PART 3

THE PANDEMIC DESIGNED TO ANNIHILATE

Contents

ISOLATED SARS-CoV-2
ELETRON MICROGRAPHS

Measurements are in nanometers.

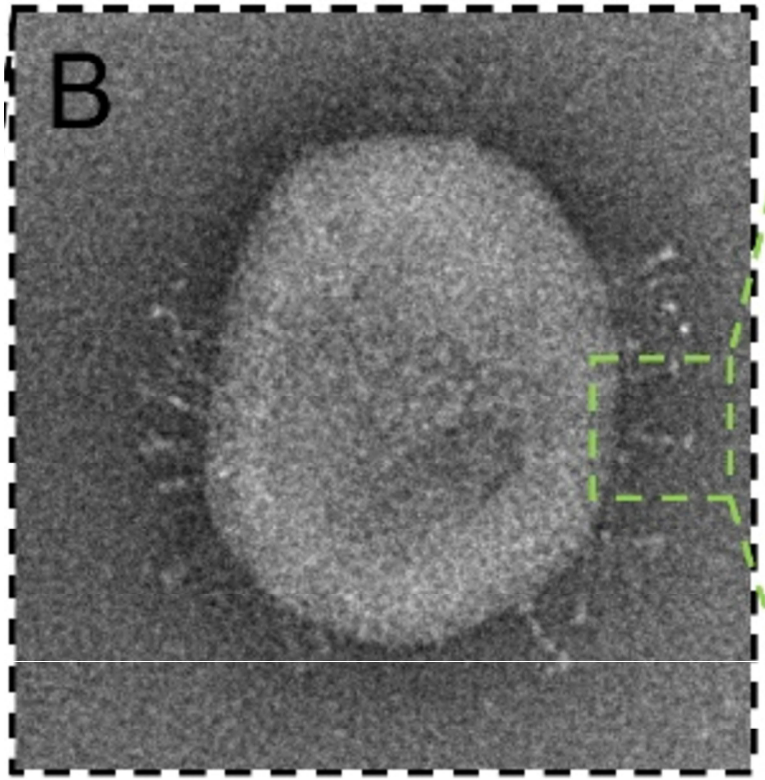
One meter= 39.3 inches

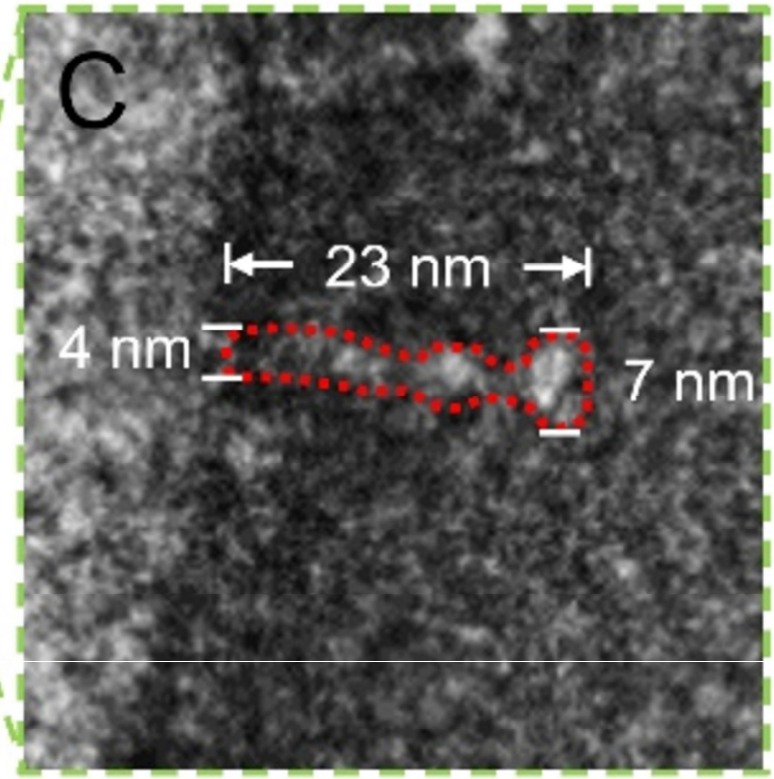
One nm= on billionth of a meter.

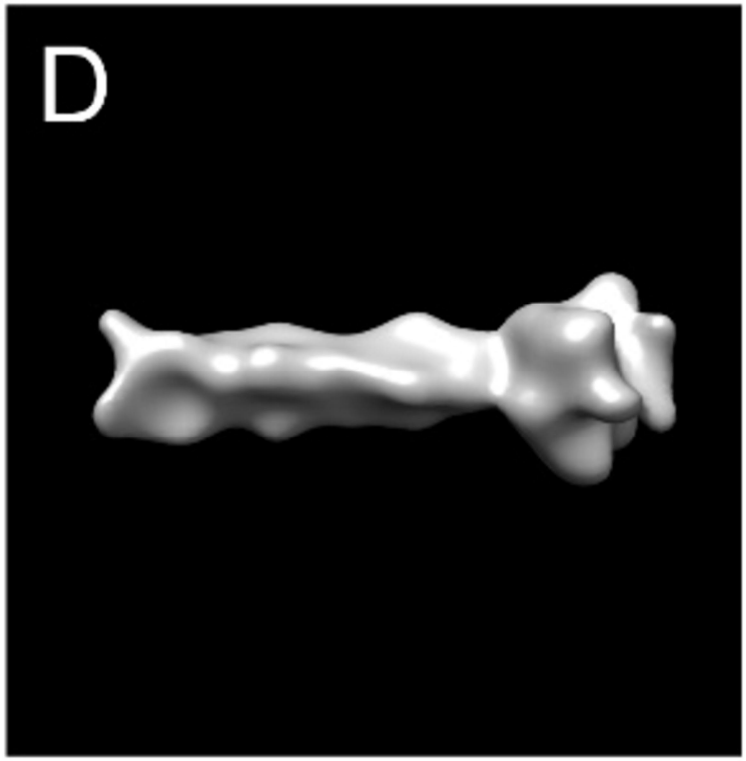
The virus diameter is 80-120 nm.

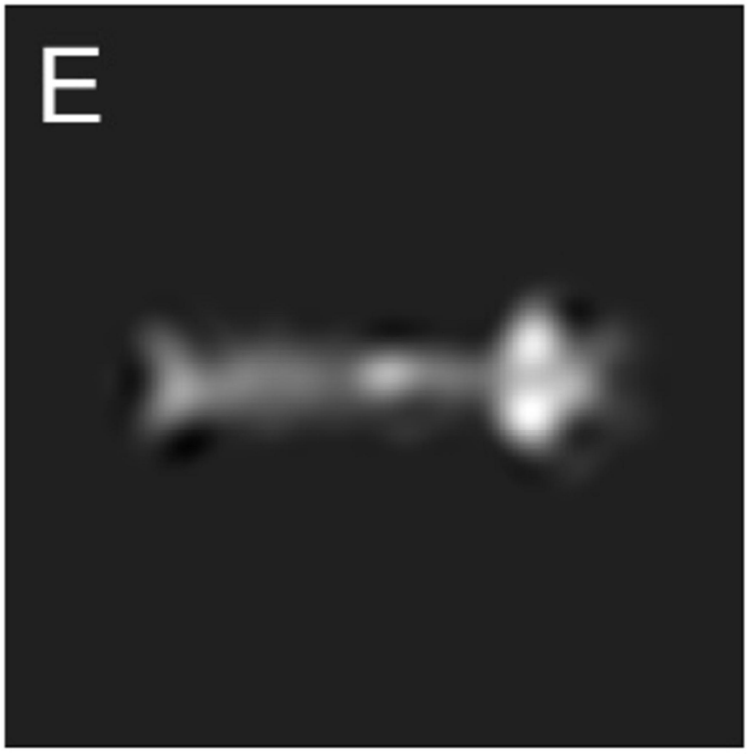
The spike outlined in red on C is 23 nm long.

