Aus der Abteilung für Infektions- und Tropenmedizin

Klinikum der Ludwig-Maximilians-Universität München

Screening and Testing of Patients at the COVID-19 Testing Unit Munich: Exposure, patient characteristics, test results and modelling of a triage scoring system

Dissertation

zum Erwerb des Doktorgrades der Medizin

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

vorgelegt von

Hannah Tuulikki Hohl

aus

Linz, Österreich

Jahr

2024

Mit Genehmigung der Medizinischen Fakultät der

Ludwig-Maximilians-Universität München

Erster Gutachter:	*Prof. Dr. med. Michael Hoelscher*
Zweiter Gutachter:	Priv. Doz. Dr. Günter Fröschl
Dritter Gutachter:	Prof. Dr. Sebastian Theurich
ggf. weitere Gutachter:	Priv. Doz. Dr. Karoline Lukaschek
Mitbetreuung durch den promovierten Mitarbeiter:	
Dekan:	Prof. Dr. med. Thomas Gudermann
Tag der mündlichen Prüfung:	14.03.2024

Affidavit

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Promotionsbüro
Medizinische Fakultät

Affidavit

Hohl, Hannah Tuulikki

Surname, first name

I hereby declare, that the submitted thesis entitled:

Screening and Testing of Patients at the COVID-19 Testing Unit Munich: Exposure, patient characteristics, test results and modelling of a triage scoring system

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the dissertation presented here has not been submitted in the same or similar form to any other institution for the purpose of obtaining an academic degree.

Munich, 25 March 2024
place, date

Hannah Tuulikki Hohl
Signature doctoral candidate

Table of content

List of abbreviations

AIDS = acquired immunodeficiency syndrome

BTS = “Bayerische Teststrategie”, a SARS-CoV-2 testing program by the Bavarian state

COVID-19 = coronavirus disease 2019

CTU = Corona Testing Unit Munich

HCW = healthcare worker

HIV = human immunodeficiency viruses

IQR = interquartile range

MERS-CoV = Middle East respiratory syndrome coronavirus

PCR = polymerase chain reaction

RNA = ribonucleic acid

Rt-PCR = real-time polymerase chain reaction

SARS-CoV-1/2 = severe acute respiratory syndrome coronavirus 1/2

WHO= World Health Organization

List of publications

Paper I

Hohl HT, Heumann C, Rothe C, Hoelscher M, Janke C, Froeschl G. COVID-19 Testing Unit Munich: Impact of Public Health and Safety Measures on Patient Characteristics and Test Results, January to September 2020. Front Public Health. 2022 Mar 22;10:856189.

Paper II

Hohl HT, Froeschl G, Hoelscher M, Heumann C. Modelling of a triage scoring tool for SARS-COV-2 PCR testing in health-care workers: data from the first German COVID-19 Testing Unit in Munich. BMC Infect Dis. 2022 Aug 1;22(1):664.

Contributions to the publications

Contribution to paper I

Together with Christian Heumann and Guenter Froeschl, Hannah Tuulikki Hohl conceived the study and conducted the data analysis. Data compilation and editing was conducted by HTH. GF and HTH wrote the manuscript, with 80% of the material written by HTH. HTH conducted the qualitative data analysis in collaboration with Christian Janke, Camilla Rothe and Michael Hoelscher. Final drafting of the manuscript was done jointly with all co-authors.

Contribution to paper II

Christian Heumann, Guenter Froeschl, and Hannah Tuulikki Hohl were involved in the design of the study as well as the data analysis. HTH was curating the data and created the original draft. CH, GF, HTH, and MH contributed to the review and editing.

Contribution to unpublished analyses (Appendix)

Christian Heumann, Guenter Froeschl, and Hannah Tuulikki Hohl together formulated the research questions and participated in the review. HTH conducted the data analysis and created the figures.

1. Introduction

Emerging (and re-emerging) infectious diseases, such as COVID-19, have the potential to spread rapidly and cause significant harm to the global community. Understanding the origins, transmission, and characteristics of these diseases is crucial for developing effective strategies for the detection of cases, containment of transmissions, and treatment. Furthermore, research can shed light on the need for response measures and preparedness in the face of future pandemics. Thus, studying emerging infectious diseases is essential for protecting public health and promoting global health security.

1.1 Public health responses to infectious disease outbreaks in the 21st century

COVID-19 is merely one of numerous infectious diseases that, in the last decades, have seen international outbreaks up to a pandemic extent. Other examples of emerging (or re-emerging) viruses from the 21st century with a widespread impact include the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1, 2002-2003), the influenza A virus subtype H1N1 (2009-2010), and the Middle East respiratory syndrome coronavirus (MERS-CoV, 2015, 2018), though other kinds of pathogens also have the potential for global spread, such as numerous outbreaks throughout the history of cholera, caused by the bacterium vibrio cholerae [1, 2].

Infectious disease outbreaks have the potential to significantly harm human health. According to estimations of the World Health Organization (WHO), infectious diseases were responsible for approximately 14 percent of global deaths in 2019 [3]. Low- and middle-income countries have shown to be disproportionally affected [4]. In high-income countries, indigenous populations and disadvantaged minorities bear the highest mortality rates through infectious diseases [5]. Apart from mortality and morbidity, the multifaceted ‘burdens of disease’ also include an economic and social impact and can be at times difficult to quantify.

A future rise in pandemics has to be expected due to emerging infectious pathogens similar to SARS-CoV-2: Firstly, factors that benefit zoonotic (animal-to-human) transmission are increasing (e.g., intrusion of humans into the habitat of wild species, intensive livestock farming, and geographic shifts and expansions of habitats due to climate change), with zoonoses being estimated to involve a majority of emerging infectious diseases [6]. Secondly, increased connectivity due to urbanization, globalization, and displacement of populations facilitates human-to-human transmission [7].

McNeill [8] summarizes the importance for the international community to evaluate and improve its abilities to respond to emerging diseases, stating that:

> *In any effort to understand what lies ahead, as much as what lies behind, the role of infectious disease cannot properly be left out of consideration. Ingenuity, knowledge, and organization alter but cannot cancel humanity's vulnerability to invasion by parasitic forms of life. Infectious disease which antedated the emergence of humankind will last as long as humanity itself, and will surely remain, as it has been hitherto, one of the fundamental parameters and determinants of human history.*

1.2 Components of the primary response to emerging infectious diseases

From the perspective of healthcare providers, relevant elements of the first response to emerging infectious diseases include the detection of cases, containment of transmission, and treatment, where necessary. All of these factors vary widely between pathogens and therefore, research about said factors has to be at the center of attention in the case of a newly spread, unknown pathogen. Being primarily involved in the diagnosis of COVID-19 cases, our research focused on the first two elements.

