expectation and reality. *Inflammopharmacology*. 2020;28(5):1141-1152. doi:10.1007/s10787-020-00745-z
32. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020;56(1):105949. doi:10.1016/j.ijantimicag.2020.105949
33. Machiels JD, Bleeker-Rovers CP, Heine R ter, et al. Reply to Gautret et al: hydroxychloroquine sulfate and azithromycin for COVID-19: what is the evidence and what are the risks? *Int J Antimicrob Agents*. 2020;56(1):106056. doi:10.1016/j.ijantimicag.2020.106056

34. Crowley M, Thomas K, Haberman M. Ignoring Expert Opinion, Trump Again Promotes Use of Hydroxychloroquine. Published April 5, 2020. https://www.nytimes.com/2020/04/05/us/politics/trump-hydroxychloroquine-coronavirus.html
35. Cohen MS. Hydroxychloroquine for the Prevention of Covid-19 - Searching for Evidence. *N Engl J Med*. 2020;383(6):585-586. doi:10.1056/NEJMe2020388
36. Singh B, Ryan H, Kredo T, Chaplin M, Fletcher T. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. *Cochrane Database Syst Rev*. 2021;2:CD013587. doi:10.1002/14651858.CD013587.pub2
37. Pan H, Peto R, Henao-Restrepo A-M, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med*. 2021;384(6):497-511. doi:10.1056/NEJMoa2023184
38. Kim S-W, Kang H-J, Jhon M, et al. Statins and Inflammation: New Therapeutic Opportunities in Psychiatry. *Front Psychiatry*. 2019;10:103. doi:10.3389/fpsyt.2019.00103
39. Zhang X-J, Qin J-J, Cheng X, et al. In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19. *Cell Metab*. 2020;32(2):176-187.e4. doi:10.1016/j.cmet.2020.06.015
40. Deutsches Ärzteblatt. Statine könnten Sterberisiko bei COVID-19 senken. Accessed June 24, 2021. https://www.aerzteblatt.de/nachrichten/114149/Statine-koennten-Sterberisiko-bei-COVID-19-senken
41. Dashti-Khavidaki S, Khalili H. Considerations for Statin Therapy in Patients with COVID-19. *Pharmacotherapy*. 2020;40(5):484-486. doi:10.1002/phar.2397
42. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. 2020;382(19):1787-1799. doi:10.1056/NEJMoa2001282
43. Slomski A. No Benefit for Lopinavir-Ritonavir in Severe COVID-19. *JAMA*. 2020;323(20):1999. doi:10.1001/jama.2020.6793
44. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med*. 2020;382(17):1653-1659. doi:10.1056/NEJMsr2005760
45. Feng Y, Ling Y, Bai T, et al. COVID-19 with Different Severities: A Multicenter Study of Clinical Features. *Am J Respir Crit Care Med*. 2020;201(11):1380-1388. doi:10.1164/rccm.202002-0445OC
46. Baral R, White M, Vassiliou VS. Effect of Renin-Angiotensin-Aldosterone System Inhibitors in Patients with COVID-19: a Systematic Review and Meta-analysis of 28,872 Patients. *Curr Atheroscler Rep*. 2020;22(10):61. doi:10.1007/s11883-020-00880-6
47. https://www.sciencealert.com. Updated: WHO Now Doesn't Recommend Avoiding Ibuprofen For COVID-19 Symptoms. Published October 16, 2020. Accessed October 16, 2020. https://www.sciencealert.com/who-recommends-to-avoid-taking-ibuprofen-for-covid-19-symptoms
48. Smith AM, Huber VC. The Unexpected Impact of Vaccines on Secondary Bacterial Infections Following Influenza. *Viral Immunol*. 2018;31(2):159-173. doi:10.1089/vim.2017.0138
49. Robert Koch Institut. Mitteilungen der STIKO zum Impfen bei eingeschränkter Verfügbarkeit von Impfstoffen. Published July 10, 2020. https://www.rki.de/DE/Content/Kommissionen/STIKO/Lieferengpaesse/Lieferengpaesse_node.html;jsessionid=0F44F490A1DB40158F5BAECF711024BD.internet071
50. Arzneimittelkommission der Deutschen Apotheker. Übersicht zentral beschaffter Arzneimittel zur (Off-label) Behandlung von COVID-19. Published March 31, 2020. Accessed February 5, 2021. https://www.abda.de/fileadmin/user_upload/assets/Arzneimittelkommission/PDF/Sonstiges_Anhaenge_fuer_Nachrichten/20_15_AMK_UEbersicht_zentral_beschaffter_Arzneimittel.pdf
51. Gelbe Liste. Potentielle Arzneimittel gegen COVID-19. Accessed February 5, 2021. https://www.gelbe-liste.de/nachrichten/potentielle-arzneimittel-covid-19

52. Medizinische Medien Informations GmbH. Gelbe Liste Pharmindex. Accessed September 20, 2021. https://www.gelbe-liste.de/
53. Pang J, Wang MX, Ang IYH, et al. Potential Rapid Diagnostics, Vaccine and Therapeutics for 2019 Novel Coronavirus (2019-nCoV): A Systematic Review. *J Clin Med*. 2020;9(3). doi:10.3390/jcm9030623
54. Vaduganathan M, van Meijgaard J, Mehra MR, Joseph J, O'Donnell CJ, Warraich HJ. Prescription Fill Patterns for Commonly Used Drugs During the COVID-19 Pandemic in the United States. *JAMA*. 2020;323(24):2524-2526. doi:10.1001/jama.2020.9184
55. Deutsches Arzneiprüfungsinstitut e.V. DAPI - Deutsches Arzneiprüfungsinstitut e.V. Accessed August 31, 2021. https://www.dapi.de/
56. AVOXA - Mediengruppe Deutscher Apotheker. ABDATA Pharma-Daten-Service. Accessed August 31, 2021. https://www.abdata.de/
57. German Institute of Medical Documentation and Information. German anatomical therapeutic chemical (ATC)-classification with defined daily doses (DDD) for Germany. https://www.dimdi.de/dynamic/en/drugs/atc-classification/
58. GKV-Spitzenverband. Berichte zum Quartalsende. https://www.gkv-gamsi.de/gamsi_berichte/quartalsberichte.jsp
59. PKV Verband. PKV-Zahlenportal. Accessed February 5, 2021. https://www.pkv.de/wissen/pkv-zahlenportal/
60. Rudolph UM, Enners S, Kieble M, et al. Impact of angiotensin receptor blocker product recalls on antihypertensive prescribing in Germany. *J Hum Hypertens*. 2020. doi:10.1038/s41371-020-00425-z
61. German Institute of Medical Documentation and Information. German anatomical therapeutic chemical (ATC)-classification with defined daily doses (DDD) for Germany. https://www.dimdi.de/dynamic/en/drugs/atc-classification/
62. Federal Ministry of Health. Federal Ministry of Health, KM6-statistics. Accessed September 23, 2021. http://www.bmg.bund.de
63. Insight Health GmbH & Co. KG. APO Fusion Plus 2020. https://www.insight-health.de/
64. Ravnskov U. Rapid Response: Cholesterol-lowering treatment may worsen the outcome of a Covid-19 infection. *BMJ (Clinical research ed.)*. 2020. Accessed June 24, 2021. https://www.bmj.com/content/368/bmj.m1182/rr-10
65. https://www.sciencealert.com. Updated: WHO Now Doesn't Recommend Avoiding Ibuprofen For COVID-19 Symptoms. Published March 19, 2020. Accessed June 23, 2021. https://www.sciencealert.com/who-recommends-to-avoid-taking-ibuprofen-for-covid-19-symptoms
66. Schulz M, Schumacher PM, Schneider J, Said A, Laufs U. Ugly drug information: ibuprofen and COVID-19. Published March 24, 2020. Accessed June 24, 2021. https://www.schulz-martin.com/2020/03/24/ugly-drug-information-ibuprofen-and-covid-19/
67. t-online. Deutsche horten Klopapier, Spanier und Italiener Wein. [Erstaunliche Unterschiede]. Accessed July 29, 2021. https://www.t-online.de/leben/familie/id_87589288/hamsterkaeufe-in-coronakrise-so-unterschiedlich-hortet-europa.html
68. Alexander GC, Tajanlangit M, Heyward J, Mansour O, Qato DM, Stafford RS. Use and Content of Primary Care Office-Based vs Telemedicine Care Visits During the COVID-19 Pandemic in the US. *JAMA Netw Open*. 2020;3(10):e2021476. doi:10.1001/jamanetworkopen.2020.21476
69. Deutsches Ärzteblatt. Weniger Besuche bei Fachärzten. [Ärzteschaft]. Published May 26, 2020. Accessed September 20, 2021. https://www.aerzteblatt.de/nachrichten/113171/Weniger-Besuche-bei-Fachaerzten
70. Huang Y, Lin C, Wang P, Xu Z. Saving China from the Coronavirus and Economic Meltdown: Experiences and Lessons. *SSRN Journal*. 2020. doi:10.2139/ssrn.3570696