The spike is shown in 3D on D and in 2D on E .









Early Outpatient Treatment: An Essential Part of a COVID-19 Solution

Full Committee Hearing

November 19, 2020 09:00 AM

Location: SD-342, Dirksen Senate Office Building and via Videoconference

Member Statements

Chairman Ron Johnson, R (WI)
Download Statement (133.4 KB)

Ranking Member Gary C. Peters D (MI)
Download Statement (119 KB)

Witnesses

Peter A. McCullough, M.D., M.P.H.
Vice Chief of Internal Medicine
Baylor University Medical Center
Download Testimony (143.9 KB)

Harvey Risch, M.D., PH.D.
Professor of Epidemiology
Yale University
Download Testimony (96.1 KB)

George C. Fareed, M.D.
Medical Director and Family Medicine Specialist
Pioneers Medical Center
Testimony-Fareed-2020-11-19 (155.1 KB)

Ashish K. Jha, M.D., M.P.H.
Dean of the School of Public Health
Brown University
Download Testimony (180.5 KB)

Statement of Harvey A. Risch, MD, PhD
Professor of Epidemiology, Yale School of Public Health

Senators and colleagues: thank you for convening this hearing. We all understand the endemic disease that we are facing, that we have to face it head-on and not hide from it hoping that it will go away. I want to give you my perspective.

In May of this year I observed that results of studies of a drug suggested to treat Covid, hydroxychloroquine, were being misrepresented by what I thought at the time was sloppy reporting. We have heard from Dr. McCullough how Covid disease progresses in phases, from viral replication, to florid pneumonia to multi-organ attack. Viral replication is an outpatient condition, but the pneumonia that fills the lungs with immune-system debris is hospitalizable and potentially life-threatening. We have also heard how each phase, each pathologic aspect of the disease, has to have its own specific treatments that apply to its own biologic mechanisms. Thus, I was frankly astounded that studies of hospital treatments were being represented as applying to outpatients, in violation of what I learned in medical school about how to treat patients.

We are now finally coming to address why over the last six months, our government research institutions have invested billions of dollars in expensive patent medication and vaccine development but almost nothing in early outpatient treatment, the first line of response to managing the pandemic. It is not that we lacked candidate medications to study, we have had a number of promising agents. But I believe that the early-on conflation of hospital with outpatient disease served to imply that treatment of outpatient disease had been studied and found ineffective. This illogical premise motivated me to look at the evidence for outpatient treatment.

I reiterate: we are considering the evidence for early treatment of high-risk outpatients to prevent hospitalization and mortality. That is it. Treatment starting in the first five days or so after the onset of symptoms. Treatment of older patients or patients with chronic conditions such as diabetes, obesity, heart diseases, lung diseases, kidney diseases, immune-system diseases, survivors of cancer etc. These are the people most likely to die from Covid, and they are the people most needing protection. I have sought to obtain reports of every study of every medication pertaining to early treatment of high-risk outpatients. I monitor the literature daily. And what I have found is actually quite remarkable. What I have observed is that while there have been positive reports about a number of drugs, every study of outpatient use of one drug, hydroxychloroquine, with or without accompanying agents, has shown substantial benefit in reducing risks of hospitalization and mortality.

These studies break down into two major types. The first is double-blinded, randomized controlled trials, and the second is non-randomized but still controlled trials. You have heard from various government and scientific personalities that randomized controlled trials provide the strongest form of evidence. Many of these people have also claimed that randomized trials

provide the only trustworthy form of evidence. There is some truth in these assertions, but there is also lots of falsehood. We know for example that the great majority of drugs used to treat heart diseases were established with non-randomized trials. Cholesterol-lowering drugs were in widespread use before randomized trials were ever done. Azithromycin, the most commonly used antibiotic in children, was not established by randomized trials. The idea that only randomized trials provide trustworthy evidence is a simplistic notion that may sound good in theory, but the comparison between randomized and non-randomized trials is something that has actually been extensively studied in the medical literature. I am an epidemiologist because even though I love biological theories, I develop them all the time to study how nature works, but it is from the human empirical data that we learn how indeed nature works.

And we have huge amounts of empirical data to show that randomized trials and their corresponding non-randomized trials give the same answers. Dr. Tom Frieden, previously Director of the CDC, in 2017 wrote an extensive essay in the New England Journal of Medicine showing that non-randomized trials can provide fully compelling evidence, especially when they are done carefully to account for reasons why patients received the drugs, and importantly, when circumstances are such that the cost of waiting for randomized trials involves major sickness and mortality as we have been experiencing this year. But Dr. Frieden's essay, as authoritative as it is, provides only snapshots of the empirical evidence for his observations. The real evidence comes from a meta-analysis of meta-analyses done by the Cochrane Library Consortium, a British international organization formed to organize medical research findings to facilitate evidence-based choices about health interventions. The Cochrane investigators examined what involve tens of thousands of comparisons between randomized trials and their non-randomized counterparts and found that the two types of studies arrived at virtually identical conclusions. This is the real evidence about why good non-randomized trials comprise evidence every bit as important as randomized trials. Large amounts of consistent empirical data are the evidence, not plausible but simplistic assumptions, no matter who says them.

So what did I find about hydroxychloroquine in early use among high-risk outpatients? The first thing is that hydroxychloroquine is exceedingly safe. Common sense tells us this, that a medication safely used for 65 years by hundreds of millions of people in tens of billions of doses worldwide, prescribed without routine screening EKGs, given to adults, children, pregnant women and nursing mothers, must be safe when used in the initial viral-replication phase of an illness that is similar at that point to colds or flu. In fact, a study by researchers at the University of Oxford showed that in 14 large international medical-records databases of older rheumatoid arthritis patients, no significant differences were seen in all-cause mortality for patients who did or did not use hydroxychloroquine. The Oxford investigators also looked at cardiac arrhythmias and found no increase for hydroxychloroquine users. This was in more than 900,000 hydroxychloroquine users. This is examined at length in my paper in the American Journal of Epidemiology in May. Now, the FDA posted a warning on July 1 on its website about hydroxychloroquine used in outpatients, but we can discuss this later; the FDA

has had no systematic evidence in outpatients and erroneously extrapolated from hospital inpatients to outpatients, what I said earlier was invalid.

About studies of hydroxychloroquine early use in high-risk outpatients, every one of them, and there are now seven studies, has shown significant benefit: 636 outpatients in São Paulo, Brazil; 199 clinic patients in Marseille, France; 717 patients across a large HMO network in Brazil; 226 nursing-home patients in Marseille; 1,247 outpatients in New Jersey; 100 long-term care institution patients in Andorra (between France and Spain); and 7,892 patients across Saudi Arabia. All these studies pertain to the early treatment of high-risk outpatients—and all showed about 50 percent or greater reductions in hospitalization or death. The Saudi study was a national study and showed 5-fold reduction in mortality for hydroxychloroquine plus zinc vs zinc alone. Not a single fatal cardiac arrhythmia was reported among these thousands of patients attributable to the hydroxychloroquine. These are the non-randomized but controlled trials that have been published.

Now we also know that all of the outpatient randomized controlled trials this year also together show statistically significant benefit. These six studies comprised generally much younger patients, only a fraction of whom were at high risk, so they individually had too few hospitalizations or deaths to be statistically significant. But they all suggested lower risks with hydroxychloroquine use, and when they were analyzed together in meta-analysis as my colleagues and I found, this lower risk was statistically significant across the studies.