1.2.1 Detection of cases

A precise diagnosis is vital for accurate risk-assessment and treatment of patients. In case of infections, this includes the identification of the specific pathogen through a wide variety of laboratory tests, such as assessment of morphological features, biochemical tests (e.g. for catalase oxidase activity in bacteria), culturing, polymerase chain reaction (PCR), or genome sequencing [9]. Point of care testing, such as lateral flow tests, though sometimes lacking in sensitivity and specificity, tend to be easier to conduct and less costly than laboratory-based tests, which helps in making testing more widely available [10].

However, diagnostic tests need time to be developed and to be made available on a larger scale. When diagnostic resources and capabilities are limited, accurate knowledge on the specific signs and symptoms of an infection (with the emerging pathogen) are vital to, firstly, create case definitions, and secondly, allow for triage criteria for further diagnostics [11].

1.2.2 Containment of transmissions

Strategies for the containment of person-to-person transmissions exist not only on an individual level, but also at the level of social, economic and political decision-makers and stakeholders [12].

On a population-wide scale, public health and safety measures are implemented. Movement and personal contacts can be restricted in confirmed cases, suspect cases, and/or in the general public, depending on the characteristics of a disease. Possible carriers of the pathogen may be tested for infection. The distribution of personal protective equipment and the education of healthcare workers and the public on infection prevention may also play a role in curbing transmissions. Public health measures must, in their implementation, undergo constant revision as infection rates fluctuate and scientific knowledge is being developed.

On an individual level, knowledge, attitude, and practice of personal protection (combined with access to adequate personal protective equipment) can aid to prevent infections. Vaccines have proven to be a central tool in the containment of transmission of some diseases, such as influenza and poliomyelitis, while the development and roll-out of vaccines targeting other infectious diseases continues to challenge the scientific community (with prominent examples including HIV/AIDS and hepatitis C) [13-15].

1.3 The COVID-19 pandemic

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the viral agent causing the coronavirus disease 2019 (COVID-19), emerged in the Wuhan province of China in December of 2019. Its genome was first sequenced by the National Institute of Viral Disease Control and Prevention of China in January of 2020 [16]. The RNA virus mainly causes, like others in the family of Coronaviridae, respiratory tract symptoms, such as cough, rhinorrhea, and dyspnea [17, 18]. Current estimations of case fatality rates, i.e., the percentage of deaths in infected persons, vary highly among different countries, currently being between 0.0% and 18.1%, with a global average of 0.9% [19]. Naturally, these numbers do not include a presumably high number of unrecorded infections and deaths. For instance, according to a WHO estimate from 2021, six out of seven COVID-19 infections in Africa went undetected due to limited testing capacity [20]. Its high contagiousness through direct contact, aerosol- and fomite-transmission, combined with asymptomatic and presymptomatic transmissibility has led to a rapid global spread, with the WHO declaring a pandemic on 11 March 2020 [21-23]. By 4 March 2023, over 750 million infections have been reported worldwide [19].

1.3.1 Research questions from the point of view of testing units

Information on the before mentioned components of the primary response to emerging infectious diseases can aid individuals and organizations tasked with the testing for infectious diseases. In our research, we aimed to focus on questions that have emerged in our own practice in the context of the early COVID-19 pandemic in Munich, Germany.

1.3.1.1 Factors influencing testing numbers and positivity rates

In an uncertain situation such as the outbreak of a little-known pathogen, the ability to plan ahead is obviously limited. It is understood that the number of tests needed to be performed is not exclusively dependent on the basic reproduction number (R_0) of a pathogen. Knowledge about the influence of additional factors ideally allows public health stakeholders to better plan ahead and adapt their testing services in terms of resources such as personnel and equipment.

The relationship between public policies and testing is also of interest to those who wish to study the effectiveness of said public policies.

We thus aimed to, by the example of one testing unit, study the course of testing numbers and test positivity and provide insight into the complex interrelations between those and a multitude of influencing factors.

1.3.1.2 Clinical scoring models for COVID-19

In an early outbreak situation, a limit of resources is common. Some diagnostic tests can be uncomfortable for the patient or even bear potential health risks. In diagnostic tests with positive and negative predictive values below the optimum of 100 percent, false positive and false negative results can have a considerable effect on the patient and their surroundings. Moreover, the economic reasonableness of diagnostics must always be taken into account, especially so in a health care system with costs covered by the public.

For these reasons, a pre-selection or differentiation of individuals (both in diagnostics and kind of treatment) is sensible and necessary. This is often done by means of scores which, ideally easy to calculate and apply, are intended to provide a standardized decision-making aid. Examples of established scores for infectious diseases in Germany include the CRB-65 score for estimating the mortality risk of patients suffering from pneumonia, DUKE criteria for the diagnosis of endocarditis, and the SOFA score for acute organ dysfunction, which is included in the diagnosis of sepsis [24-26].

The currently most commonly applied methods for diagnosis of an acute SARS-CoV-2 infection include polymerase chain reaction (PCR) and rapid antigen tests, which by March 2023 are both widely available [27]. It can be assumed that institutions which are conducting research on COVID-19 also have the infrastructure for at least one of these methods for pathogen identification and that, for this reason, focus has shifted away from research on models that aim to predict test positivity from clinical predictors [18]. In contrast, plenty of models have been developed to predict clinical outcome following positive test results [28-36]. In resource-scarce settings, access to SARS-CoV-2 tests can still be limited though, which makes triage for testing necessary [37].

In the case of different clinical manifestations or differential outcomes between population groups, it may be appropriate to establish separate triage criteria for individual cohorts [38]. We chose to investigate healthcare workers specifically, who may differ in sociodemographic factors and potential risk behavior as compared to the general population.