71. Sucker-Sket K. Elf versorgungsrelevante Wirkstoffe kommen aus Hubei: Lieferengpässe durch das Coronavirus? Published February 21, 2020. https://www.deutsche-apotheker-zeitung.de/news/artikel/2020/02/21/elf-versorgungsrelevante-wirkstoffe-kommen-aus-hubei
72. Choo EK, Rajkumar SV. Medication Shortages During the COVID-19 Crisis: What We Must Do. *Mayo Clin Proc*. 2020;95(6):1112-1115. doi:10.1016/j.mayocp.2020.04.001
73. Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. *JAMA*. 2020;323(24):2493-2502. doi:10.1001/jama.2020.8630
74. Bai C, Chotirmall SH, Rello J, et al. Updated guidance on the management of COVID-19: from an American Thoracic Society/European Respiratory Society coordinated International Task Force (29 July 2020). *Eur Respir Rev*. 2020;29(157):200287. doi:10.1183/16000617.0287-2020
75. European Medicines Agency. COVID-19: reminder of risk of serious side effects with chloroquine and hydroxychloroquine | European Medicines Agency. Published October 22, 2020. Accessed June 23, 2021. https://www.ema.europa.eu/en/news/covid-19-reminder-risk-serious-side-effects-chloroquine-hydroxychloroquine
76. Bundesinstitut für Arzneimittel und Medizinprodukte. Hydroxychloroquin - Sicherstellung der Versorgung von chronisch kranken Patientinnen und Patienten in den zugelassenen Indikationen. Accessed June 23, 2021. https://www.bfarm.de/DE/Service/Presse/Themendossiers/Coronavirus/Anlagen/Off_Label_Use_Hydroxychloroquin.pdf?__blob=publicationFile&v=1
77. Bykerk V, Sampalis J, Esdaile JM, et al. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. *N Engl J Med*. 1991;324(3):150-154. doi:10.1056/NEJM199101173240303
78. American College of Rheumatology. Patients reported international hydroxychloroquine shortages due to COVID-19. Accessed July 29, 2021. www.sciencedaily.com/releases/2020/11/201106103103.htm
79. Sirotich E, Kennedy K, Surangiwala S, et al. Antimalarial Drug Shortages During the COVID-19 Pandemic: Results from the Global Rheumatology Alliance Patient Experience Survey [abstract]. Accessed September 2, 2021. https://acrabstracts.org/abstract/antimalarial-drug-shortages-during-the-covid-19-pandemic-results-from-the-global-rheumatology-alliance-patient-experience-survey/
80. Bundesinstitut für Arzneimittel und Medizinprodukte. Lieferengpässe für Humanarzneimittel in Deutschland (ohne Impfstoffe). https://lieferengpass.bfarm.de/ords/f?p=30274:3:6633884200576:NO::
81. Horby PW, Mafham M, Bell JL, et al. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet*. 2020;396(10259):1345-1352. doi:10.1016/S0140-6736(20)32013-4
82. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Atherosclerosis*. 2019;290:140-205. doi:10.1016/j.atherosclerosis.2019.08.014
83. Lopes RD, Macedo AVS, Barros E Silva PGM de, et al. Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: Impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)--The BRACE CORONA Trial. *Am Heart J*. 2020;226:49-59. doi:10.1016/j.ahj.2020.05.002
84. Braude P, Carter B, Short R, et al. The influence of ACE inhibitors and ARBs on hospital length of stay and survival in people with COVID-19. *Int J Cardiol Heart Vasc*. 2020;31:100660. doi:10.1016/j.ijcha.2020.100660
85. Kintscher U, Slagman A, Domenig O, et al. Plasma Angiotensin Peptide Profiling and ACE (Angiotensin-Converting Enzyme)-2 Activity in COVID-19 Patients Treated With Pharmacological

Blockers of the Renin-Angiotensin System. *Hypertension*. 2020;76(5):e34-e36. doi:10.1161/HYPERTENSIONAHA.120.15841
86. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. *Eur Heart J*. 2016;37(11):908-916. doi:10.1093/eurheartj/ehv641
87. Qiao W, Wang C, Chen B, et al. Ibuprofen attenuates cardiac fibrosis in streptozotocin-induced diabetic rats. *Cardiology*. 2015;131(2):97-106. doi:10.1159/000375362
88. Kragholm K, Gerds TA, Fosbøl E, et al. Association Between Prescribed Ibuprofen and Severe COVID-19 Infection: A Nationwide Register-Based Cohort Study. *Clin Transl Sci*. 2020;13(6):1103-1107. doi:10.1111/cts.12904
89. Rinott E, Kozer E, Shapira Y, Bar-Haim A, Youngster I. Ibuprofen use and clinical outcomes in COVID-19 patients. *Clin Microbiol Infect*. 2020;26(9):1259.e5-1259.e7. doi:10.1016/j.cmi.2020.06.003
90. Kelleni MT. ACEIs, ARBs, ibuprofen originally linked to COVID-19: the other side of the mirror. *Inflammopharmacology*. 2020;28(6):1477-1480. doi:10.1007/s10787-020-00755-x
91. Drug Commission of German Pharmacists. 14/20 Informationen der Institutionen und Behörden: BMG: Mengenbeschränkte Belieferung bzw. Abgabe von Paracetamol-haltigen Arzneimitteln durch Hersteller, pharmazeutische Großhändler und Apotheken [Federal Ministry of Health: Delivery or dispensing of paracetamol-containing drugs by manufacturers, pharmaceutical wholesalers and pharmacies]. Published March 24, 2020. Accessed June 24, 2021. https://www.abda.de/fuer-apotheker/arzneimittelkommission/amk-nachrichten/detail/14-20-informationen-der-institutionen-und-behoerden-bmg-mengenbeschraenkte-belieferung-bzw-abgabe-von-paracetamol-haltigen-arzneimitteln-durch-hersteller-pharmazeutische-grosshaendler-und-apotheken/
92. Schulz M, Schumacher PM, Schneider J, Said A, Laufs U. Explosive drug information in the time of COVID-19. *Can Pharm J (Ott)*. 2021;154(4):232-233. doi:10.1177/17151635211020306
93. Boulware DR, Pullen MF, Bangdiwala AS, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. *N Engl J Med*. 2020;383(6):517-525. doi:10.1056/NEJMoa2016638
94. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19 : A Randomized Trial. *Ann Intern Med*. 2020;173(8):623-631. doi:10.7326/M20-4207
95. Hek K. Voorschrijven van antibiotica door de huisarts tijdens de coronapandemie. Accessed June 24, 2021. https://nivel.nl/sites/default/files/bestanden/1003882_0.pdf
96. Silva TM, Estrela M, Gomes ER, et al. The Impact of the COVID-19 Pandemic on Antibiotic Prescribing Trends in Outpatient Care: A Nationwide, Quasi-Experimental Approach. *Antibiotics*. 2021;10(9):1040. doi:10.3390/antibiotics10091040
97. German College of General Practitioners and Family Physicians. [S2k Leitlinie: Ohrenschmerzen, AWMF-Reg.-Nr. 053/009], [S2k guideline: Earache]; 2014. Accessed June 24, 2021. https://www.awmf.org/uploads/tx_szleitlinien/053-009l_S2k_Ohrenschmerzen_2014-12-abgelaufen.pdf
98. German Society of Oto-Rhino-Laryngology, Head and Neck Surgery, German College of General Practitioners and Family Physicians. [S2k Leitlinie: Rhinosinusitis, AWMF-Reg.-Nr. 017/049 (HNO) und 053/012 (DEGAM)], [S2k guideline: Rhinosinusitis]; 2017. Accessed June 24, 2021. http://www.awmf.org/uploads/tx_szleitlinien/017-049_und_053-012l_S2k_Rhinosinusitis_2017-07_01.pdf
99. Rohrer B. April 2020: 15 Prozent weniger Rezepte in Apotheken: Weniger Arztbesuche wegen Corona. Published June 2, 2020. https://www.deutsche-apotheker-zeitung.de/news/artikel/2020/06/02/april-2020-15-prozent-weniger-rezepte-in-apotheken

100. Buda S, Dürrwald R, Biere B, et al. *Influenza-Wochenbericht*; 2021.
101. BMG. Bekanntmachung nach § 79 Absatz 5 des Arzneimittelgesetzes. Published October 22, 2021. Accessed June 24, 2021. https://www.bundesanzeiger.de/pub/publication/TRupGZewRRS6lTjtg0G;wwwsid=A1C9D39D6BDFD75E8267B8069B0C9EA6.web06-pub?0
102. Carneiro CFD, Queiroz VGS, Moulin TC, et al. Comparing quality of reporting between preprints and peer-reviewed articles in the biomedical literature. *Res Integr Peer Rev*. 2020;5(1):16. doi:10.1186/s41073-020-00101-3
103. Cold Spring Harbor Laboratory. bioRxiv - the preprint server for biology: COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv. Accessed June 22, 2021. www.biorxiv.org
104. Pradhan P, Pandey AK, Mishra A, et al. *Uncanny Similarity of Unique Inserts in the 2019-NCoV Spike Protein to HIV-1 Gp120 and Gag*. 2020.
105. Xiao C, Li X, Liu S, Sang Y, Gao S-J, Gao F. HIV-1 did not contribute to the 2019-nCoV genome. *Emerg Microbes Infect*. 2020;9(1):378-381. doi:10.1080/22221751.2020.1727299
106. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. *N Engl J Med*. 2020;382(10):970-971. doi:10.1056/NEJMc2001468
107. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Retraction: Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621. *N Engl J Med*. 2020;382(26):2582. doi:10.1056/NEJMc2021225
108. Mehra MR, Desai SS, Ruschitzka F, Patel AN. RETRACTED: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *The Lancet*. 2020. doi:10.1016/S0140-6736(20)31180-6
109. Voss A. Official Statement from International Society of Antimicrobial Chemotherapy (ISAC): Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial (Gautret P et al. PMID 32205204). Published April 3, 2020. Accessed July 29, 2021. https://www.isac.world/news-and-publications/official-isac-statement
110. Tennant JP, Ross-Hellauer T. The limitations to our understanding of peer review. *Res Integr Peer Rev*. 2020;5:6. doi:10.1186/s41073-020-00092-1
111. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med*. 2020;383(19):1813-1826. doi:10.1056/NEJMoa2007764
112. Kalil AC. Treating COVID-19-Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics. *JAMA*. 2020;323(19):1897-1898. doi:10.1001/jama.2020.4742
113. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *JAMA*. 2020;323(15):1488-1494. doi:10.1001/jama.2020.3204
114. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239-1242. doi:10.1001/jama.2020.2648
115. Davey RT, Dodd L, Proschan MA, et al. A Randomized, Controlled Trial of ZMapp for Ebola Virus Infection. *N Engl J Med*. 2016;375(15):1448-1456. doi:10.1056/NEJMoa1604330
116. Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ (Clinical research ed.)*. 2020;370:m2980. doi:10.1136/bmj.m2980
117. NIH - U.S. National Library of Medicine. ClinicalTrials.gov: Interventional and Observational Studies for COVID-19 treatment. Accessed September 3, 2021. https://clinicaltrials.gov/ct2/results?term=treatment&cond=Covid19&Search=Apply&age_v=&gndr=&type=Intr&rslt=