We have spent the last six months with formal government policies and warnings against early outpatient treatment, with large government investments in vaccines and expensive new treatments yet to be proven and almost no support of inexpensive but useful medications, and a quarter of a million Americans have died from this mismanaged approach. Even with newly promising vaccines, we have almost no information about how they will perform in older and high-risk patients, in whom respiratory virus vaccines are known to have weak efficacy; it will be a number of months before they become widely available; and we don't know how long vaccine immunity will last, or even if the vaccines will work for the newly increasing mutant strains of the virus. As I have said on many occasions, the evidence for benefit of hydroxychloroquine used early in high-risk outpatients is extremely strong, and the evidence against harm is also equally strong. This body of evidence dramatically outweighs the risk/benefit evidence for remdesivir, monoclonal antibodies or the difficult to use bamlanivimab that the FDA has approved for emergency use authorizations while denying the emergency use authorization for hydroxychloroquine. This egregious double standard for hydroxychloroquine needs to be overturned immediately and its emergency use authorization application approved. This is how we will get on the road to early outpatient treatment and the major curtailment of mortality. Thank you.

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Statement of George Fareed, M.D. for Senate Hearing, November 19, 2020

*I have a background in virology from a research standpoint from work at the NIAID (NIH) and as a Professor performing research at Harvard Medical School (after I graduated from Harvard Medical School in 1970 I became a professor there) and at UCLA School of Medicine. I have had **30 Years of Clinical experience**, treating HIV and other infectious diseases as well as practicing primary care medicine.*

· I have experience treating **COVID patients both in the flu stage as outpatients**, but also as hospitalized inpatients, even in the ICU

· *Like everything else in medicine, the goal is to treat early-- COVID patients are **difficult to treat when they get very sick***

· The Imperial Valley where I work became the COVID epicenter for California in June and July.

Since early March both in my Brawley clinic and Dr. Brian Tyson's The All Valley Urgent Care Clinic in El Centro (where I also work), over 25,000 fearful people were screened, over two thousand four hundred were COVID-19 positive and we treated successfully many hundreds of the high risk and symptomatic ones.

· *We have always used a **triple HCQ cocktail**: HCQ (3200 mg over 5 days), azithromycin or doxycycline and **especially zinc**, which is often left out in the studies. The cocktail is best given early **within the first 5 to 7 days** while the patient is in the flu stage (I have had success treating even as late as 14 days when patients have been sent home untreated from the ER). The timing of the drug is when the virus is in the **period of maximal replication in the upper respiratory tract** My goal is to prevent hospitalization which was achieved by reevaluating high risk patients every 2-3 days. I blend in corticosteroids and prolong the HCQ treatment for 5 to 30 more days if symptoms warrant but they generally do not. I use it especially in **high risk individual**s (over 60 or with co-morbidities and anyone with moderate to severe flu symptoms)---the healthy do not need the treatment.*

I used this regimen to successfully treat 31 elderly nursing home residents in an outbreak in June and 29 recovered fully.

· *The drug works mechanistically through multiple actions: the* ***ionophore HCQ (the "gun") and zinc ("the bullet"), HCQ blocks the sigma 1 receptor and has several other direct antiviral effects****---the antibiotic also has anti-viral effect and potentiates the action of the HCQ and zinc. As additional anti-covid agents become available they can be added to this regimen to enhance its efficacy. I am routinely now combining Ivermectin in a* ***quadruple HCQ/IVM cocktail*** *with excellent results since Ivermectin is safe and has a different anti-covid action. Monoclonal antibodies from Regeneron and Lilly will be suitable also when readily available.*

· *The results are consistently good, often dramatic, with improvement within 48 hours*

· *I have seen very few hospitalizations, and only a few deaths in patients that were sick to begin with and received the medication late while hospitalized.*

· ***I have not seen a single negative cardiac event and few other side effects, despite what we hear in the media***

My experience is in-line *with all the studies regarding* ***early use of the HCQ cocktail***

LET ME BE CLEAR: THIS IS ONLY ABOUT THE SCIENCE----THE SCIENCE OF VIRAL REPLICATION, THE SCIENCE OF THE STAGES OF COVID, AND THE SCIENCE WHY EARLY TREATMENT WORKS.

· *AND THE SCIENCE TELLS US THAT EARLY treatment would be an effective strategy to use on a national level, which motivated me and a few of my colleagues to write a letter to the President, a letter to my congressman, a letter to California health department, an Open Letter to Dr. Fauci, and a National Plan for COVID-19.*

This is not about an opinion of an "expert"- this is about science and data.

· *As we describe in the National Plan, this approach would be* ***the solution to the pandemic****---protect the vulnerable, and if high risk individuals get sick, there is a solution for them with early treatment with the antiviral cocktail.*

If early treatment was available, people would be much more confident going back to work and sending their kids back to school.

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COVID-19 outpatients: early risk-stratified treatment with zinc plus low-dose hydroxychloroquine and azithromycin: a retrospective case series study

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ABSTRACT

The aim of this study was to describe the outcomes of patients with coronavirus disease 2019 (COVID-19) in the outpatient setting after early treatment with zinc, low-dose hydroxychloroquine and azithromycin (triple therapy) dependent on risk stratification. This was a retrospective case series study in the general practice setting. A total of 141 COVID-19 patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the year 2020 were included. The main outcome measures were risk-stratified treatment decision and rates of hospitalisation and all-cause death. A median of 4 days [interquartile range (IQR) 3–6 days; available for $n = 66/141$ patients] after the onset of symptoms, 141 patients (median age 58 years, IQR 40–67 years; 73.0% male) received a prescription for triple therapy for 5 days. Independent public reference data from 377 confirmed COVID-19 patients in the same community were used as untreated controls. Of 141 treated patients, 4 (2.8%) were hospitalised, which was significantly fewer ($P < 0.001$) compared with 58 (15.4%) of 377 untreated patients [odds ratio (OR) = 0.16, 95% confidence interval (CI) 0.06–0.5]. One patient (0.7%) in the treatment group died versus 13 patients (3.4%) in the untreated group (OR = 0.2, 95% CI 0.03–1.5; $P = 0.12$). No cardiac side effects were observed. Risk stratification-based treatment of COVID-19 outpatients as early as possible after symptom onset using triple therapy, including the combination of zinc with low-dose hydroxychloroquine, was associated with significantly fewer hospitalisations.

1. Introduction

In December 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started as an outbreak in Wuhan, China. This coronavirus has spread rapidly as a pandemic around the world [1], causing coronavirus disease 19 (COVID-19) pneumonia, acute respiratory distress syndrome (ARDS), cardiac injury, liver and renal injury, thrombosis and death [2].

As of June 2020, the diagnosis and treatment of COVID-19 have been almost exclusively studied from an inpatient perspective, including intensive care with mechanical ventilation. Only one study has described the characteristics and key health outcomes of COVID-19 diagnosed patients in an outpatient setting [3]. This is surprising as primary care physicians often see COVID-19 patients first. Thus, they could play a critical role in early diagnosis, treatment and management of disease progression and virus spread. This assumption is supported by the established principle in medicine that speed of eradication is linked to the outcome of life-threatening infections [4].

The early clinical phase of COVID-19 has not been the focus of much research so far, even though timing of antiviral treatment seems to be critical [5]. The optimal window for therapeutic intervention would seem to be before the infection spreads from the upper to lower respiratory tract and before severe inflammatory reaction ensues [6]. Therefore, diagnosis and treatment of COVID-19 outpatients as early as possible, even based on clinical diagnosis only, may have been an underestimated first step to slow down or even stop the pandemic more effectively. Based on clinical application principles of antiviral therapies, as demonstrated in the case

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of influenza A [7], antiviral treatments should be used early in the course of infection.