1.3.2 Research setting

The COVID-19 Testing Unit (CTU) of the Department of Tropical Medicine and Infectious Diseases of the LMU Munich, Germany was involved in the detection of cases and containment of transmissions. Having conducted the first SARS-CoV-2 test with a positive result in Germany on 27 January 2020, it played a role especially in the very early phase of the pandemic in southern Germany [22]. By the time of completion of the project on 26 March, 2021, over 10,000 tests were recorded [39]. Facing limited capacities in space, resources, and staff and to adhere to guidelines by the Robert Koch Institute (RKI), a German federal government agency responsible for disease control and prevention, triage was conducted to identify a clinical indication and to prioritize population groups that were considered essential in pandemic response and maintenance of public infrastructure, such as healthcare workers. Laboratory testing was conducted by external partners through real-time polymerase chain reaction (PCR) of naso- or oropharyngeal swabs. The subsequent research analyses were performed retrospectively on anonymized data derived from case report forms (which were, in most cases, filled out by patients at the time of admission for testing) and their corresponding PCR test results from 27 January to 30 September 2020. Since the observations cover the first until the beginning of the second infection wave in Munich, our research reflects very time- and space-specific data from a single center at the beginning of the pandemic in Bavaria.

2. Summary (in English)

2.1 Interactions between public health measures, testing numbers and test results [40]

In public health research, a multitude of influencing factors on health must be paid attention to. Information about these factors can change especially rapidly at the beginning of a widespread outbreak of a previously unknown pathogen, as the scientific community combines efforts to generate answers to vital questions. As case numbers increase rapidly, fast-paced changes in public health and safety measures might be implemented to try and keep control of the situation. All of these changes combined can, from our own experience, make healthcare work challenging and rather unforeseeable. In our publication in *Frontiers in Public Health*, we collected and classified some of the multitude of factors that had an influence on the number of performed tests and their results at the CTU Munich in the observed period. From the perspective of a monocentric organization, changes in testing strategies (such as indication-free, free of charge testing through the “Bayerische Teststrategie”) and testing capacities (of the unit itself as well as of surrounding providers) appeared to have a bigger impact on testing numbers and test results than public health measures (such as mask mandates or lockdowns). Other possible influencing factors on individual testing demand include release from isolation after having tested positive and distance between the testing unit and the place of residence. The latter are not separately analyzed in our previous publications but are included in the “Appendix” section below. A profound understanding of these influences might help infectious disease testing units to anticipate changes in demand and supply and to react accordingly. Moreover, the mere knowledge that a multitude of factors that dictate this work, such as testing demand and supply, triage criteria and methods might change rapidly can help to keep organizational structures quickly adaptable.

The reported case numbers of COVID-19 are still commonly used by researchers, policy makers and the press as a proxy measure for the infection rate, although it has to be assumed that in every system in which universal, long-term testing of all individuals is not achievable, the number of positive test results will never be equal to the real number of infections. We show that a multitude of confounders can be identified, which influence the utilization of testing offers, test positivity rate and the total number of positive cases. Therefore, the measured incidence, although a valuable item for research and policy making, must not be considered equal, or even proportional, to the real incidence in a population.

2.2 Development of a COVID-19 triage scoring model for healthcare workers [41]

As previously argued, triage can be used to cut down on as many resources and any potential risks arising from the testing process, while leaving as few positive cases undetected as possible. Our goal was both to generate a triage model from our data set and to highlight potential pitfalls in developing such a score.

In our publication in *BMC Infectious Diseases*, we chose to investigate healthcare workers specifically, who differ in sociodemographic factors and potential risk behavior as compared to the general population: our cohort of healthcare workers (HCW) was shown to be predominantly young, female, and to have undergone healthcare training as compared to the general population. Naturally, many of them are in more intensive personal contact with a comparatively large number of people, and, especially at the beginning of the pandemic when resources to protect against infection were rather inadequate, were at particular risk when working at healthcare facilities.

This claim is supported by the fact that in our triage score, the correlation between a separate query of contact with SARS-CoV-2 positive patients and testing results was shown to be statistically significant. It has to be acknowledged that the external validity of our proposed score is limited, especially when being applied to a population that is not comprised of HCW. Of course, a focus on testing HCW in the context of an infectious disease with partly low- to asymptomatic courses is particularly relevant to prevent nosocomial infections in both patients and staff, and to preserve the already limited HCW work force [22].

The further variables included in our score are now widely recognized as classic symptoms of COVID-19 infection [18]. The common feature of all variables is that they are available with a focused anamnesis and without any further time-, resource-consuming or invasive tests, which makes them suitable for low-threshold testing in pre-hospital or outpatient conditions.

By plotting odds ratios in logistic regressions of the test result depending on individual variables at different time points with a growing data set, we were able to clearly show why a constant revision and further development of triage criteria is meaningful and necessary.

2.3 Conclusion

The COVID-19 pandemic has once again shown that systems have to be in place in preparation of emerging infections: ways to detect and report new infections, an infrastructure to study new infectious agents, an adaptive and robust health system, and national and international coordination mechanisms represent only a few amongst many [42].

The WHO resolution on new, emerging, and re-emerging infectious diseases of 1995 already called for immediate action from member states [43]:

> *(…) to strengthen national and local programmes of active surveillance for infectious diseases, ensuring that efforts are directed to early detection of outbreaks and prompt identification of new, emerging and re-emerging infectious diseases; (…) to control outbreaks and promote accurate and timely reporting of cases at national and international levels; (…).*

Despite these urgings, shortcomings in previous pandemics and the ongoing COVID-19 outbreak have shown the need for continuing efforts to improve preventative measures and preparations ahead of the emergence of infectious diseases [12, 44]. The Global Health Security Index of 2021 [45] states that *"(…) despite significant steps taken by countries to respond to the COVID-19 pandemic, all countries remain dangerously unprepared to meet future epidemic and pandemic threats".* Apart from numerous countries lacking necessary resources, it is not always possible to predict how effectively any preexisting resources will be employed by decision makers. One example mentioned is the subpar outbreak response of the government at the time of the United States of America, considering the available economic and research resources. The Global Health Security Index has also assessed the extent to which countries are willing to use resources gained in this pandemic for future outbreaks, such as ensuring that testing capacity can be used for other pathogens in the long term.

Now that the World Health Organization has acknowledged the COVID-19 pandemic to be at a “transition point” [46] with some experts even declaring the end of the pandemic [47], the global community must begin to start preparing for the inevitable next infectious disease outbreak.