118. NIH - U.S. National Library of Medicine. PubMed.gov. Accessed September 3, 2021. https://pubmed.ncbi.nlm.nih.gov/?term=%28%22COVID-19%22%5BMesh%5D+OR+%22SARS-CoV-2%22%5BMesh%5D%29+AND+LitCTREATMENT%5Bfilter%5D&filter=pubt.randomizedcontrolledtrial&filter=years.2020-2021&sort=date
119. Cochrane. Cochrane COVID-19 Study Register: COVID-19 Studies with Study Aim "Treatment and Management". Accessed September 3, 2021. https://covid-19.cochrane.org/?q=c(study-aims/treatment-management:Treatment%20and%20Management).c(study-types/interventional:Interventional)&pn=1

Appendix

Received: 10 February 2021 | Revised: 14 June 2021 | Accepted: 2 July 2021

DOI: 10.1002/pds.5324

ORIGINAL ARTICLE

WILEY

Utilization of drugs with reports on potential efficacy or harm on COVID-19 before, during, and after the first pandemic wave

Salka Enners[1] | Gabriele Gradl[1] | Marita Kieble[1] | Michael Böhm[2] | Ulrich Laufs[3] | Martin Schulz[1,4,5]

[1]German Institute for Drug Use Evaluation (DAPI), Berlin, Germany

[2]Department of Internal Medicine III – Cardiology, Angiology and Intensive Care Medicine, Saarland University Medical Center, Homburg, Germany

[3]Department of Cardiology, University Hospital Leipzig, Leipzig, Germany

[4]Drug Commission of German Pharmacists (AMK), Berlin, Germany

[5]Institute of Pharmacy, Freie Universität Berlin, Berlin, Germany

Correspondence
Salka Enners and Martin Schulz, German Institute for Drug Use Evaluation (DAPI), Heidestr. 7, 10557 Berlin, Germany.
Email: s.enners@dapi.de (S. E.) and m.schulz@fu-berlin.de (M. S.)

Abstract

Purpose: Conflicting information on potential benefits of drugs as well as reports on hypothetical harm of commonly used drugs in COVID-19 treatment have challenged clinicians and healthcare systems. We analyzed the change in ambulatory drug utilization before, during, and after the first wave of the pandemic in 2020.

Methods: We explored dispensing data of nearly 19 000 pharmacies at the expense of the statutory health insurance funds covering 88% of Germany's population. We analyzed utilization of publicly discussed drugs with conflicting information. Drug utilization as number of packages dispensed per week from January to June 2020, reflecting 314 million claims, was compared with 2019.

Results: Utilization of hydroxychloroquine increased +110% during March 2020 and then slightly decreased until week April 13–19. Renin–angiotensin–aldosterone system inhibitors and simvastatin/atorvastatin increased, +78% and +74%, respectively, and subsequently decreased below 2019 levels. Utilization of azithromycin and all systemic antibiotics decreased continuously from March 2–8 until June to levels considerably lower compared to 2019 (June 22–28: azithromycin: −55%, all systemic antibiotics: −27%). Pneumococcal vaccines utilization initially increased +373%, followed by supply shortages. Paracetamol utilization showed an initial increase of +111%, mainly caused by an increase of over-the-counter dispensings.

Conclusions: Apart from the pandemic itself, the data suggest that dissemination of misinformation and unsound speculations as well as supply shortages influenced drug prescribing, utilization, and purchasing behavior. The findings can inform post-pandemic policy to prevent unfounded over- and underprescribing and off-label use as well as drug shortages during a public health crisis.

Abbreviations: ACE2, angiotensin-converting enzyme 2; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices); COVID-19, coronavirus disease 2019; OTC, over-the-counter (drugs); PHI, private health insurance; RAASi, renin–angiotensin–aldosterone system inhibitor; RAS, renin–angiotensin system; SARS-CoV-2, severe acute respiratory coronavirus 2; SHI, statutory health insurance (funds).

KEYWORDS
COVID-19, drug utilization, hydroxychloroquine, pandemic, pharmacy claims, renin–angiotensin–aldosterone system, statins

Key Points

- Drug utilization was significantly altered during the COVID-19 pandemic, particularly during the first weeks.
- Conflicting information on potential benefits of drugs in COVID-19 and reports on hypothetical harm of commonly used drugs could have influenced utilization.
- Course of utilization hints stockpiling at the beginning of the first pandemic wave, most probably caused by the anticipated intensification of nationwide restrictions for public life and concerns of continuous drug supply.
- Findings can inform post-pandemic policy to prevent unfounded over- and underprescribing, off-label use and drug shortages during a public health crisis.

1 | INTRODUCTION

Healthcare systems and clinicians around the world faced major challenges in drug supply during the coronavirus disease (COVID-19) pandemic in 2020. The spreading of the severe acute respiratory coronavirus 2 (SARS-CoV-2) was accompanied by dissemination of misinformation and unsound speculations concerning potential treatment efficacy or harm of some drugs, primarily via public media and social networks.[1]

A media analysis identified 2311 reports of rumors, stigma, and conspiracy theories in 25 languages from 87 countries. 19% of the claims were related to treatment and cure.[2]

Several drugs were being tested for treatment or prevention of COVID-19 and might have been used off-label.[1,3–5] Consequently, patients may have been exposed to adverse effects of these drugs without proven benefits.

Hydroxychloroquine, approved for malaria prophylaxis and treatment as well as treatment of rheumatoid arthritis and systemic lupus erythematosus (SLE), is a potent in vitro replication inhibitor of most coronaviruses. It was therefore discussed for treating COVID-19.[1] The human immunodeficiency virus therapeutics lopinavirs' and ritonavirs' protease inhibiting abilities were discussed to be effective against SARS-CoV-2.[6,7]

For other drugs, an increasing risk for infection and critical outcomes of COVID-19 was hypothesized. This has been mainly discussed for drugs inhibiting the renin–angiotensin–aldosterone system (RAAS), among them widely used angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB).[8] The mechanism for SARS-CoV-2 infection is the requisite binding of the virus to the membrane-bound form of the angiotensin-converting enzyme 2 (ACE2) and internalization of the complex by the host cell.[8,9] ACE2, however, is a key enzymatic component of the RAAS. Experimental evidence suggests that RAAS blockade enhance ACE2, which, in part, contributes to the benefit of these regimens.[8]

Statins were proposed as an adjunct therapy for COVID-19 because of their anti-inflammatory and other potential beneficial effects.[10] However, statins have been shown to upregulate the expression of ACE2,[11] with the potential for increasing viral entry into cells.[12] It was even suggested to cease cholesterol-lowering therapy in patients with COVID-19.[13]

Fang et al.[14] suggested that ACE2 can also be increased by the non-steroidal inflammatory drug ibuprofen. This theoretical concern led to a recommendation by the World Health Organization (WHO)[15] on March 17, 2020 that ibuprofen should not be used by patients who show symptoms of COVID-19, but be replaced by paracetamol.[16]

Pneumococci infections can lead to severe pneumonia and sepsis and can potentially require artificial ventilation of intensive care patients. It has been hypothesized that pneumococcal vaccinations could stimulate an immune response in older adults potentially lowering the severity of other infections.[17] However, clinical data supporting this hypothesis with regard to COVID-19 are scarce.[18–21]

Data on drug utilization during the pandemic is limited[4] but potentially helpful for future public health crises. We aimed, therefore, to investigate the change in ambulatory drug utilization before, during, and after the first wave of the COVID-19 pandemic in 2020. We hypothesized an increase in utilization for drugs reported to be beneficial, such as hydroxychloroquine, and a decline in utilization of drugs, such as RAASi and ibuprofen, for which an increase of risk was speculated.

2 | METHODS

We performed a descriptive drug utilization study. Drug prescriptions were analyzed using the database of the German Institute for Drug Use Evaluation (DAPI), which contains anonymous dispensing data of community pharmacies claimed to the statutory health insurance (SHI) funds and thus covers 88% of Germany's population, that is, approximately 73.3 million people.[22] All claims data from a representative sample of more than 80% (until June 2019) and more than 95% (from July 2019 onwards) of community pharmacies were available. The data were extrapolated by regional factors to 100% of the SHI-insured population.

Dispensing data were linked to a database containing information on the name, composition, active ingredients, package size, dosage

form, and route of administration using the specific product code (*Pharmazentralnummer*, an identification number for pharmaceutical products in Germany). Allocation of active ingredients was based on the official version of the Anatomical Therapeutic Chemical classification system published by the German Institute of Medical Documentation and Information.[23]

We analyzed the time course of utilization for hydroxychloroquine, RAASi (ACEi and ARB), azithromycin, the two most frequent used statins (simvastatin and atorvastatin), pneumococcal vaccines, ibuprofen and lopinavir–ritonavir. We also analyzed the time course of paracetamol utilization.