Due to the lack of a vaccine or SARS-CoV-2 specific therapies, the proposed use of repurposed antiviral drugs remains a valid practical consideration [8]. One of the most controversial drugs during the current SARS-CoV-2 pandemic is the well-known oral antimalarial drug hydroxychloroquine (HCQ), routinely used in the treatment of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE) [9,10]. HCQ is currently listed as an essential medication for SLE by the World Health Organization (WHO) [11]. With more than 5.6 million prescriptions in the USA, HCQ was the 128th most commonly prescribed medication in 2017 [12]. In the meantime, the first observational studies concluding beneficial therapeutic effects of HCQ as monotherapy or in combination with the antibiotic azithromycin were reported just a few weeks after the start of the SARS-CoV-2 outbreak [13]. All studies that used HCQ with rather contradictory results were in hospitalised and often sicker patients [13–16], and one publication was recently withdrawn [17,18]. As of June 2020, no studies of COVID-19 outpatients treated with HCQ at an early stage of the disease have been reported.

The antiviral effects of HCQ are well documented [19]. It is also known that chloroquine, and probably HCQ, have zinc ionophore characteristics, increasing intracellular zinc concentrations [20]. Zinc itself is able to inhibit coronavirus RNA-dependent RNA polymerase (RdRp) activity [21]. It has been hypothesised that zinc may enhance the efficacy of HCQ in treating COVID-19 patients [22]. The first clinical trial results confirming this hypothesis were recently published as a preprint [23]. Nevertheless, many studies with HCQ as monotherapy or in combination with the antibiotic azithromycin have been inconclusive so far [13–16]. In all of these studies, HCQ was used later than 5 days after the onset of symptoms when hospitalised patients most likely had already progressed to stage II or III of the disease [6]. Regardless of the established antiviral effects of zinc and that many COVID-19 patients are prone to zinc deficiency, dependent on co-morbidities and drug treatments [22], none of these studies were designed to include zinc supplementation as combination treatment.

This first retrospective case series study of COVID-19 outpatients was done to show whether (i) a simple-to-perform outpatient risk stratification might allow for a rapid treatment decision shortly after onset of symptoms and (ii) whether the 5-day triple therapy with zinc, low-dose HCQ and azithromycin might result in fewer hospitalisations and fatalities compared with relevant public reference data of untreated patients.

2. Methods

2.1. Setting

This retrospective case series study analysed data from COVID-19 outpatients with confirmed SARS-CoV-2 infection treated in a community in New York State, USA, between 18 March 2020 and 14 May 2020. The outcome of patients treated with a specific triple therapy was compared with public reference data of patients in the same community who were not treated with this therapy.

2.2. Confirmation of COVID-19 diagnosis

The COVID-19 diagnosis was confirmed if patients tested positive for SARS-CoV-2 by PCR of nasal or pharyngeal swab specimens (majority of tests by Roche, Basel, Switzerland; 99.1% sensitivity and 99.7% specificity; other tests used with lower frequency included: DiaSorin: 500 copies/mL; Thermo Fisher: 10 genomic copy equivalents/reaction; Seegene: 1250 copies/mL; Hologic: $TCID_{50}$/mL: 1×10^{-2}) or retrospectively by IgG detection tests [DiaSorin: sensitivity 97.6% (≥15 days after diagnosis), specificity 99.3%; Diazyme: sensitivity 91.2%, specificity 97.3%]. Only patients who had a record of a positive test result were included in the analysis. The PCR assays were authorised by the US Food and Drug Administration (FDA) without clinical sensitivity/specificity data owing to the urgent nature of the pandemic. Only one positive test was necessary for the patient to be included in the retrospective analysis.

2.3. Patients

Sequentially consecutive COVID-19 outpatients aged >18 years at diagnosis were included in the analysis as the treatment group. All patients were White. Patients received a prescription for triple therapy only if they met one of the following risk stratification requirements during a medical office-based or telehealth consultation: Group A, age >60 years, with or without clinical symptoms; Group B, age ≤60 years and shortness of breath (SOB); or Group C, age ≤60 years, clinically symptomatic and with at least one of the following co-morbidities: hypertension, hyperlipidaemia, diabetes mellitus, obesity [body mass index (BMI) ≥ 30 kg/m^2], cardiovascular disease, heart failure, history of stroke, history of deep vein thrombosis or pulmonary embolism, asthma, chronic obstructive pulmonary disease (COPD), other lung disease, kidney disease, liver disease, autoimmune disease or history of cancer. Pregnant women, if any, were also included in this group.

Laboratory-confirmed COVID-19 patients from the same community who were not treated with the described triple therapy and their related outcome data represented the untreated control group, which comprised both low-risk and high-risk patients (public reference data).

2.4. Procedure and treatment

Data for treated patients were collected from electronic health records in the year 2020. Demographics, as reported by the patient, and current medical history of hypertension, hyperlipidaemia, diabetes mellitus, obesity (BMI ≥ 30 kg/m^2), cardiovascular disease, heart failure, stroke, asthma, COPD, other lung disease, kidney disease, liver disease, autoimmune disease, history of cancer, thyroid disease psychiatric disorder or pregnancy were collected.

The presence of the following clinical symptoms of treated patients was documented: cough/dry cough; fever; SOB; changes to or no smell or taste; sore throat; headache; runny nose/clear rhinorrhoea; sinus congestion; diarrhoea/vomiting; cold symptoms; feeling sick; weakness; and low back pain. If reported, the number of days since onset of symptoms was documented.

The following vital signs, if available, were collected and documented: heart rate (beats/min), respiratory rate (breaths/min), systolic and diastolic blood pressure (mmHg), body temperature (°C), oxygen saturation measured by pulse oximetry (O_2 %), body weight (kg) and/or BMI.

The main co-medications were characterised based on primary care prescriptions active at the time of diagnosis, documented as categorical variables, included beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin 2 antagonists, calcium channel blockers, hydrochlorothiazide, statins, bronchodilators, antidiabetics and insulin.

Only diagnosed COVID-19 patients who met the defined risk stratification requirements of group A, B or C received a prescription for the following triple therapy for 5 consecutive days in addition to standard supportive care: zinc sulfate (220 mg capsule once daily, containing 50 mg elemental zinc); HCQ (200 mg twice daily); and azithromycin (500 mg once daily). No loading dose was used. Patients who did not meet the risk stratification requirements received standard of care to treat common upper respiratory

tract infections. Patients were not treated with HCQ if they had known contraindications, including QT prolongation, retinopathy or glucose-6-phosphate dehydrogenase deficiency. As usual and following best practice, patients were informed about possible drug-related side effects. Reported events, if any, were documented as required.

Selection of the used zinc supplement and of drugs, dosages and the combination thereof were based on treatment guidelines, positive reports from other countries such as South Korea, emerging first clinical evidence, and based on the discretion of the treating physicians.

2.5. Outcomes

Two outcomes were studied: COVID-19 related hospital admission and all-cause death during time of follow-up of ≥28 days in the treatment group and in the untreated control group (public reference). The outcome of COVID-19 patients in the untreated control group was reported by the responsible health department.

2.6. Statistical analyses

Only patients in the treatment group who met the defined risk stratification requirements and who received at least one prescription for HCQ, with or without zinc, for 5 days were included in the retrospective analysis and were categorised accordingly. If the patient's electronic health record did not include information on a clinical characteristic, it was assumed that the characteristic was not present. In the group of the public reference data, only confirmed COVID-19 patients who were not treated in the respective general practice with triple therapy were included in the analysis. For this untreated control group, only outcome data for hospitalisation and all-cause death were available and used for the statistical comparison with the treatment group.