3. Zusammenfassung (deutsch)

3.1 Wechselwirkung zwischen öffentlichen Maßnahmen, Testzahlen und -Ergebnissen [40]

In der "Public Health"-Forschung muss eine Vielzahl von Einflussfaktoren auf das öffentliche Gut Gesundheit beachtet werden. Informationen über diese Faktoren können sich zu Beginn eines Ausbruchs eines bisher unbekannten Krankheitserregers besonders schnell ändern, wenn die wissenschaftliche Gemeinschaft ihre Kräfte auf Pandemie-relevante Forschung konzentriert. Bei raschem Anstieg der Fallzahlen wird womöglich mit sprunghaften Änderungen von öffentlichen Maßnahmen versucht, die Situation unter Kontrolle zu halten. All diese Veränderungen zusammengenommen können, wie wir aus eigener Erfahrung wissen, die Arbeit im Gesundheitswesen herausfordernd und oft auch unvorhersehbar machen. In unserer Publikation in *Frontiers in Public Health* haben wir einige der vielen Faktoren, die die Anzahl der durchgeführten Tests und deren Ergebnisse an der CTU München im beobachteten Zeitraum beeinflusst haben, gesammelt und klassifiziert. Aus der Perspektive einer monozentrischen Organisation schienen Veränderungen in den Teststrategien (wie z.B. indikationslose, kostenlose Tests durch die "Bayerische Teststrategie") und Testkapazitäten (der CTU selbst sowie umliegender Anbieter) einen größeren Einfluss auf die Testzahlen und -ergebnisse zu haben als andere Maßnahmen des öffentlichen Gesundheitswesens (wie z.B. Maskenpflicht oder Lockdowns). Weitere mögliche Einflussfaktoren auf die Inanspruchnahme von Testangeboten sind die Entlassung aus der Isolation nach einem positiven Test und die Entfernung zwischen der Teststelle und dem Wohnort. Letztere wurden in unseren bisherigen Veröffentlichungen nicht gesondert analysiert, sind aber im nachstehenden Abschnitt "Appendix" aufgeführt. Das Bewusstsein für diese Einflüsse kann Testzentren für Infektionskrankheiten helfen, Veränderungen bei Nachfrage und Angebot zu antizipieren und entsprechend zu reagieren. Auch alleine durch das Wissen, dass sich eine Vielzahl von Faktoren, die den Testdurchsatz beeinflussen (wie Testnachfrage und -Angebot, Triage-

Kriterien und -Methoden) schnell ändern, können Gesundheitseinrichtungen schneller und bedarfsgerechter angepasst werden.

Die gemeldete Inzidenz von COVID-19 wird von Forschern, politischen Entscheidungsträgern und der Presse immer noch häufig als Maß für die Infektionsrate verwendet, obwohl davon ausgegangen werden muss, dass in jedem System, in dem eine umfassende Testung aller Personen langfristig nicht möglich ist, die Zahl der positiven Testergebnisse niemals der tatsächlichen Zahl der Infizierten entsprechen wird. Wir konnten zeigen, dass eine Vielzahl von Confoundern identifiziert werden kann, die die Testpositivitätsrate und die Gesamtzahl der positiven Fälle beeinflusst. Daher darf die gemessene Inzidenz, auch wenn sie für die Forschung und die politische Entscheidungsfindung wertvoll ist, nicht als gleichwertig oder gar proportional zur tatsächlichen Inzidenz in einer Bevölkerung angesehen werden.

3.2 Entwicklung eines COVID-19 Triage-Scoring-Modells für Gesundheitspersonal [41]

Wie schon zuvor erörtert, sind Triage-Kriterien sinnvoll, um möglichst Ressourcen einzusparen sowie etwaige durch den Testablauf entstehende Risiken einzudämmen, während möglichst wenige positive Fälle unentdeckt bleiben sollten. Unser Ziel war es, einen Triage-Score aus unserem Datensatz zu generieren und mögliche Fallstricke bei der Erarbeitung eines solchen Triage-Scores aufzuzeigen.

Im Falle von unterschiedlicher klinischer Manifestation oder unterschiedlichem Outcome zwischen Bevölkerungsgruppen kann es sinnvoll sein, für Bevölkerungsgruppen individuelle Triage-Kriterien festzulegen. So haben wir uns für eine gesonderte Betrachtung von Gesundheitspersonal entschieden, welche sich im Vergleich zur Gesamtbevölkerung in soziodemografischen Faktoren unterscheiden: Unsere Kohorte von Gesundheitspersonal stellte sich im Vergleich zur Gesamtbevölkerung als überwiegend jung, weiblich und naturgemäß mit einer absolvierten Ausbildung im Gesundheitswesen dar. Natürlich steht sie in intensiverem Kontakt mit einer vergleichsweise großen Anzahl Menschen, und war, vor allem am Anfang der Pandemie bei unzureichenden Ressourcen zum Schutz vor Ansteckung, bei der Arbeit in Gesundheitseinrichtungen einem besonderen Risiko ausgesetzt.

Der dargestellte Umstand wird gespiegelt durch die Tatsache, dass sich bei unserem Triage-Score die Korrelation zwischen einer gesonderten Abfrage von Kontakt zu SARS-CoV-2-positiven Patienten und dem Testergebnis als statistisch signifikant zeigte. Eine Anwendung eines solchen Scores bei der Gesamtbevölkerung ist als kaum sinnvoll zu betrachten, die externe Validität ist damit vor allem in Bezug auf Personengruppen außerhalb des Gesundheitswesens eingeschränkt. Natürlich ist ein Fokus auf die Testung von Gesundheitspersonal in dem Kontext einer Infektionskrankheit mit teils wenig- bis asymptomatischen Verläufen besonders relevant, um nosokomiale Ansteckungen von sowohl PatientInnen als auch MitarbeiterInnen zu verhindern [22].

Die weiteren in unserem Score enthaltenen Variablen sind mittlerweile als klassische Symptome für eine COVID-19-Infektion allgemein bekannt [18]. Allen Variablen ist gemein, dass sie mit einer gezielten Anamnese und ohne weitere zeit- und ressourcenaufwendige oder invasive Tests zu erheben sind, was sie für niedrigschwellige Tests bei vorstationären beziehungsweise in ambulanten Situationen geeignet macht.

Mit der graphischen Aufarbeitung von Odds-Ratios in logistischen Regressionen mit dem Testergebnis als Zielvariable und abhängig von einzelnen Variablen an verschiedenen Zeitpunkten mit wachsendem Datensatz konnten wir anschaulich zeigen, warum eine stete Überarbeitung und Weiterentwicklung von Triage-Kriterien sinnvoll und notwendig ist.

3.3 Ausblick

Die COVID-19-Pandemie hat einmal mehr gezeigt, dass Systeme zur Vorbereitung auf neu auftretende Infektionen vorhanden sein müssen - Möglichkeiten zur Erkennung und Meldung neuer Infektionen, eine Infrastruktur zur Erforschung neuer Erreger, ein anpassungsfähiges und robustes Gesundheitssystem sowie nationale und internationale Koordinierungsmechanismen sind nur einige von vielen [42].