For an overview on the general course of utilizations in 2020, we analyzed dispensings of all prescribed drugs, all systemic antibiotics, the most frequently used substance in the classes of penicillins (amoxicillin), cephalosporins (cefuroxime), and quinolones (ciprofloxacin).

We determined three periods: A, from January 2020 until week March 16–22 (on March 22, nationwide restrictions on public and social life were implemented); B, from week March 23–29 until week April 13–19 during nationwide restrictions, and C, the period after first relaxation of restrictions on April 20 until the end of June 2020.

We measured drug utilization as number of packages dispensed per week and determined the percentage change in number of utilized packages from January to June 2020 in comparison with 2019. For pneumococcal vaccines, we calculated dispensed vaccine doses. Dispensing data from 2020 and 2019 were matched by weeks in consideration of public holidays to account for seasonal fluctuations.

For ibuprofen und paracetamol, we included dispensing data from private health insurance (PHI)-insured patients and self-medication utilization from the INSIGHT Health database to portray full utilization since those drugs are not primarily prescription drugs but over-the-counter (OTC) products. This database includes extrapolated data from a representative sample of over 4500 community pharmacies.[24]

We determined the distribution of the package sizes per analyzed drug in 2020 compared to 2019 to rule out possible bias due to different amounts of drugs per package in both evaluation periods. Further, we supplemented the data on dispensed packs of the study drugs with defined daily doses[23] per 1000 SHI-insured persons per day (DID). The number of persons insured by the SHI system was obtained from the Federal Ministry of Health.[25]

3 | RESULTS

There were no relevant differences in the distribution of package sizes in the analyzed drugs in 2020 compared to 2019 (Table S1 in Data S1). There were no differences in the weekly time courses between DID and packages (Table S2 in Data S1).

3.1 | All prescription drugs

Until week February 17–23, utilization of all prescription drugs remained at 2019 levels (+2%). During the remaining of period A, utilization increased continuously in comparison with 2019, peaked at 17.6 million packages per week (+43%) and subsequently decreased below the level of 2019 with 12.1 million packages (−18%) at the beginning of period C (Table 1, Figure 1A).

3.2 | Hydroxychloroquine

Compared to 2019, utilization of hydroxychloroquine increased +110% to 10 700 packages per week at the end of period A, and then decreased to 4700 packages per week at the end of period B with still +22% packages compared to 2019 (Table 1, Figure 1A).

3.3 | Renin–angiotensin–aldosterone system inhibitors (RAASi)

Until week February 17–23, utilization of RAASi remained at similar levels compared to 2019 (+5%). During the remaining of period A, utilization increased continuously and subsequently decreased in period B below the level of 2019 (Table 1, Figure 1A). Utilization peaked at 1.89 million packages (+78%) and then fell below 2019 levels with up to −17% during period C. RAASi utilization first reached similar prior-year levels during week June 8–14 with 1.06 million dispensed packages.

3.4 | Statins, lopinavir–ritonavir

Simvastatin and atorvastatin, similar to RAASi and all prescription drugs, peaked at 623 000 packages per week (+74%) at the end of period A and then dropped to 405 500 packages (−15%) at the beginning of period C. Utilization approximated to 2019 values until the end of the observation period (Table 1, Figure 1A).

The amount of ambulatory dispensed packages of lopinavir–ritonavir was low (approximately 102 packages per week) and did not show differences between 2020 and 2019 (Table 1).

3.5 | Antibiotics

During period A, azithromycin use slightly increased to 77 400 packages (+9%) in week March 2–8 and 72 000 packages (+16%) in week March 9–15. Amoxicillin use increased to 159 700 packages (+6%) and 154 200 packages (+11%) in the weeks of March 2–8 and March 9–15 (Table 1, Figure 1B). After implementation of restrictions, dispensing levels of all analyzed antibiotics decreased to values substantially lower than in 2019. All systemic antibiotics dropped from 780 700 packages during week March 2–8 −37%, azithromycin −58%, amoxicillin −48%, and cefuroxime −47%, at the end of period B in week April 13–19. Ciprofloxacin use, which was markedly reduced in the first quarter of 2020 compared to 2019 (−37%), returned to slightly below 2019 levels during period C (average: −6%) (Table 1).

TABLE 1 Weekly dispensed drug packages before (Period A), during (Period B), and after (Period C) the first COVID-19 pandemic wave and relative change from 2019

Drug	January 6–12 Period A	...	February 24–March 1	March 2–8	March 9–15	March 16–22 Period B	March 23–29	March 30–April 5	April 6–12	April 13–19 Period C	April 20–26	April 27–May 3	May 4–10	...	June 22–28
All prescription drugs															
Change from 2019, %	1.0%		7.8%	12.3%	18.8%	42.9%	−14.9%	−18.1%	−16.1%	−7.4%	−18.0%	−9.7%	−10.3%		−17.6%
Packages dispensed	14 331 957		12 878 475	15 360 267	15 297 938	17 612 702	12 062 613	11 734 236	9 737 995	8 992 123	12 093 385	10 205 599	11 897 790		11 647 779
Hydroxychloroquine															
Change from 2019, %	−4.9%		32.2%	24.7%	36.5%	109.9%	38.7%	13.2%	8.7%	22.1%	3.5%	10.7%	5.1%		−10.6%
Packages dispensed	5572		6123	7036	7344	10 726	7956	6710	5365	4732	6349	5309	6206		5592
RAAS inhibitors															
Change from 2019, %	5.8%		12.0%	21.6%	30.7%	77.9%	−8.8%	−11.5%	−11.5%	−1.3%	−16.6%	−10.7%	−7.2%		−19.0%
Packages dispensed	1 364 377		1 168 590	1 489 546	1 480 982	1 888 470	1 185 012	1 160 730	935 786	858 281	1 172 412	966 063	1 149 883		1 121 710
Simvastatin, atorvastatin															
Change from 2019, %	5.7%		10.5%	17.6%	27.3%	73.9%	−11.2%	−10.3%	−9.6%	0.7%	−15.0%	−9.4%	−6.1%		−20.5%
Packages dispensed	467 600		390 065	494 644	493 013	622 989	398 868	402 012	324 179	298 297	405 450	330 941	397 744		382 767
Lopinavir + ritonavir															
Change from 2019, %	−22.9%		−19.0%	−25.5%	16.0%	43.0%	−9.4%	−25.5%	−22.2%	−15.7%	−29.9%	2.2%	−36.1%		−38.8%
Packages dispensed	121		124	108	116	143	125	108	98	75	101	79	99		85
Systemic antibiotics															
Change from 2019, %	−3.4%		−0.7%	−0.5%	5.3%	−2.8%	−27.2%	−36.8%	−38.7%	−36.7%	−44.0%	−31.1%	−38.6%		−27.2%
Packages dispensed	729 275		728 055	780 733	763 758	680 693	510 407	432 291	357 195	312 653	372 403	335 860	367 660		402 300
Azithromycin															
Change from 2019, %	12.8%		2.3%	8.5%	15.8%	5.2%	−22.9%	−40.8%	−51.9%	−57.6%	−62.0%	−58.0%	−65.0%		−55.3%
Packages dispensed	71 201		70 190	77 382	72 002	61 218	44 758	32 630	21 577	16 165	18 411	14 725	15 312		14 830
Amoxicillin															
Change from 2019, %	−1.2%		6.4%	5.9%	11.2%	−2.1%	−31.2%	−45.6%	−50.0%	−47.5%	−53.2%	−40.5%	−49.7%		−32.3%
Packages dispensed	138 658		151 755	159 660	154 216	132 104	90 030	70 135	55 803	48 302	55 306	50 344	53 725		62 032
Cefuroxime															
Change from 2019, %	−1.0%		−6.2%	−4.3%	2.7%	−2.0%	−28.9%	−40.2%	−44.4%	−46.9%	−51.3%	−39.2%	−45.9%		−37.5%
Packages dispensed	86 579		82 401	88 705	85 265	76 863	56 811	46 659	37 784	32 172	38 047	34 004	36 656		39 486
Ciprofloxacin															
Change from 2019, %	−40.9%		−35.3%	−35.7%	−31.5%	−31.6%	−40.8%	−30.9%	−9.6%	−1.8%	−17.2%	−2.0%	−6.1%		−10.0%
Packages dispensed	29 813		28 164	30 384	30 610	29 575	26 027	25 232	22 754	20 896	25 370	22 830	26 098		25 172
Pneumococcal vaccines															
Change from 2019, %	−15.4%		82.8%	96.9%	372.7%	267.7%	222.0%	136.2%	55.2%	22.6%	10.9%	150.5%	294.3%		42.0%
Doses dispensed	73 360		89 782	123 009	302 715	350 483	225 863	159 752	74 573	58 438	80 619	151 863	306 057		90 209

Abbreviation: RAAS, renin–angiotensin–aldosterone system.