No sample size calculations were performed. Descriptive statistics are presented as median and interquartile range (IQR) for continuous variables and as frequencies (%) for categorical variables. For comparison with the results of other studies, the mean and standard deviation were calculated as needed. Normality of distribution for continuous variables was assessed by the Shapiro–Wilk test. A two-tailed Student's *t*-test was used for parametric analysis, and a Wilcoxon signed-rank test was used for non-parametric data analysis. For calculation of correlation, the point-biserial correlation coefficient was applied if one variable was dichotomous. Associations between two categorical variables were calculated with the χ^2 test. The odds ratio (OR) was calculated for comparison of the outcome of the treatment group with the untreated control group. An α value of 0.05 was considered as a significance level. Data were analysed using Microsoft Excel for Microsoft 365 MSO (32-bit), the Excel add-on Real Statistics, SigmaStat 4 and Sigma Plot 14.0.

2.7. Study approval

The study was approved by the Western Institutional Review Board and was exempt under 45 CFR § 46.104(d)(4). Ref. number: D4-Exemption-Zelenko (06-16-2020). The analysis was conducted with de-identified patient data, according to the USA Health Insurance Portability and Accountability Act (HIPAA), Safe Harbor. For that reason, exact dates and locations are not mentioned in this study.

3. Results

3.1. Patients

In accordance with available public reference data, 712 confirmed SARS-CoV-2 PCR-positive COVID-19 patients were reported for the respective community at the defined time point of the analysis. Of these 712 patients, 335 presented as outpatients at a general practice and 127 were treated with the triple combination therapy. Of these 127 patients, 104 met the risk stratification criteria and were included in the analysis (Table 1). Of the 335 patients, 208 did not meet the defined risk stratification criteria and were treated with standard of care and recovered at home. The SARS-CoV-2 infection of 37 additional patients who were clinically diagnosed with COVID-19 who met the risk stratification criteria and who were also treated with triple therapy was later confirmed by IgG tests (Table 1). These patients were included additionally in the analysis resulting in a total number of 141 patients, all with a confirmed SARS-CoV-2 infection by PCR or IgG tests. None of these patients were lost to follow-up for the defined outcome. The outcome of the remaining 377 positively tested but not treated COVID-19 patients, e.g. from other practices of the community, served as public reference (Fig. 1). Analysis of the 141 patients in the treatment group showed that all of these patients (100%) received a prescription of HCQ, 136 (96.5%) of zinc sulfate and 133 (94.3%) of azithromycin, while 1 patient (0.7%) received doxycycline instead. Instead of triple therapy, 1 patient (0.7%) in the treatment group received HCQ only, 7 patients (5.0%) received HCQ and zinc, and 4 patients (2.8%) received HCQ and azithromycin.

3.2. Baseline characteristics of the patients

Table 2 shows the baseline demographics and clinical characteristics of all 141 patients in the treatment group and for the risk stratification groups A, B and C. Of the 141 patients, 69 (48.9%) belonged to group A, 48 (34.0%) to group B and 24 (17.0%) to group C. The age ranged from 18–80 years and the median age was 58 years (IQR 40–67 years). The median age of patients in groups A, B and C was 67, 39 and 45 years, respectively. A total of 103 patients (73.0%) were male with a male-to-female ratio of 2.71. The most common co-morbidities included hypertension (28%), obesity (28%), hyperlipidaemia (23%) and diabetes mellitus (18%), whilst the least common co-morbidities were liver disease (2%), heart failure (1%) and stroke (1%). One patient (0.7%) was pregnant at initiation of treatment. There was a positive and significant correlation between age and hypertension ($r = 0.3309$, $P = 0.001$), hyperlipidaemia ($r = 0.26306$, $P < 0.001$) and cardiovascular disease ($r = 0.16757$, $P < 0.05$), whilst asthma was negatively correlated with age ($r = -0.30867$, $P < 0.001$).

The median time between onset of clinical symptoms and medical consultation was 4 days (IQR 3–6 days; available for 66/141 patients; mean 4.8 ± 2.7 days) (Table 3). There was no significant correlation between age and days from onset of clinical symptoms to consultation ($P > 0.05$). Days from onset of symptoms to consultation were not significantly different between the groups ($P > 0.05$).

The most common clinical symptoms included cough (87.2%), fever (77.3%), SOB (46.1%) and changes to or no smell or taste (30%), whilst the least common clinical symptoms were sinus congestion (16%), diarrhoea/vomiting (5%) and low back pain (3%). Table 4 shows the symptoms of all patients and stratified by groups A, B and C. There was a significant negative correlation between age and changes to smell or taste ($r = -0.43$, $P < 0.001$). No patient had a clinical diagnosis of pneumonia.

Table 5 shows the vital signs, if available, for all patients. Many patients consulted the general practice during the COVID-19 crisis

Table 1
COVID-19 diagnostics by PCR and IgG tests of patients in the treatment group

COVID-19 diagnostic [*n* (%)]	Risk-stratified group			All patients (*N* = 141)
	Group A (*N* = 69)	Group B (*N* = 48)	Group C (*N* = 24)	
SARS-CoV-2 PCR test	51 (74)	39 (81)	14 (58)	104 (74)
SARS-CoV-2 IgG test	18 (26)	9 (19)	10 (42)	37 (26)

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2
Baseline demographic and clinical characteristics of patients in the treatment group

Characteristic	Risk-stratified group			All patients (*N* = 141)
	Group A (*N* = 69)	Group B (*N* = 48)	Group C (*N* = 24)	
Age (years) [median (IQR)]	67 (64–69)	39 (24–47)	45 (36–50)	58 (40–67)
Male sex [*n* (%)]	46 (67)	40 (83)	17 (71)	103 (73)
		Co-morbidities/coexisting conditions [*n* (%)]		
Any condition	44 (64)	31 (65)	24 (100)	99 (70)
Hypertension	27 (39)	4 (8)	8 (33)	39 (28)
Hyperlipidaemia	21 (30)	7 (15)	5 (21)	33 (23)
Diabetes mellitus	16 (23)	4 (8)	5 (21)	25 (18)
Obesity[a]	20 (29)	10 (21)	10 (42)	40 (28)
Cardiovascular disease	9 (13)	1 (2)	3 (13)	13 (9)
Heart failure	2 (3)	0 (0)	0 (0)	2 (1)
Stroke	1 (2)	0 (0)	0 (0)	1 (1)
Asthma	2 (3)	9 (19)	2 (8)	13 (9)
COPD	0 (0)	0 (0)	0 (0)	0 (0)
Other lung disease	6 (9)	5 (10)	4 (17)	15 (11)
Kidney disease	1 (2)	3 (6)	2 (8)	6 (4)
Liver disease	1 (2)	2 (4)	0 (0)	3 (2)
Autoimmune disease	2 (3)	4 (8)	4 (17)	10 (7)
History of cancer	6 (9)	2 (4)	1 (4)	9 (6)
Thyroid disease	7 (10)	4 (8)	2(8)	13 (9)
Psychiatric disorder	7 (10)	4 (8)	5 (21)	16 (11)
Pregnancy	–	–	1 (4)	1 (1)

IQR, interquartile range; COPD, chronic obstructive pulmonary disease.
[a] Body mass index (BMI) ≥30 kg/m^2.

Table 3
Patients with reported days since onset of symptoms in the treatment group

Characteristic	Risk-stratified group			All patients (*N* = 141)
	Group A (*N* = 69)	Group B (*N* = 48)	Group C (*N* = 24)	
Patients with reported days [*n* (%)]	32 (46)	25 (48)	9 (38)	66 (47)
Days since onset of symptoms [median (IQR)]	4 (3–6)	3 (3–6.5)	4 (3–5.5)	4 (3–6)

IQR, interquartile range.