Bereits in der WHO-Resolution über neue, neu auftretende und wiederauftauchende Infektionskrankheiten von 1995 wurden die Mitgliedsstaaten zu sofortigem Handeln aufgefordert [43]:

“(…) to strengthen national and local programmes of active surveillance for infectious diseases, ensuring that efforts are directed to early detection of outbreaks and prompt identification of new, emerging and re-emerging infectious diseases; (…) to control outbreaks and promote accurate and timely reporting of cases at national and international levels; (…).” [(...) nationale und lokale Programme zur aktiven Überwachung von Infektionskrankheiten zu stärken, um sicherzustellen, dass die Bemühungen auf die frühzeitige Erkennung von Ausbrüchen und die unverzügliche Identifizierung neuer, neu auftretender und wiederauftretender Infektionskrankheiten gerichtet sind; (...) Ausbrüche zu kontrollieren und die genaue und rechtzeitige Meldung von Fällen auf nationaler und internationaler Ebene zu fördern; (...).]

Trotz dieser Forderungen haben Versäumnisse in früheren Pandemien und im aktuellen Ausbruch von COVID-19 gezeigt, dass kontinuierliche Anstrengungen zur Verbesserung der Präventionsmaßnahmen und der Vorbereitung auf die Eindämmung von Ausbrüchen von Infektionskrankheiten erforderlich sind [12, 44]. Der „Global Health Security Index“ [Globaler Gesundheits-Sicherheitsindex] von 2021 [45] stellt fest, dass *“(…) despite significant steps taken by countries to respond to the COVID-19 pandemic, all countries remain dangerously unprepared to meet future epidemic and pandemic threats” [(...) trotz bedeutender Schritte, die Staaten als Reaktion auf die COVID-19-Pandemie unternommen haben, alle Länder in gefährlicher Weise unvorbereitet sind, um künftigen epidemischen und pandemischen Bedrohungen zu begegnen].* Abgesehen davon, dass es zahlreichen Staaten an den notwendigen Ressourcen mangelt, ist selbst dann, wenn die Ressourcen im Vorfeld eines Ausbruchs vorhanden sind, nicht immer möglich vorherzusagen, wie effizient sie von den EntscheidungsträgerInnen eingesetzt werden. Als Beispiel dafür wird im Bericht die mangelhafte Reaktionsbereitschaft der Regierung in den Vereinigten Staaten von Amerika am Pandemiebeginn genannt, obwohl das Land über beträchtliche wirtschaftliche Mittel und Forschungsressourcen verfügt. Der Globale Gesundheitssicherheitsindex bewertet auch, inwieweit Staaten bereit sind, die bei dieser Pandemie dazugewonnenen Ressourcen für kommende Ausbruchsgeschehen einzusetzen, z.B. ob sie sicherstellen, dass geschaffene Testkapazitäten auch langfristig für andere Erreger genutzt werden können.

Nun, da die Weltgesundheitsorganisation zur Kenntnis nimmt, dass sich die COVID-19-Pandemie an einem "Übergangspunkt" [46] befindet und manche Experten sogar das Ende der Pandemie [47] ausgerufen haben, muss die globale Gemeinschaft damit beginnen, sich auf den unvermeidlichen nächsten Ausbruch einer Infektionskrankheit vorzubereiten.

4. Paper I

Available online via:

https://www.frontiersin.org/journals/public-health/articles/10.3389/fpubh.2022.856189/full

5. Paper II

Available online via:
https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-022-07627-5

6. References

1. Piret J, Boivin G. Pandemics Throughout History. Frontiers in Microbiology. 2021;11.

2. Peiris J, Yuen K, Osterhaus A, Stöhr K. The severe acute respiratory syndrome. N Engl J Med. 2003;349(25):2431-41.

3. World Health Organization. Global Health Estimates 2020: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2019 [cited 2023 28 February]. Available from: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death.

4. Guerrant R, Blackwood B. Threats to global health and survival: the growing crises of tropical infectious diseases--our "unfinished agenda". Clin Infect Dis. 1999;28(5):966-86.

5. Butler J, Crengle S, Cheek J, Leach A, Lennon D, O'Brien K, et al. Emerging infectious diseases among indigenous peoples. Emerg Infect Dis. 2001;7(3 Suppl):554-5.

6. Heymann D, Lee V. Emerging and re-emerging infections. In: Detels R, Gulliford M, Abdool Karim Q, Chuan Tan C, editors. Oxford Textbook of Global Public Health. Sixth Edition ed: Oxford University Press; 2015. p. 1192-205.

7. Institute of Medicine. Microbial Threats to Health: Emergence, Detection, and Response. Smolinski MS, Hamburg MA, Lederberg J, editors. Washington, DC: The National Academies Press; 2003. 397 p.

8. McNeill W. Plagues and Peoples. 3 ed. New York: Doubleday; 1998. 365 p.

9. Váradi L, Luo J, Hibbs D, Perry J, Anderson R, Orenga S, et al. Methods for the detection and identification of pathogenic bacteria: past, present, and future. Chem Soc Rev. 2017;46(16):4818-32.

10. Koczula K, Gallotta A. Lateral flow assays. Essays Biochem. 2016;60(1):111-20.

11. Buckeridge D, Cadieux G. Surveillance for Newly Emerging Viruses. In: Edward T, editor. Emerging Viruses in Human Populations. PERSPECTIVES IN MEDICAL VIROLOGY. 16. Amsterdam: Elsevier; 2006. p. 325-43.

12. Griffiths S. Strategies and structures for public health intervention. In: Detels R, Gulliford M, Abdool Karim Q, Chuan Tan C, editors. Oxford Textbook of Global Public Health. Sixth Edition ed: Oxford University Press; 2015. p. 1542-62.

13. Plotkin S, Plotkin S. A Short History of Vaccination. In: Stanley A. Plotkin PAO, Walter A. Orenstein, Kathryn M. Edwards, editor. Vaccines. 7 ed: Elsevier; 2018. p. 1-23.

14. Abrignani S, Neddermann P, Houghton M, De Francesco R. Hepatitis C Vaccines. In: Stanley A. Plotkin PAO, Walter A. Orenstein, Kathryn M. Edwards, editor. Vaccines. 7 ed: Elsevier; 2018. p. 375-90.