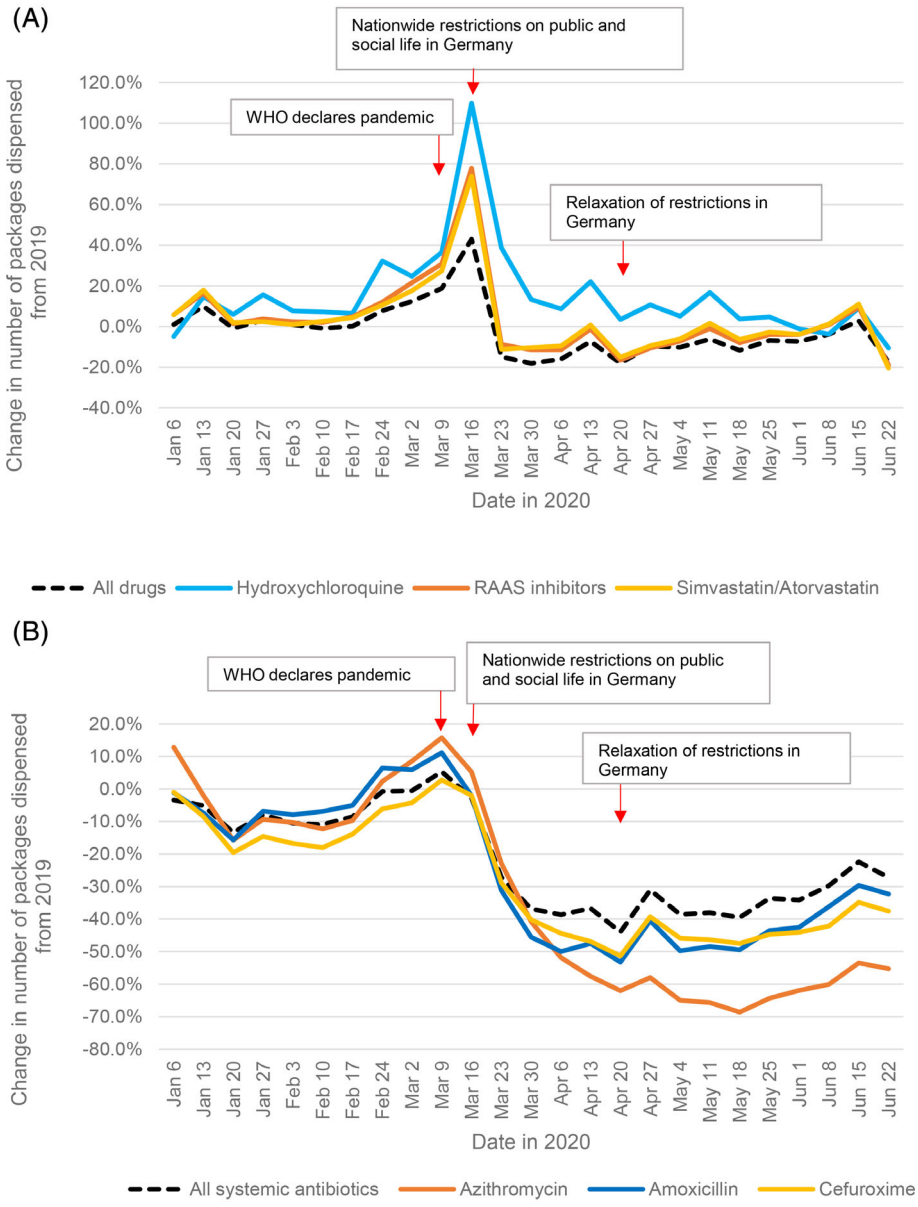


FIGURE 1 Dispensings of prescription drugs before, during, and after the first COVID-19 pandemic wave. Relative change in weekly dispensings in 2020, compared to 2019. Each date on the x-axis refers to the first day of the week. **A**, All prescription drugs, hydroxychloroquine, RAAS inhibitors, and simvastatin/atorvastatin. **B**, All systemic antibiotics, azithromycin, amoxicillin, and cefuroxime. Abbreviations: RAAS, renin–angiotensin–aldosterone system; WHO, World Health Organization [Colour figure can be viewed at wileyonlinelibrary.com]

3.6 | Pneumococcal vaccines

Until week February 17–23, utilization of pneumococcal vaccines hovered around 2019 levels, then substantially increased to 302 700 doses (+373%) and peaked at 350 500 doses (+268%) at the end of period A. After decreasing back to 58 400 doses with still +23% compared to 2019, utilization increased again to 306 000 doses (+294%) during week May 4–10, then decreased again (Table 1, Figure 2).

3.7 | Ibuprofen and paracetamol

While the utilizations per month increased moderately for ibuprofen to 7.47 million packages in March 2020 with +19% compared to 2019, all paracetamol utilizations showed a huge increase with +111% to 8.04 million packages. These increases were mainly caused by the increase of OTC dispensings: +31% for ibuprofen with 4.66 million packages and +127% for paracetamol with 7.28 million packages.

In April 2020, all utilized packages for both drugs decreased markedly in comparison to 2019; ibuprofen: 3.73 million, −36%; paracetamol: 2.64 million, −19%, and slowly recovered by June with 4.37 million dispensed packages for ibuprofen (−15%) and 2.29 million (−15%) for paracetamol. Decreases were evenly distributed among OTC dispensings as well as SHI- and PHI prescriptions (Table 2, Figure 3).

4 | DISCUSSION

The main finding of our analyses is that drug prescribing, utilization, and purchasing behavior was significantly altered, particularly during the first weeks of the COVID-19 pandemic in early 2020, possibly influenced by misinformation and speculations on potential treatment

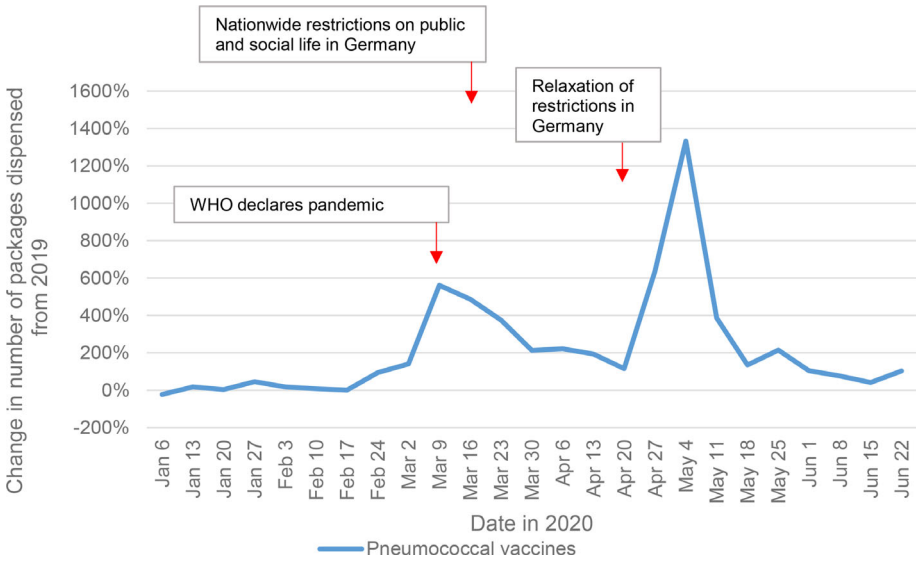


FIGURE 2 Dispensings of pneumococcal vaccine doses before, during, and after the first COVID-19 pandemic wave. Relative change in weekly dispensings in 2020, compared to 2019. Each date on the x-axis refers to the first day of the week [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Monthly dispensings of ibuprofen and paracetamol from January to June 2020 (OTC dispensings, SHI- and PHI prescriptions)

	January	February	March	April	May	June
Ibuprofen						
OTC	3 597 354	4 022 403	4 657 881	2 188 182	2 272 510	2 521 809
SHI	2 530 391	2 506 373	2 440 847	1 370 304	1 431 638	1 641 885
PHI	379 558	403 379	373 825	168 396	176 477	202 889
Total	6 507 303	6 932 155	7 472 553	3 726 882	3 880 625	4 366 583
Paracetamol						
OTC	3 298 893	3 607 558	7 280 035	2 298 097	1 871 681	1 957 676
SHI	400 980	413 921	410 980	200 989	191 492	211 746
PHI	261 388	275 553	344 126	142 123	117 067	124 222
Total	3 961 261	4 297 032	8 035 141	2 641 209	2 180 240	2 293 644

Abbreviations: OTC, over-the-counter (drug); PHI, private health insurance; SHI, statutory health insurance.

efficacy as well as hypothetical concerns on harmfulness of commonly used drugs.[2,9,13–16,26]

4.1 | Overall drug use and stockpiling

The observed peak of drug utilization of all prescription drugs at the end of period A, that is, March 16–22 indicates stockpiling and was most likely caused by the anticipated intensification of nationwide restrictions for public life and social interactions and, hence, concerns with regard to continuous drug supply.

We assume that patients contacted their prescribers prematurely to issue new prescriptions and physicians prescribed multiple packages with the intention to decrease the necessity for contacts in the near future. The latter is supported by analyzing the percentage of prescriptions with more than one package per drug prescribed in March 2020 compared to March 2019 (data not shown).

Reduced physician visits[27] and, subsequently, pharmacies under conditions of social interaction restriction correlate with the documented subsequent decrease of dispensings for all analyzed drugs. Other possible reasons for this subsequent decrease are drug shortages or the sufficient supply of patients due to previous stockpiling.

The total time course for utilization data of all prescription drugs in 2020 supports the hypothesis of initial stockpiling. However, the data reveal that the number of all packages dispensed from January to June 2020 differed from 2019 by only −2%, showing that the initial increase was compensated by the subsequent decrease.

Utilization data of RAASi, hydroxychloroquine, and simvastatin/atorvastatin show a similar course to all prescribed drugs, again indicating initial stockpiling and giving no signs of under-prescribing within those drug groups.