Table 4
COVID-19 diagnostics and baseline reported clinical symptoms of patients in the treatment group

Clinical symptom [*n* (%)]	Risk-stratified group			All patients (*N* = 141)
	Group (*N* = 69)	Group B (*N* = 48)	Group C (*N* = 24)	
Cough/dry cough	60 (87)	39 (81)	24 (100)	123 (87)
Fever	53 (77)	38 (79)	18 (75)	109 (77)
Shortness of breath	17 (25)	48 (100)	0 (0)	65 (46)
Changes to or no smell or taste	21 (30)	19 (40)	2 (8)	42 (30)
Sore throat	19 (28)	8 (17)	7 (29)	34 (24)
Headache	19 (28)	6 (13)	7 (29)	32 (23)
Runny nose/clear rhinorrhoea	16 (23)	8 (17)	4 (17)	28 (20)
Sinus congestion	10 (15)	9 (19)	4 (17)	23 (16)
Diarrhoea/vomiting	1 (2)	5 (10)	1 (4)	7 (5)
Cold symptoms	31 (45)	16 (33)	12 (50)	59 (42)
Feels sick	40 (58)	38 (79)	17 (71)	95 (67)
Weakness	44 (64)	22 (46)	11 (46)	77 (55)
Low back pain	3 (4)	0 (0)	1 (4)	4 (3)

COVID-19, coronavirus disease 2019.

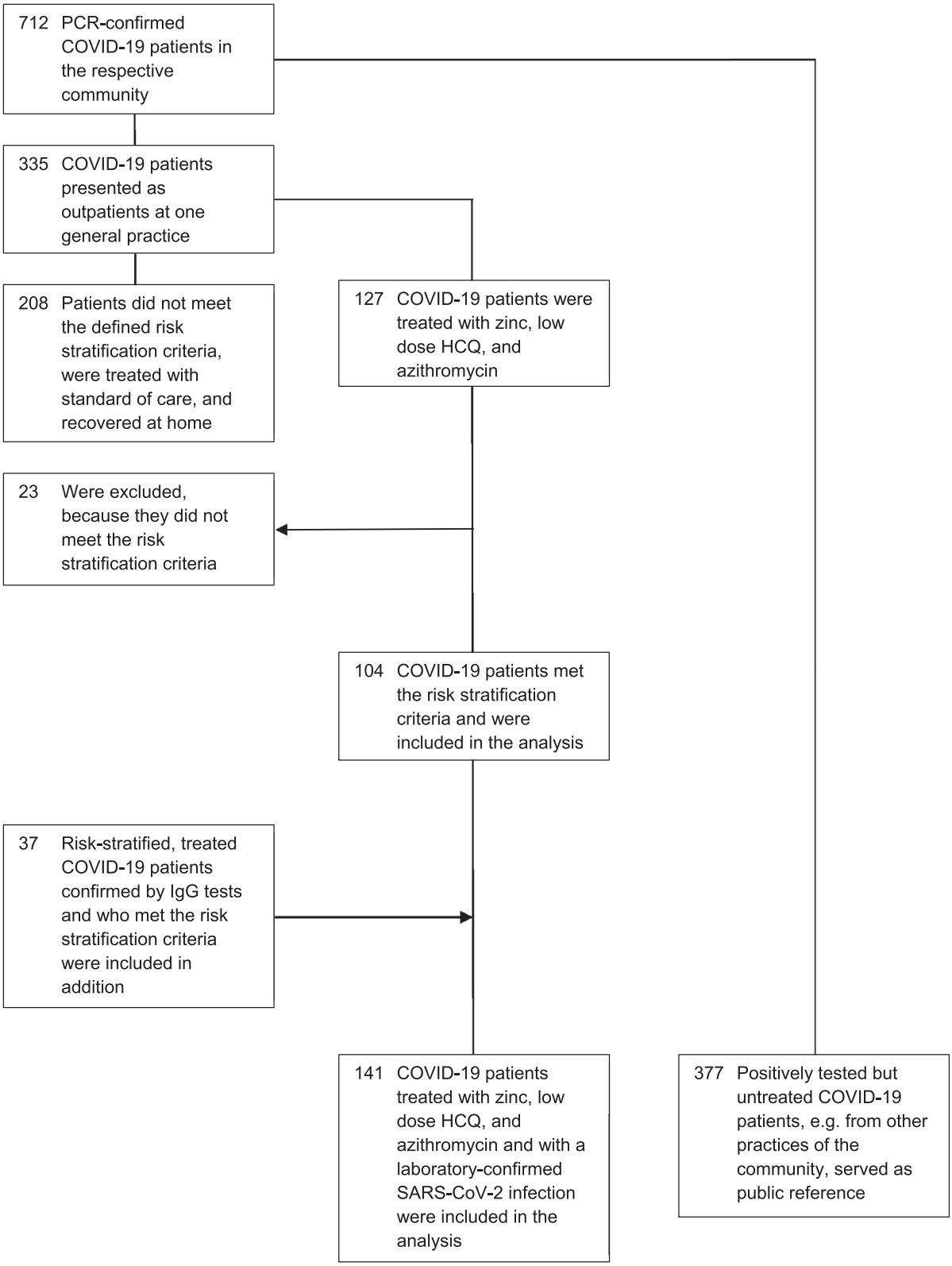

Fig. 1. Study population. $N = 141$ COVID-19 patients, all with a laboratory-confirmed SARS-CoV-2 infection, were included in the analysis as the treated group. $N = 377$ positively tested COVID-19 patients of the public reference were included in the analysis as the untreated group. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 5
Physical examination: vital signs of patients in the treatment group

Parameter	Median (IQR)	Patients with available parameters [*n* (%) of *N* = 141]
Heart rate (beats/min)	86 (80–94)	89 (63)
Respiratory rate (breaths/min)	16 (15–18)	43 (31)
Systolic blood pressure (mmHg)	126 (120–139)	66 (47)
Diastolic blood pressure (mmHg)	80 (74–85.5)	66 (47)
Body temperature (°C)	37.2 (37–37.8)	79 (56)
Pulse oximetry (O_2 %)	97 (96–98)	85 (60)
Body weight (kg)	88 (72.6–98.4)	43 (31)
BMI (kg/m^2)	32.2 (28.5–36.3)	30 (21)

IQR, interquartile range; BMI, body mass index.

Table 6
Co-medications of patients in the treatment group

Drug class	Patients [*n* (%) of *N* = 141]
Beta-blockers	17 (12)
Angiotensin-converting enzyme inhibitors	8 (6)
Angiotensin 2 antagonists	13 (9)
Calcium channel blockers	8 (6)
Hydrochlorothiazide	6 (4)
Statins	28 (20)
Bronchodilators	10 (7)
Antidiabetics	11 (8)
Insulin	26 (18)
Oral corticosteroids	13 (9)
Antibiotics	3 (2)

via telehealth so vital signs were not available for all of these patients. The highest proportion of patients had available measurements for heart rate (63%) and pulse oximetry (60%). Vital signs were not significantly different between risk stratification groups ($P > 0.05$) except for systolic blood pressure of groups A and B ($P < 0.05$).

Table 6 summarises the most important co-medications. Of the patients, 16% were taking angiotensin-converting enzyme inhibitors, angiotensin 2 antagonists, hydrochlorothiazide or a combination thereof. The most common long-term therapies at the time of COVID-19 diagnosis were statins (20%), beta-blockers (12%) and insulin (18%). A few patients had chronic prescriptions for oral corticosteroids (9%) for co-morbidities such as asthma or autoimmune diseases, and 3 patients (2.1%) received an additional antibiotic (levofloxacin) because of superinfections.