15. Girard M, WC K. Human Immunodeficiency Virus Vaccines. In: Stanley A. Plotkin PAO, Walter A. Orenstein, Kathryn M. Edwards, editor. Vaccines. 7 ed: Elsevier; 2018. p. 400-54.

16. Tan W, Zhao X, Ma X, Wang W, Niu P, Xu W, et al. A Novel Coronavirus Genome Identified in a Cluster of Pneumonia Cases - Wuhan, China 2019-2020. China CDC Wkly. 2020;2(4):61-2.

17. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.

18. Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MM, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19. Cochrane Database Syst Rev. 2022;5(5):Cd013665.

19. World Health Organization. WHO Coronavirus (COVID-19) Dashboard [Internet]. 2023 [cited 28 February 2023]. Available from: https://covid19.who.int/.

20. WHO Africa. Six in seven COVID-19 infections go undetected in Africa. 2021 [cited 28 February 2023]. Available from: https://www.afro.who.int/news/six-seven-covid-19-infections-go-undetected-africa.

21. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med. 2020;382(16):1564-7.

22. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. N Engl J Med. 2020;382(10):970-1.

23. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [cited 28 February 2023]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.

24. Bauer T, Ewig S, Marre R, Suttorp N, Welte T. CRB-65 predicts death from community-acquired pneumonia. J Intern Med. 2006;260(1):93-101.

25. Durack D, Lukes A, Bright D. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med. 1994;96(3):200-9.

26. Vincent J, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707-10.

27. ECDC. Diagnostic testing and screening for SARS-CoV-2 2022 [updated 15 August 2022; cited 28 February 2023]. Available from: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/diagnostic-testing.

28. Miller JL, Tada M, Goto M, Chen H, Dang E, Mohr NM, et al. Prediction models for severe manifestations and mortality due to COVID-19: A systematic review. Acad Emerg Med. 2022;29(2):206-16.

29. de Jong VMT, Rousset RZ, Antonio-Villa NE, Buenen AG, Van Calster B, Bello-Chavolla OY, et al. Clinical prediction models for mortality in patients with covid-19: external validation and individual participant data meta-analysis. Bmj. 2022;378:e069881.

30. Long B, Carius BM, Chavez S, Liang SY, Brady WJ, Koyfman A, et al. Clinical update on COVID-19 for the emergency clinician: Presentation and evaluation. Am J Emerg Med. 2022;54:46-57.

31. Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. Bmj. 2020;370:m3339.

32. Haimovich AD, Ravindra NG, Stoytchev S, Young HP, Wilson FP, van Dijk D, et al. Development and Validation of the Quick COVID-19 Severity Index: A Prognostic Tool for Early Clinical Decompensation. Ann Emerg Med. 2020;76(4):442-53.

33. Gidari A, De Socio G, Sabbatini S, Francisci D. Predictive value of National Early Warning Score 2 (NEWS2) for intensive care unit admission in patients with SARS-CoV-2 infection. Infect Dis (Lond). 2020;52(10):698-704.

34. Goodacre S, Thomas B, Sutton L, Burnsall M, Lee E, Bradburn M, et al. Derivation and validation of a clinical severity score for acutely ill adults with suspected COVID-19: The PRIEST observational cohort study. PLoS One. 2021;16(1):e0245840.

35. Wang K, Zuo P, Liu Y, Zhang M, Zhao X, Xie S, et al. Clinical and Laboratory Predictors of In-hospital Mortality in Patients With Coronavirus Disease-2019: A Cohort Study in Wuhan, China. Clin Infect Dis. 2020;71(16):2079-88.

36. Clift A, Coupland C, Keogh R, Diaz-Ordaz K, Williamson E, Harrison E, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. BMJ. 2020;371:m3731.

37. Chowdhury A, Jomo K. Responding to the COVID-19 Pandemic in Developing Countries: Lessons from Selected Countries of the Global South. Development. 2020:1-10.

38. Juthani-Mehta M, Quagliarello V. Prognostic scoring systems for infectious diseases: their applicability to the care of older adults. Clin Infect Dis. 2004;38(5):692-6.

39. Abteilung für Infektions- und Tropenmedizin LMU Klinikum München. COVID-19 Walk-through-Teststation 2021 [cited 28 February 2023]. Available from: www.coronatest-tropeninstitut.de.

40. Hohl HT, Heumann C, Rothe C, Hoelscher M, Janke C, Froeschl G. COVID-19 Testing Unit Munich: Impact of Public Health and Safety Measures on Patient Characteristics and Test Results, January to September 2020. Front Public Health. 2022;10:856189.

41. Hohl HT, Froeschl G, Hoelscher M, Heumann C. Modelling of a triage scoring tool for SARS-COV-2 PCR testing in health-care workers: data from the first German COVID-19 Testing Unit in Munich. BMC Infect Dis. 2022;22(1):664.

42. Roberts L, Brennan R. Emergency public health and humanitarian assistance in the twenty-first century. In: Detels R, Gulliford M, Abdool Karim Q, Chuan Tan C, editors. Oxford Textbook of Global Public Health. 6 ed: Oxford University Press; 2015. p. 1594-607.

43. World Health Organization. Forty-eight World Health Assembly, Agenda item 19. Communicable diseases prevention and control: new, emerging, and re-emerging infectious diseases. Geneva 1995.

44. International Federation of Red Cross and Red Crescent Societies. World Disasters Report 2022. Trust, Equity and Local Action. Lessons from the COVID-19 pandemic to avert the next global crisis. Geneva; 2023. Available from: https://www.ifrc.org/document/world-disasters-report-2022.

45. Bell JA, Nuzzo JB. Global Health Security Index: Advancing Collective Action and Accountability Amid Global Crisis.; 2021. Available from: www.GHSIndex.org.

46. World Health Organization. Statement on the fourteenth meeting of the International Health Regulations (2005) Emergency Committee regarding the coronavirus disease (COVID-19) pandemic. Geneva 2023.

47. Christian Drosten zur Corona-Lage in Deutschland: „Nach meiner Einschätzung ist die Pandemie vorbei“. Tagesspiegel, [Internet]. 2022 [cited 4 March 2023]. Available from: https://www.tagesspiegel.de/wissen/corona-experte-drosten-nach-meiner-einschatzung-ist-die-pandemie-vorbei-9089959.html.

48. Fries C. Drei Wochen auf der Isolierstation: "Ich will einfach nur nach Hause". Sueddeutsche Zeitung, [Internet]. 2020 [cited 4 March 2023]. Available from: https://www.sueddeutsche.de/muenchen/starnberg/starnberg-coronavirus-krankenhaus-quarantaene-1.4857304.