4.2 | Use of drugs with positive reports on COVID-19

On March 17, hence immediately before the start of period B, a small clinical trial on COVID-19 treatment showed a positive effect of

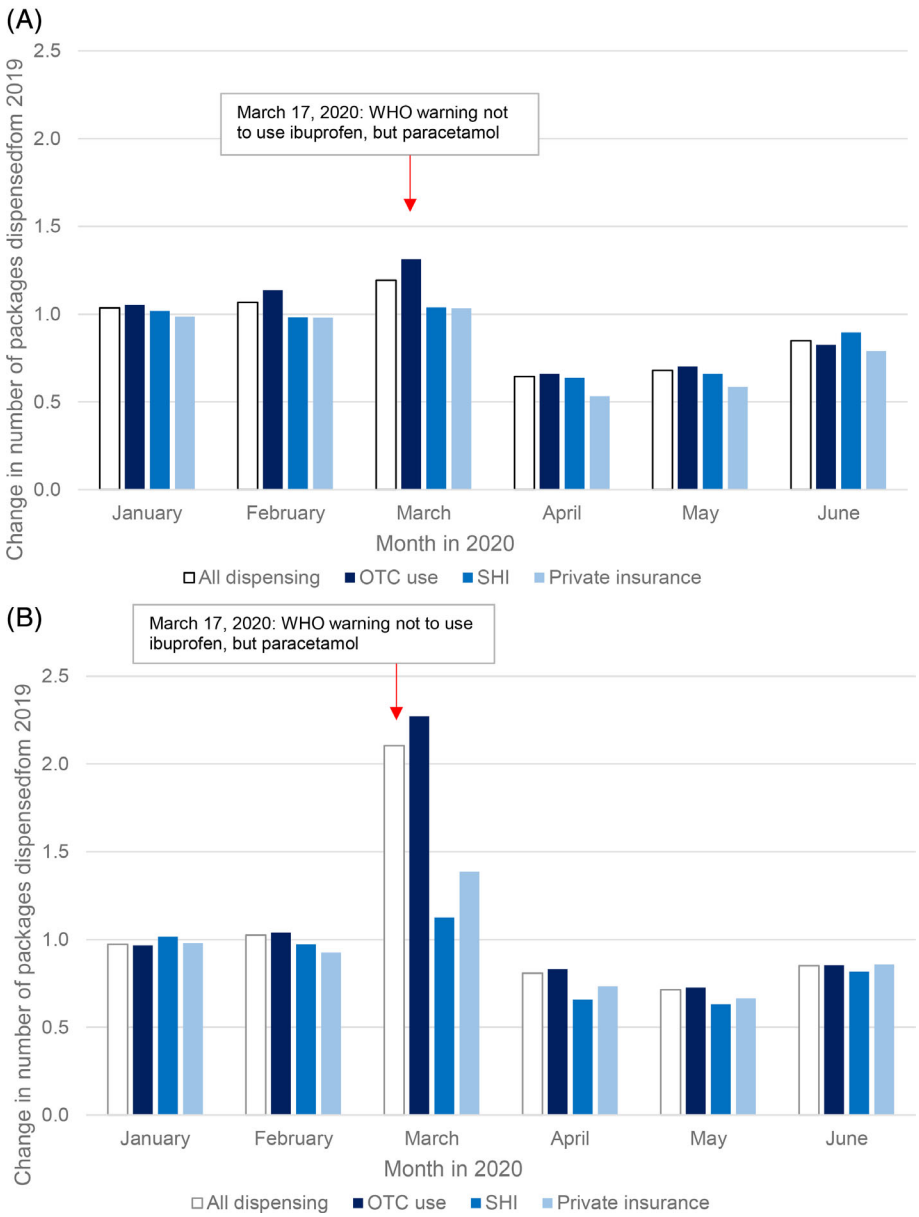


FIGURE 3 Dispensings of ibuprofen and paracetamol before, during, and after the first COVID-19 pandemic wave. Relative change in monthly dispensings January to June 2020, compared to 2019. **A**, Ibuprofen. **B**, Paracetamol. Abbreviations: OTC, over-the-counter (drug); PHI, private health insurance; SHI, statutory health insurance [Colour figure can be viewed at wileyonlinelibrary.com]

hydroxychloroquine and additional benefit when adding azithromycin.[26] This report received high attention despite major methodological issues, including the design (open-label, non-randomized) and outcome measure (clearance of viremia alone as surrogate endpoint).[28] Several subsequent clinical trials falsified these reported beneficial effects of chloroquine/hydroxychloroquine in the context of COVID-19 and even raised major safety concerns.[29–31]

Moreover, the European Medicines Agency[32] and the Federal Institute for Drugs and Medical Devices (BfArM)[33] have warned of serious side effects, including cardiac arrhythmias and cardiac arrest due to prolongation of the QT interval (time from the beginning of the QRS complex to the end of the T wave in the electrocardiogram). In addition to myocardial effects, hydroxychloroquine may cause neuropsychiatric disorders. According to the warning, chloroquine/hydroxychloroquine is also known to affect the liver, cause neuronal damage that can lead to seizures, and hypoglycemia.[34,35]

Our data show that the time-course in prescription fills for hydroxychloroquine corresponded to the WHO declaring a global pandemic on March 11.[36] The BfArM reported a supply shortage for hydroxychloroquine sulfate 200 mg tablets from April to August 2020.[37] This drug shortage may have contributed to the observed subsequent decline in dispensings and may have affected hydroxychloroquine patients with SLE and rheumatoid arthritis. To counteract this limited availability of hydroxychloroquine for chronically ill patients, on April 4, the BfArM issued a "recommendation" that hydroxychloroquine should only be prescribed with an approved indication documented on the prescription and in a maximum supply of 100 tablets.[38] Misinformation on hydroxychloroquine may have provoked or sustained pre-emptive stockpiling of packages, which ultimately were only used short-term for (prophylactic) use, if any. Further, stock shifting from outpatient to clinic supply could have provoked and pinnacled drug shortages.

Despite the proposed beneficial effect of co-treatment of hydroxychloroquine with azithromycin,[26,31] prescriptions of azithromycin rose only slightly and in contrast to the sharp increase in those of hydroxychloroquine, suggesting that off-label co-treatment was not prevalent in ambulatory care. Currently, there is no evidence of a beneficial use or effectiveness of hydroxychloroquine (in combination with azithromycin) at any disease stage of COVID-19.[29,31,39,40] Of note, the antiviral effects of azithromycin remain questionable.[28]

The combination of lopinavir–ritonavir was mainly administered to hospitalized patients with COVID-19 infection.[6,41] We confirm this finding with only approximately 102 packages per week dispensed in German ambulatory care. Several randomized trials did not find significant clinical benefits or reduction of viral load in patients hospitalized for COVID-19 and gastrointestinal adverse effects were more common in the lopinavir–ritonavir group.[6,7]

4.3 | Use of drugs with conflicting information regarding risks for COVID-19

Our data indicate an inconsistent impact on utilization of drugs with conflicting information regarding risks for or critical outcomes of COVID-19.

Our data do not suggest an insufficient supply of patients with RAASi or statins during or after the first pandemic wave. Pharmacological blockade of the RAAS[42] with ACEi or ARB as well as low-density cholesterol lowering with statins[43] reduces morbidity and mortality in various cardiovascular diseases.

It was shown that RAASi may lead to upregulation of ACE2 expression/activity, and that, therefore, use of ACEi or ARB might be associated with an increased risk for and severity of COVID-19 infection.[9,14] Various studies investigated the association of hypertension, treatment with RAASi and developing severe COVID-19 disease progression. Although there was initial evidence for a difference in the severity of disease in a cohort in Wuhan, China,[44] several other studies concluded that data are insufficient to recommend discontinuation of RAASi.[42,45] Moreover, robust evidence is strongly encouraging patients to continue ACEi or ARB pharmacotherapy during the COVID-19 pandemic.[45–47] Indeed, there is evidence suggesting that these medications might be rather protective against serious lung complications in patients with COVID-19 infection.[46,48] Recently, it was shown that COVID-19 patients are not characterized by major changes in RAS activity in plasma including ACE2 activity.[49]

A study showed an association of lower risk of all-cause mortality in in-hospital COVID-19 patients being treated with statins, compared to patients without statin therapy.[9] We speculate that this observation in a retrospective cohort study might have been influenced by confounding. Experts advise continuation of guideline-based statin therapy, but do not recommend routine intake for COVID-19 patients[50,51] without risk factors for atherosclerotic cardiovascular diseases. Our data indicate for the two most frequently used statins, simvastatin and atorvastatin, a sufficient supply during and after the first pandemic wave indicating that patients continued statin therapy despite public speculations.[52]

A study in diabetic rats found upregulation of ACE2 by ibuprofen, however, lower ACE2-levels were documented in the diabetic compared to healthy rats.[53] Other in vitro studies suggested ibuprofen may even facilitate cleavage of ACE2 from the membrane, preventing membrane-dependent viral entry into the cell.[54,55] In a nationwide register-based cohort study, there was no significant association between ibuprofen prescription claims and severe COVID-19.[56] Recently, ibuprofen use in COVID-19 patients was shown not to be associated with worsening clinical outcomes, compared with paracetamol or no antipyretic.[57] Hence, there is no experimental and clinical data demonstrating appropriate evidence to avoid ibuprofen in COVID-19 patients.[58]

Our data show that recommendations on the avoidance for ibuprofen had a marginal impact on utilization. Dispensings for SHI- and PHI prescriptions as well as OTC-use increased only slightly in March but decreased in April, indicating similar stockpiling of ibuprofen to paracetamol, although not as pronounced. Though unconfirmed, recommendations to avoid intake of ibuprofen[15] and to prefer paracetamol led to a disproportional purchase of paracetamol drug products, as strongly supported by our data for March. Our data show that misinformation of ibuprofen only had a minor impact on patients and prescribers into choosing paracetamol over ibuprofen, with utilization of ibuprofen remaining higher than paracetamol utilization, except for OTC products in March and April.

The BfArM[33] reported several supply shortages of paracetamol since March 2020, partially estimated to last until March and June 2021.[37] In accordance with the Federal Ministry of Health, the Drug Commission of German Pharmacists in March 2020 asked pharmacists to dispense and physicians to prescribe paracetamol only if needed and to limit the number of tablets to treat the actual course of a disease.[59] This highlights the weakness of the distribution system and its vulnerability to sudden (justified) peaks in demands during pandemics.