3.3. Hospitalisations and all-cause death

In the treatment group, 4 (2.8%) of 141 patients were hospitalised, which was significantly fewer than the 58 (15.4%) of 377 patients in the untreated group (Fig. 2) [OR = 0.16, 95% confidence interval (CI) 0.06–0.5; $P < 0.001$] (Table 7; Fig. 3). Therefore, the odds of hospitalisation of treated patients was 84% less than in the untreated patients. All hospitalised patients were male, with one in his twenties, two in their forties and one in his seventies. Three (75%) of the four hospitalised patients belonged to risk stratification group B and one (25%) to group A. All patients (100%) reported SOB at the time of consultation. The median time from onset of symptoms to consultation was 4 days. In the treatment group, one patient had to stay only 1 day in hospital, two other patients were discharged as cured and one patient died (see below). No patient was on a ventilator.

Of the 141 patients, 1 (0.7%) in treatment group A died after being hospitalised. This patient had a history of cancer and only took one daily dose of the triple therapy before hospital admission. More patients (13/377; 3.4%) died in the untreated group (Fig. 4)

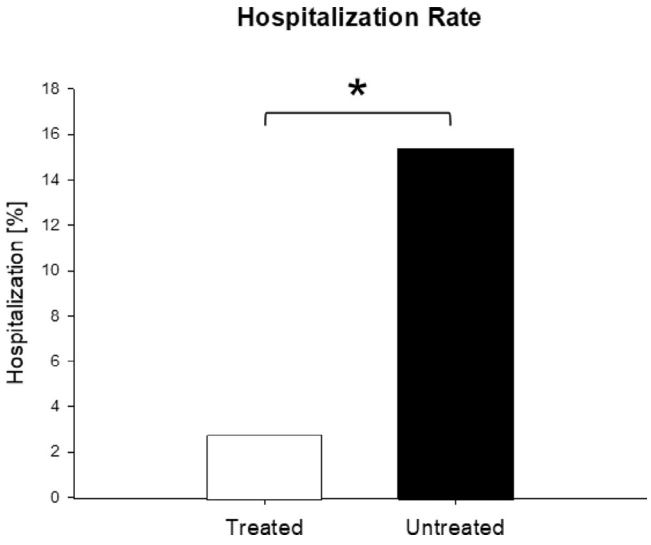

Fig. 2. Hospitalisation. Treatment with triple therapy of zinc, low-dose hydroxychloroquine and azithromycin was associated with significantly fewer hospitalisations compared with untreated patients of the public reference data. χ^2 (1, $N = 518$) = 14.17; * $P < 0.001$.

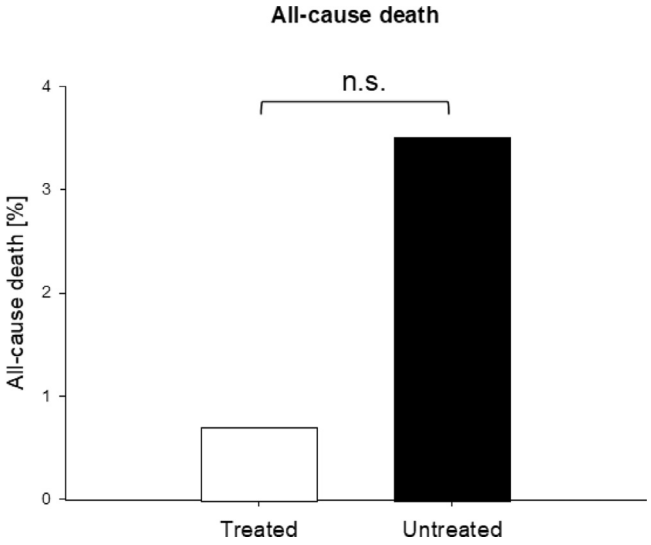

Fig. 3. All-cause deaths. Treatment with triple therapy of zinc, low-dose hydroxychloroquine and azithromycin was associated with numerically fewer all-cause deaths compared with untreated patients of the public reference data. n.s., not significant. χ^2 (1, $N = 518$) = 1.98; $P = 0.12$.

Table 7
Clinical outcomes in the treated patient group versus the untreated patient group

Outcome	Treated group [*n* (%) of *N* = 141]	Untreated group [*n* (%) of *N* = 377]	OR (95% CI)	*P*-value
Hospitalisation	4 (2.8)	58 (15.4)	0.16 (0.06–0.5)	<0.001
All-cause death	1 (0.71)	13 (3.5)	0.2 (0.03–1.5)	0.12

OR, odds ratio; CI, confidence interval.

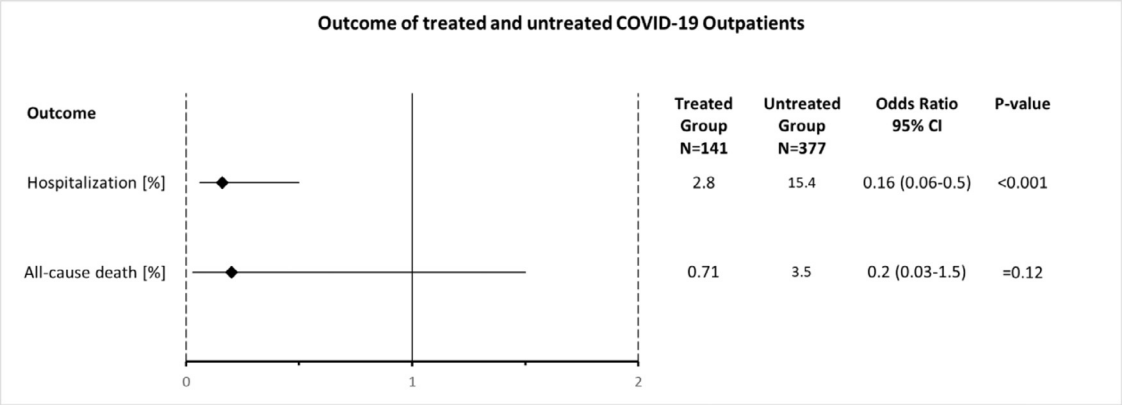

Fig. 4. Odds ratios (ORs). The odds of hospitalisation in the treated patient group was 84% less than in the untreated patient group and was statistically significant ($P < 0.001$). The odds of all-cause death in the treated patient group was 80% less than in the untreated patient group but did not reach statistical significance ($P = 0.12$). COVID-19, coronavirus disease 2019; CI, confidence interval.

Table 8
Summary of adverse events in the treatment group

Event	Patients [*n* (%) of *N* = 141]
Any adverse event	67 (48)
Weakness	30 (21)
Nausea	20 (14)
Diarrhoea	15 (11)
Rash	2 (1)

(OR = 0.2, 95% CI 0.03–1.5) (Table 7; Fig. 3). Although the odds of all-cause death of treated patients was 80% less than in the untreated group, this difference did not reach statistical significance ($P = 0.12$).

All patients in the treatment group with the clinical outcome of hospitalisation or all-cause death received a prescription for the complete triple therapy including zinc, low-dose HCQ and azithromycin.

The outcome of the three different risk-stratified groups (A, B and C) was not significantly different.

The 208 patients presenting at the general practice who did not meet the risk stratification requirements and who were not treated with the triple therapy recovered at home and no hospital admissions or deaths were reported.

3.4. Safety

In general, triple therapy with zinc, low-dose HCQ and azithromycin was well tolerated. After initiation of treatment in the 141 patients, 30 (21.3%) reported weakness, 20 (14.2%) nausea, 15 (10.6%) diarrhoea and 2 (1.4%) rash (Table 8). No patient reported palpitations or any cardiac side effects.