49. Böhmer M, Buchholz U, Corman V, Hoch M, Katz K, Marosevic D, et al. Investigation of a COVID-19 outbreak in Germany resulting from a single travel-associated primary case: a case series. Lancet Infect Dis. 2020;20(8):920-8.

50. "suche-postleitzahl.org" open source download center [Internet]. 2023 [cited 13 February 2023]. Available from: https://www.suche-postleitzahl.org/downloads.

6.1 Table of figures

Appendix: Further analyses not included in previous publications

Follow-up testing in SARS-CoV-2 positive patients

Upon examination of tests carried out on individuals after their first positive test result for SARS-CoV-2, differences can be seen both over time and between different cohorts of patients, which allows for an inference of motivations for testing (see Figure 1). Patients with positive test results were offered the option of follow-up visits and testing at the CTU, if not implemented through the Bavarian health department or other institutions. From 27 January to 17 March 2020, positive patients were mainly affiliated with the car parts manufacturer Webasto cohort or travel returnees and did not present for follow-up, as these groups were not routinely subjected to re-testing after a positive test result, but were asked to isolate for 14 days [48, 49]. From 17 March 2020 on, positive patients were primarily healthcare workers (HCW). Guidelines by healthcare providers were implemented, according to which employees with COVID-19 needed a negative test result to return to work. HCW presented for follow-up testing after a median of 13 days (IQR: 8-15 days). From July to September 2020, the number of re-tests after a positive test result can be observed to decline. Patients could have been lost for follow-up as decreasing fear of transmission in the general population might have lessened the motivation of patients to get re-tested, or the growing number of testing providers may have led patients to get tested elsewhere.

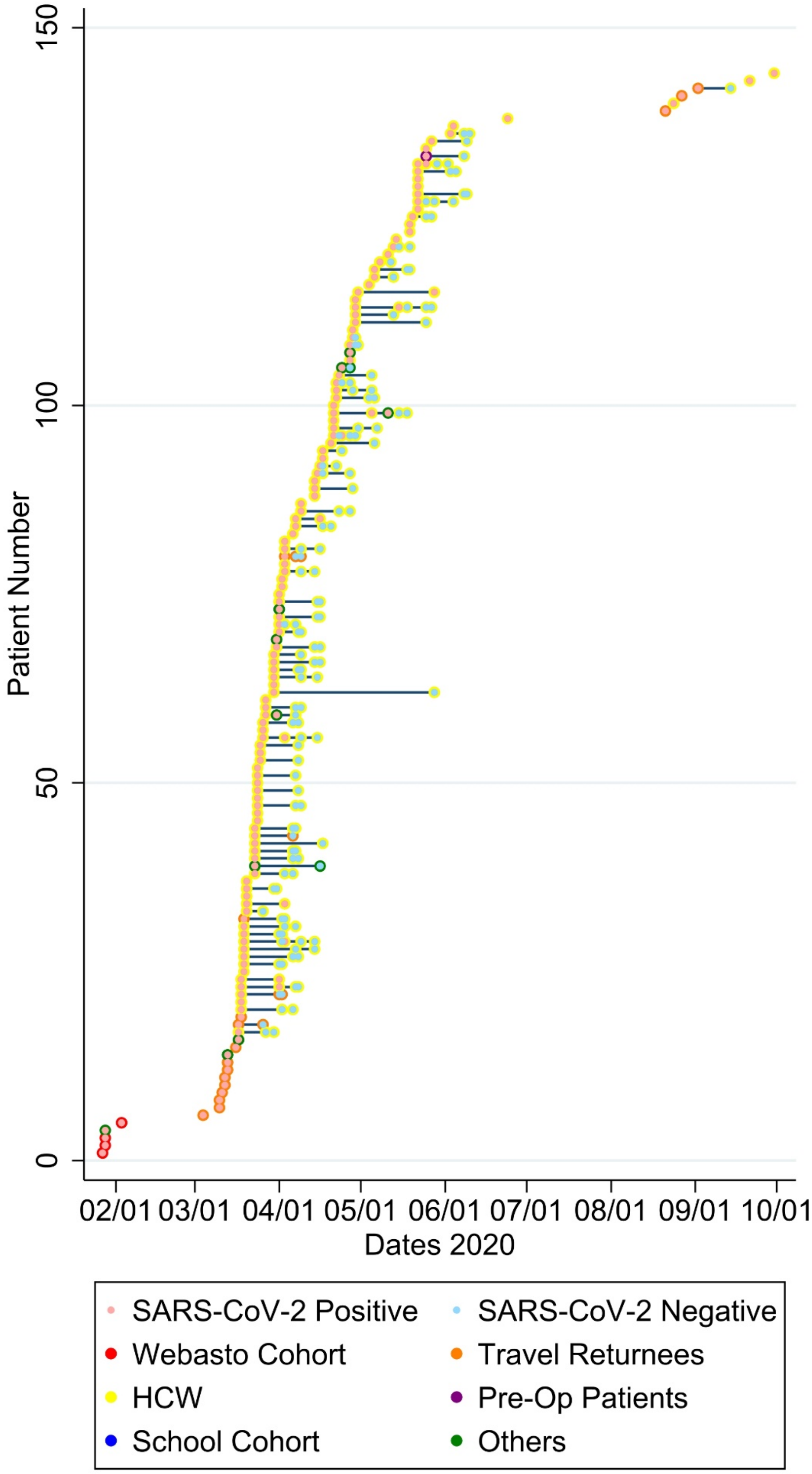

Figure 1. Follow-up visits of patients with SARS-CoV-2 positive test result, color-coded by patient cohort and test results.

Geographic distribution of patients' home districts

For a graphical breakdown of the geographic distribution of patients' places of residence, we plotted the density of our patients (CTU patients per 10 000 inhabitants) in the postal code districts of Munich (see Figure 2) [50]. The higher testing frequencies in the first wave from March to May 2020 and the beginning of the second wave from September 2020 on can be observed clearly. It is evident that between March and August, a large proportion of patients came from the vicinity of their place of work (i.e., the zip code areas around our referring facilities). While the availability of tests was still limited and test centers were specialized in certain test criteria, patients came in for testing from districts more distant to the CTU. After the implementation of the "Bayerische Teststrategie" (BTS), a frequentation of our testing unit mainly from nearby districts became apparent.