4.4 | Use of antibiotics

Prescription fills for all systemic antibiotics, amoxicillin, cefuroxime as well as for azithromycin declined substantially (between −37% and −58%). These data were unexpected and in contrast to hydroxychloroquine.

The sharp fall in antibiotic prescriptions compared to 2019, and in particular, the decline in prescriptions for amoxicillin, azithromycin, and cefuroxime, suggests a corresponding decrease in the occurrence of respiratory tract infections. It is possible that this was due to the pandemic-related measures of hygiene, such as the wearing of face masks, frequent hand washing, and social distancing. This observation is in line with data from the Netherlands, where general practitioners have also prescribed fewer antibiotics for respiratory tract infections within a similar time period.[60]

The use of ciprofloxacin did not decrease considerably after the start of the pandemic, as in previous years. We assume that this fluoroquinolone antibiotic was only used for severe infections of the lower respiratory tract and for complicated urinary tract infections, but not for non-serious respiratory tract infections, according to guidelines and recommendations.[61,62]

4.5 | Use of pneumococcal vaccines

The data show that the use of pneumococcal vaccines peaked after a recommendation by the German Federal Minister of Health on March 9, followed by drug shortages and increased again after imports of vaccines from England and Japan.[63–65] Our findings demonstrate that an unexpected rise in use of vaccines, for example, pneumococcal can result in drug shortages. These are difficult to counteract as vaccines have a long manufacturing time.

4.6 | Limitations

Since pseudonymized data were unavailable we do not have patient level information including prescription indications and potential impact on patients' outcome. Whether intake of potentially beneficial drugs against COVID-19 is associated with an increase in long-term adverse events remains to be seen. We can only speculate that increase in utilization was connected to off-label use for COVID-19.

5 | CONCLUSIONS

Apart from the pandemic itself, the data suggest that dissemination of misinformation and unsound speculations as well as supply shortages influenced drug prescribing, utilization, and purchasing behavior. The findings can inform post-pandemic policy to prevent unfounded over- and underprescribing and off-label use as well as drug shortages during a public health crisis.

CONFLICT OF INTEREST

All authors have completed the Pharmacoepidemiology and Drug Safety Conflict of Interest disclosure form and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could have influenced the submitted work.

ETHICS STATEMENT

This study used anonymized claims data, so no ethical approval was needed.

ORCID

Salka Enners https://orcid.org/0000-0001-6706-295X
Gabriele Gradl https://orcid.org/0000-0003-1810-090X
Michael Böhm https://orcid.org/0000-0002-2976-2514
Ulrich Laufs https://orcid.org/0000-0003-2620-9323
Martin Schulz https://orcid.org/0000-0002-5876-7322

REFERENCES

1. Tuccori M, Convertino I, Ferraro S, et al. The impact of the COVID-19 "Infodemic" on drug-utilization behaviors: implications for pharmacovigilance. *Drug Saf*. 2020;43:699-709. https://doi.org/10.1007/s40264-020-00965-w
2. Islam MS, Sarkar T, Khan SH, et al. COVID-19-related Infodemic and its impact on public health: a global social media analysis. *Am J Trop Med Hyg*. 2020;103(4):1621-1629. https://doi.org/10.4269/ajtmh.20-0812
3. Ahn D-G, Shin H-J, Kim M-H, et al. Current status of epidemiology, diagnosis, therapeutics, and vaccines for novel coronavirus disease 2019 (COVID-19). *J Microbiol Biotechnol*. 2020;30(3):313-324. https://doi.org/10.4014/jmb.2003.03011
4. Vaduganathan M, van Meijgaard J, Mehra MR, Joseph J, O'Donnell CJ, Warraich HJ. Prescription fill patterns for commonly used drugs during the COVID-19 pandemic in the United States. *JAMA*. 2020;323(24):2524-2526. https://doi.org/10.1001/jama.2020.9184
5. National Institutes of Health. Considerations for Certain Concomitant Medications in Patients with COVID-19; 2020. https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_13.pdf. Accessed October 16, 2020.
6. Cao B, Wang Y, Wen D, et al. A trial of Lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med*. 2020;382(19):1787-1799. https://doi.org/10.1056/NEJMoa2001282
7. Slomski A. No benefit for Lopinavir-ritonavir in severe COVID-19. *JAMA*. 2020;323(20):1999. https://doi.org/10.1001/jama.2020.6793
8. South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. *Am J Physiol Heart Circ Physiol*. 2020;318(5):H1084-H1090. https://doi.org/10.1152/ajpheart.00217.2020
9. Zhang X-J, Qin J-J, Cheng X, et al. In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. *Cell Metab*. 2020;32(2):176-187.e4. https://doi.org/10.1016/j.cmet.2020.06.015
10. Rodrigues-Diez RR, Tejera-Muñoz A, Marquez-Exposito L, et al. Statins: could an old friend help in the fight against COVID-19? *Br J Pharmacol*. 2020;177(21):4873-4886. https://doi.org/10.1111/bph.15166
11. Li Y-H, Wang Q-X, Zhou J-W, et al. Effects of rosuvastatin on expression of angiotensin-converting enzyme 2 after vascular balloon injury in rats. *J Geriatr Cardiol*. 2013;10(2):151-158. https://doi.org/10.3969/j.issn.1671-5411.2013.02.009
12. Subir R, Jagat JM, Kalyan KG. Pros and cons for use of statins in people with coronavirus disease-19 (COVID-19). *Diabetes Metab Syndr*. 2020;14(5):1225-1229. https://doi.org/10.1016/j.dsx.2020.07.011
13. Ravnskov U. Rapid response: cholesterol-lowering treatment may worsen the outcome of a Covid-19 infection. *BMJ*. 2020;368:m1182.https://www.bmj.com/content/368/bmj.m1182/rr-10 Accessed November 5, 2020.
14. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8(4):e21. https://doi.org/10.1016/S2213-2600(20)30116-8
15. Updated: WHO Now Doesn't Recommend Avoiding Ibuprofen For COVID-19 Symptoms; 2020. https://www.sciencealert.com/who-recommends-to-avoid-taking-ibuprofen-for-covid-19-symptoms. Accessed October 16, 2020.
16. Schulz M, Schumacher PM, Schneider J, Said A, Laufs U. Ugly drug information: ibuprofen and COVID-19; 2020. https://www.schulz-martin.com/2020/03/24/ugly-drug-information-ibuprofen-and-covid-19/. Accessed November 5, 2020.
17. Smith AM, Huber VC. The unexpected impact of vaccines on secondary bacterial infections following influenza. *Viral Immunol*. 2018;31(2):159-173. https://doi.org/10.1089/vim.2017.0138
18. Zanettini C, Omar M, Dinalankara W, Imada EL, Colantuoni E, Parmigiani G, et al. Influenza vaccination and COVID19 mortality in the USA. *medRxiv*. 2020. https://doi.org/10.1101/2020.06.24.20129817