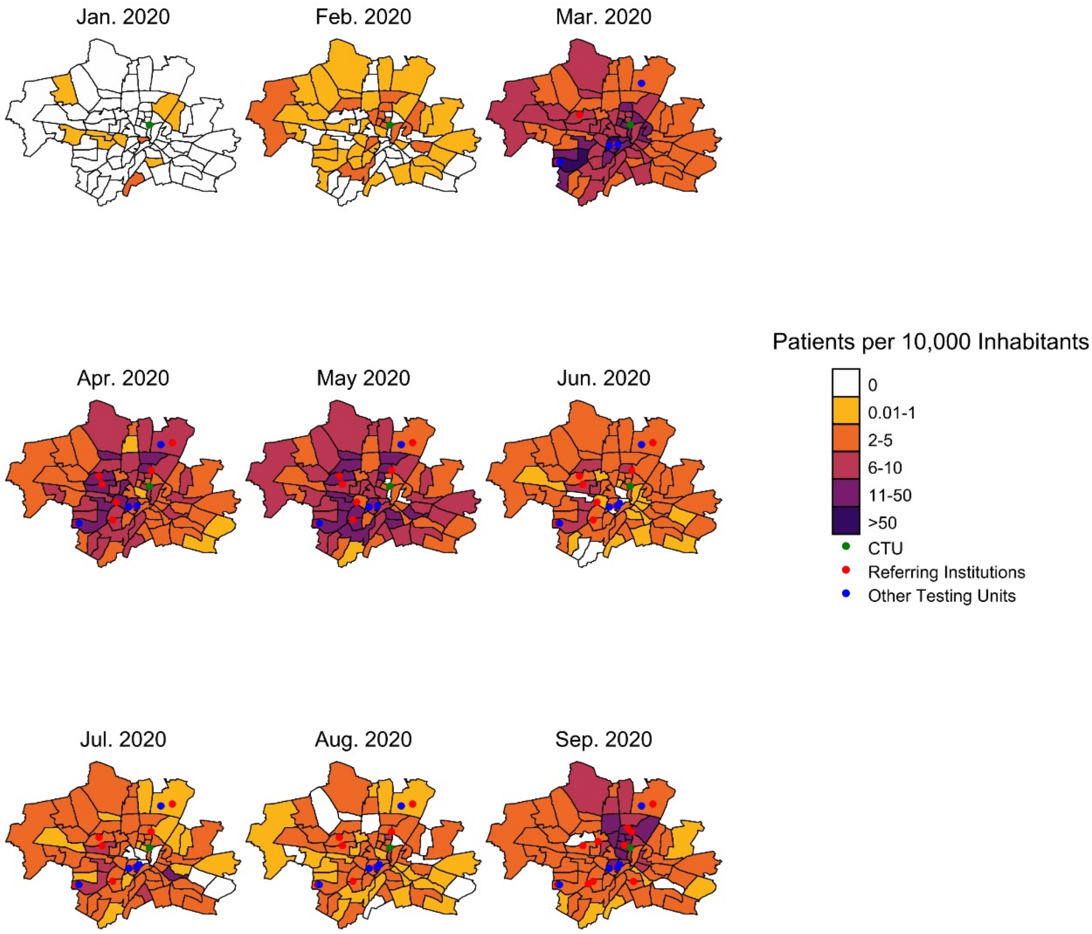

Figure 2. Number of CTU patients per inhabitants in postal code districts of Munich, per month. Referring institutions are displayed in the months of cooperation, other test providers are shown for the duration of their operation.

Many of the patients from the beginning of the pandemic are not depicted in Figure 1, as some of them travelled long distances from outside the city to attend testing. This becomes apparent when looking at the median distance between patients' home and the CTU, which shows a slight decline over time (see Figure 3). As the number of test providers increased with the BTS, a further decrease in travel distance could probably be observed in autumn of 2020 in a more extensive dataset. Testing and treatment options close to home can help to reduce the likelihood of infection in the public, especially in population groups that rely on public transport.

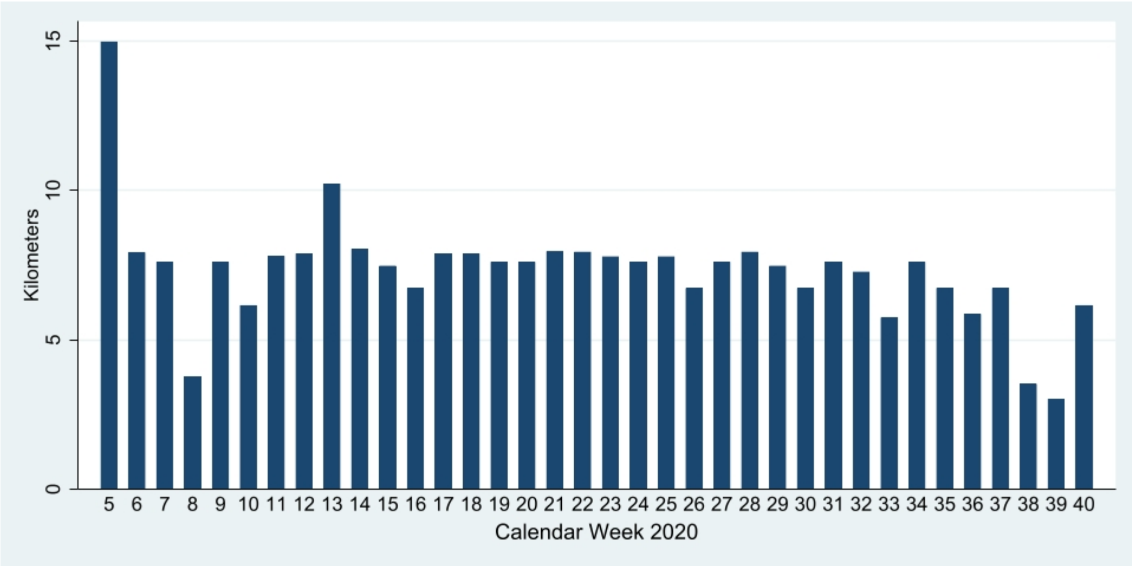

Figure 3. Median distance between patients' home districts and the CTU, by calendar week.

Acknowledgements

Many thanks to my supervisors and co-authors for their collaboration, constructive advice, and patience. A big thank you goes to my family, who, with their invaluable support, carried me through my studies. And of course, I would also like to thank the CTU team. Through you, trying times have left priceless memories of teamwork and comradery.