19. Fink G, Orlova-Fink N, Schindler T, Grisi S, Ferrer AP, Daubenberger C, et al. Inactivated trivalent influenza vaccine is associated with lower mortality among Covid-19 patients in Brazil; 2020.
20. Marín-Hernández D, Schwartz RE, Nixon DF. Epidemiological evidence for association between higher influenza vaccine uptake in the elderly and lower COVID-19 deaths in Italy. *J Med Virol*. 2020;93(5):2600-2601. https://doi.org/10.1002/jmv.26120
21. Noale M, Trevisan C, Maggi S, et al. The association between influenza and pneumococcal vaccinations and SARS-Cov-2 infection: data from the EPICOVID19 web-based survey. *Vaccines*. 2020;8(3):471. https://doi.org/10.3390/vaccines8030471
22. Rudolph UM, Enners S, Kieble M, et al. Impact of angiotensin receptor blocker product recalls on antihypertensive prescribing in Germany. *J Hum Hypertens*. 2020. https://doi.org/10.1038/s41371-020-00425-z
23. German Institute of Medical Documentation and Information. German anatomical therapeutic chemical (ATC)-classification with defined daily doses (DDD) for Germany. https://www.dimdi.de/dynamic/en/drugs/atc-classification/
24. Insight Health GmbH & Co. KG. APO Fusion Plus 2020. https://www.insight-health.de/
25. Federal Ministry of Health. KM6-statistics; 2021. http://www.bmg.bund.de
26. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020;56(1):105949. https://doi.org/10.1016/j.ijantimicag.2020.105949
27. Alexander GC, Tajanlangit M, Heyward J, Mansour O, Qato DM, Stafford RS. Use and content of primary care office-based vs telemedicine care visits during the COVID-19 pandemic in the US. *JAMA Netw Open*. 2020;3(10):e2021476. https://doi.org/10.1001/jamanetworkopen.2020.21476
28. Machiels JD, Bleeker-Rovers CP, ter Heine R, et al. Reply to Gautret et al: hydroxychloroquine sulfate and azithromycin for COVID-19: what is the evidence and what are the risks? *Int J Antimicrob Agents*. 2020;56(1):106056. https://doi.org/10.1016/j.ijantimicag.2020.106056
29. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *JAMA*. 2020;323(24):2493-2502. https://doi.org/10.1001/jama.2020.8630
30. Bai C, Chotirmall SH, Rello J, et al. Updated guidance on the management of COVID-19: from an American Thoracic Society/European Respiratory Society coordinated international task force (29 July 2020). *Eur Respir Rev*. 2020;29(157):200287. https://doi.org/10.1183/16000617.0287-2020
31. Abella BS, Jolkovsky EL, Biney BT, et al. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial. *JAMA Intern Med*. 2020;181(2):195-202. https://doi.org/10.1001/jamainternmed.2020.6319
32. European Medicines Agency. COVID-19: reminder of risk of serious side effects with chloroquine and hydroxychloroquine; 2020. https://www.ema.europa.eu/en/news/covid-19-reminder-risk-serious-side-effects-chloroquine-hydroxychloroquine. Accessed November 5, 2020.
33. Bundesinstitut für Arzneimittel und Medizinprodukte. Hydroxychloroquin: Risiko für schwerwiegende Nebenwirkungen bei Anwendung zur Behandlung von COVID-19; 2020. https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RI/2020/RI-hydroxychloroquin.html. Accessed November 5, 2020.
34. European Medicines Agency. *COVID-19: Reminder of Risk of Serious Side Effects with Chloroquine and Hydroxychloroquine*. Amsterdam: European Medicines Agency. 2020. https://www.ema.europa.eu/en/news/covid-19-reminder-risk-serious-side-effects-chloroquine-hydroxychloroquine. Accessed October 22, 2020
35. Bundesinstitut für Arzneimittel und Medizinprodukte. Weitere Arzneimittelrisiken - Hydroxychloroquin: Risiko für schwerwiegende Nebenwirkungen bei Anwendung zur Behandlung von COVID-19; 2020. https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RI/2020/RI-hydroxychloroquin.html. Accessed October 22, 2020
36. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. *Acta Biomed*. 2020;91(1):157-160. https://doi.org/10.23750/abm.v91i1.9397
37. Bundesinstitut für Arzneimittel und Medizinprodukte. Lieferengpässe für Humanarzneimittel in Deutschland (ohne Impfstoffe). https://lieferengpass.bfarm.de/ords/f?p=30274:3:6633884200576:NO
38. Bundesinstitut für Arzneimittel und Medizinprodukte. Hydroxychloroquin - Sicherstellung der Versorgung von chronisch kranken Patientinnen und Patienten in den zugelassenen Indikationen. https://www.bfarm.de/DE/Service/Presse/Themendossiers/Coronavirus/Anlagen/Off_Label_Use_Hydroxychloroquin.pdf?__blob=publicationFile&v=1. Accessed October 31, 2020.
39. Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. *N Engl J Med*. 2020;383(6):517-525. https://doi.org/10.1056/NEJMoa2016638
40. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. *Ann Intern Med*. 2020;173(8):623-631. https://doi.org/10.7326/M20-4207
41. Horby PW, Mafham M, Bell JL, et al. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet*. 2020;396(10259):1345-1352. https://doi.org/10.1016/S0140-6736(20)32013-4
42. Vaduganathan M, Michel T, McMurray J, Pfeffer M, Solomon S. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. *N Engl J Med*. 2020;382(17):1653-1659. https://doi.org/10.1056/NEJMsr2005760
43. Mach F, Baigent C, Catapano A, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Atherosclerosis*. 2019;290:140-205. https://doi.org/10.1016/j.atherosclerosis.2019.08.014
44. Feng Y, Ling Y, Bai T, et al. COVID-19 with different severities: a multicenter study of clinical features. *Am J Respir Crit Care Med*. 2020;201(11):1380-1388. https://doi.org/10.1164/rccm.202002-0445OC
45. Baral R, White M, Vassiliou VS. Effect of renin-angiotensin-aldosterone system inhibitors in patients with COVID-19: a systematic review and meta-analysis of 28,872 patients. *Curr Atheroscler Rep*. 2020;22(10):61. https://doi.org/10.1007/s11883-020-00880-6
46. Lopes RD, Macedo AVS, Moll-Bernardes RJ, et al. Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—the BRACE CORONA trial. *Am Heart J*. 2020;226:49-59. https://doi.org/10.1016/j.ahj.2020.05.002
47. de Simone G. Position statement of the ESC Council on hypertension on ACE-inhibitors and angiotensin receptor blockers; 2020. https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang. Accessed July 21, 2020.
48. Braude P, Carter B, Short R, et al. The influence of ACE inhibitors and ARBs on hospital length of stay and survival in people with COVID-19. *Int J Cardiol Heart Vasc*. 2020;31:100660. https://doi.org/10.1016/j.ijcha.2020.100660
49. Kintscher U, Slagman A, Domenig O, et al. Plasma angiotensin peptide profiling and ACE (angiotensin-converting enzyme)-2 activity in COVID-19 patients treated with pharmacological blockers of the renin-angiotensin system. *Hypertension*. 2020;76(5):e34-e36. https://doi.org/10.1161/HYPERTENSIONAHA.120.15841
50. Dashti-Khavidaki S, Khalili H. Considerations for statin therapy in patients with COVID-19. *Pharmacotherapy*. 2020;40(5):484-486. https://doi.org/10.1002/phar.2397

51. Deutsches Ärzteblatt. Statine könnten Sterberisiko bei COVID-19 senken. https://www.aerzteblatt.de/nachrichten/114149/Statine-koennten-Sterberisiko-bei-COVID-19-senken. Accessed November 5, 2020.
52. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. *Eur Heart J*. 2016;37(11):908-916. https://doi.org/10.1093/eurheartj/ehv641
53. Qiao W, Wang C, Chen B, et al. Ibuprofen attenuates cardiac fibrosis in streptozotocin-induced diabetic rats. *Cardiology*. 2015;131(2):97-106. https://doi.org/10.1159/000375362
54. Moore N, Carleton B, Blin P, Bosco-Levy P, Droz C. Does ibuprofen worsen COVID-19? *Drug Saf*. 2020;43(7):611-614. https://doi.org/10.1007/s40264-020-00953-0
55. Smart L, Fawkes N, Goggin P, et al. A narrative review of the potential pharmacological influence and safety of ibuprofen on coronavirus disease 19 (COVID-19), ACE2, and the immune system: a dichotomy of expectation and reality. *Inflammopharmacology*. 2020;28(5):1141-1152. https://doi.org/10.1007/s10787-020-00745-z
56. Kragholm K, Gerds TA, Fosbøl E, et al. Association between prescribed ibuprofen and severe COVID-19 infection: a Nationwide register-based cohort study. *Clin Transl Sci*. 2020;13(6):1103-1107. https://doi.org/10.1111/cts.12904
57. Rinott E, Kozer E, Shapira Y, Bar-Haim A, Youngster I. Ibuprofen use and clinical outcomes in COVID-19 patients. *Clin Microbiol Infect*. 2020;26(9):1259.e5-1259.e7. https://doi.org/10.1016/j.cmi.2020.06.003
58. Kelleni MT. ACEIs, ARBs, ibuprofen originally linked to COVID-19: the other side of the mirror. *Inflammopharmacology*. 2020;28(6):1477-1480. https://doi.org/10.1007/s10787-020-00755-x
59. Drug Commission of German Pharmacists. 14/20 Informationen der Institutionen und Behörden: BMG: Mengenbeschränkte Belieferung bzw. Abgabe von Paracetamol-haltigen Arzneimitteln durch Hersteller, pharmazeutische Großhändler und Apotheken [Federal Ministry of Health: Delivery or dispensing of paracetamol-containing drugs by manufacturers, pharmaceutical wholesalers and pharmacies]; 2020. https://www.abda.de/fuer-apotheker/arzneimittelkommission/amk-nachrichten/detail/14-20-informationen-der-institutionen-und-behoerden-bmg-mengenbeschraenkte-belieferung-bzw-abgabe-von-paracetamol-haltigen-arzneimitteln-durch-hersteller-pharmazeutische-grosshaendler-und-apotheken/. Accessed June 2, 2021.
60. Hek K. Voorschrijven van antibiotica door de huisarts tijdens de coronapandemie. https://nivel.nl/sites/default/files/bestanden/1003882_0.pdf. Accessed October 20, 2020.
61. German College of General Practitioners and Family Physicians. [S2k Leitlinie: Ohrenschmerzen, AWMF-Reg.-Nr. 053/009], [S2k guideline: Earache]; 2014. https://www.awmf.org/uploads/tx_szleitlinien/053-009l_S2k_Ohrenschmerzen_2014-12-abgelaufen.pdf. Accessed November 4, 2020.
62. German Society of Oto-Rhino-Laryngology, Head and Neck Surgery, German College of General Practitioners and Family Physicians. [S2k Leitlinie: Rhinosinusitis, AWMF-Reg.-Nr. 017/049 (HNO) und 053/012 (DEGAM)], [S2k guideline: Rhinosinusitis]; 2017. http://www.awmf.org/uploads/tx_szleitlinien/017-049_und_053-012l_S2k_Rhinosinusitis_2017-07_01.pdf. Accessed May 31, 2018.
63. BMG. Bekanntmachung nach § 79 Absatz 5 des Arzneimittelgesetzes; 2020. https://www.bundesanzeiger.de/pub/publication/TRupGZewRRS6lTjtg0G;wwwsid=A1C9D39D6BDFD75E8267B8069B0C9EA6.web06-pub?0. Accessed October 22, 2020.
64. Wallenfels M. Pneumokokken-Vakzine: Corona führt zu hoher Impfbereitschaft. *Deutsches Ärzteblatt*. 2020;17(9):29. https://doi.org/10.1007/s11298-020-8043-4
65. Robert Koch-Institut. COVID-19 und Impfen: FAQ. https://www.rki.de/SharedDocs/FAQ/COVID-Impfen/COVID-19-Impfen.html. Accessed November 5, 2020.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Enners S, Gradl G, Kieble M, Böhm M, Laufs U, Schulz M. Utilization of drugs with reports on potential efficacy or harm on COVID-19 before, during, and after the first pandemic wave. *Pharmacoepidemiol Drug Saf*. 2021;1-11. https://doi.org/10.1002/pds.5324