4. Discussion

This first retrospective case series study of COVID-19 outpatients in a primary care setting showed that risk-stratified treatment early after onset of clinical symptoms with triple therapy of zinc, low-dose HCQ and azithromycin was associated with significantly fewer hospitalisations (OR = 0.16; $P < 0.001$) in comparison with untreated patients (public reference data) of the same community. Based on the performed risk stratification, the prevalences of the co-morbidities hypertension, hyperlipidaemia and diabetes mellitus were the highest in group A (>60 years and clinical symptoms), asthma and other lung diseases were the highest in group B (≤60 years and SOB), and obesity and autoimmune disease were the highest in group C (<60 years, clinical symptoms and defined co-morbidities). The most frequent symptoms of these COVID-19 patients were cough followed by fever while available median body temperature measurements were in a normal range. Almost 50% of risk-stratified and treated patients were suffering from SOB while breaths per minute and blood oxygen saturation were still in the normal range. The median time from onset of symptoms to first medical consultation was 4 days (IQR 3–6 days). Approximately 16% of patients received co-medications known to be associated with zinc deficiency, such as antihypertensive drugs. No patient experienced any known severe adverse events that were considered drug-related during treatment or follow-up.

A growing number of reports provide evidence for the effectiveness or otherwise of a range of COVID-19 drug treatments. Therefore, a living systematic review and network meta-analysis was published to assess how trustworthy the evidence is using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [24]. Based on their most recent update from 21 July 2020, the authors conclude that glucocorticoids probably reduce mortality and mechanical ventilation in patients with COVID-19 compared with standard care. However, the effectiveness of most interventions is uncertain because most of the randomised controlled trials so far have been small and have important study limitations [24].

Another meta-analysis focused on the effectiveness of chloroquine derivatives in COVID-19 therapy [25]. The authors concluded that chloroquine derivatives are effective in improving clinical and virological outcomes and may reduce mortality by a factor of 3 in patients affected with COVID-19. They further conclude that big data are lacking basic treatment definitions and are the subject of

conflict of interest [25]. At the time of this manuscript submission, only one peer-reviewed study had analysed the key health outcomes of COVID-19 patients diagnosed in a primary care setting [3]. Because of this gap in the data, the value of this study is multifold. It provides much needed recommendations for risk stratification and a treatment regimen to prevent hospitalisation and death of COVID-19 patients. The diagnosis of COVID-19 for all patients in this analysis was confirmed by PCR or IgG tests compared with a recent study in which <3% had a diagnosis confirmed by laboratory tests [26]. Starting triple therapy as early as possible after symptom onset is critical for treatment success because SARS-CoV-2 viral load appears to peak at Days 5–6 after symptom onset [27–29] and severe cases progress to ARDS after only 8–9 days [30,31]. Early antiviral treatment is an established protocol to manage severe disease progression, as was shown, for example, by a cumulative case–control study during the 2009 H1N1 influenza pandemic in Canada [32]. For patients at high risk for severe viral disease progression, it is recommended to start antiviral therapy as early as possible [33,34]. Early treatment might be also critically important to effectively reduce the SARS-CoV-2 viral load [5] and this underscores the role of early intervention by primary care physicians as reported herein.

A further strength of this approach was the simple risk stratification of symptomatic outpatients to determine the need for therapy, a strategy not yet applied in COVID-19 primary care [35] but routinely implemented in primary care for other diseases [36]. Underlying assumptions of the risk stratification used in this setting are different to other recommendations [37]. Here, age-stratified high risk was defined as >60 years (typically defined as >65 years) to encompass the common increase of co-morbidity incidences in this age group [38]. Patients ≤60 years with SOB, even without reduced pulse oximetry values, were treated because it was assumed the virus will likely spread from the upper to lower respiratory tract [39]. Also treated were patients ≤60 years with clinical symptoms and prognostically relevant co-morbidities [37]. By applying this risk stratification approach, respective care was tailored to patients with a higher likelihood for hospitalisation or fatality, which ensured that the medical principles of 'patient first' and 'doing no harm' were maintained [40]. As a result, 61.8% of COVID-19 patients were treated with standard of care only and recovered at home, and only 37.9% needed treatment with the triple therapy.

The antiviral potential of HCQ has been broadly described in vitro and in vivo [41–43]. HCQ has a long terminal elimination half-life of 32 days in plasma and 50 days in blood [44]. Therefore, the treatment approach was conservative, with the starting dose being the same as the maintenance dose and with a short treatment duration of only 5 days, being even more conservative than other recommendations [42]. HCQ-dependent intracellular increases in pH might directly interfere with pH-dependent SARS-CoV-2 replication [19]. Also, chloroquine and probably HCQ have characteristics of a zinc ionophore resulting in increasing intracellular zinc concentrations [20]. The dose of elementary zinc in this study was similar to doses previously studied to successfully prevent infections in the elderly [45]. The antiviral effects of zinc against a variety of viruses have been demonstrated during the last decades [46]. Zinc, in addition to its role as a general stimulant of antiviral immunity, is known to specifically inhibit coronavirus RNA-dependent RNA polymerase (RdRp) [21]. Based on the ionophore properties of HCQ, it has been hypothesised that zinc may enhance the efficacy of HCQ in treating COVID-19 patients [22]. In addition, zinc might inhibit the serine protease furin [47]. Furin is expressed on endothelial cells, monocytes/macrophages and smooth muscle cells in human atherosclerotic plaques [48] and therefore might play a critical role for the severe cardiovascular complications of COVID-19. As furin might be responsible to favour SARS-CoV-2 spread compared with other Betacoronaviruses [49,50] and as furin inhibition protects from certain viral-dependent infections [51], it may be important to evaluate the potential role of zinc in inhibiting this pathway.

Azithromycin was added to the treatment regimen as preliminary data provided evidence for more efficient or synergic virus elimination in conjunction with bacterial superinfection [13,52]. Although there is a synergistic antiviral effect between zinc, HCQ and azithromycin, zinc supplementation may be instrumental for the outcome of patient populations with severe clinical courses. Zinc deficiency was confirmed in a large number of healthy elderly [53] and in diabetic patients [54]. In addition, it has been documented that the antihypertensive drugs hydrochlorothiazide, angiotensin-converting enzyme inhibitors and angiotensin 2 receptor antagonists can result in increased urinary excretion of zinc with subsequent systemic zinc deficiency [55]. Age, co-morbidities and relevant co-medications align well with the majority of described COVID-19 patients at high risk, including the risk-stratified population of this analysis. Zinc deficiency might explain why certain patient groups seem not to benefit from HCQ monotherapy. During the 5-day treatment with the triple therapy and during follow-up, no severe adverse events were observed and no cases of cardiac arrhythmia were reported in this general practice, which is in accordance with available safety data for more than 300 000 patients [56].

Inherent to all retrospective analyses, our study has certain limitations, such as non-randomisation and blinding of treatment. Also, only the outcome data of the untreated control group based on the public reference were available; because no other data on patient characteristics or clinical symptoms were available, no risk adjustment was possible. Therefore, confounding factors and selection bias, among other issues, might exist. The demographic composition of the treatment group might also have had an influence on our findings. Because many physician appointments had to be managed by telehealth, vital parameters were not available for the majority of patients. Viral load and electrocardiogram (ECG) data were not analysed. Treatment with the triple therapy resulted in a numerically lower rate of all-cause death. In the absence of clinical details about the untreated patient group, the lower rate of all-cause death in the treated group was not statistically significant. However, patients in the treated group were all positively risk-stratified while the risk of the untreated group was obviously lower as this group included high- and low-risk patients. When we compared the outcome of all risk-stratified patients in the study group (treated and non-treated) with the control patients (not stratified, treated with standard therapy), hospitalisation and all-cause death were significantly less in the study group ($P < 0.0001$ and $P = 0.0154$, respectively). These data were not shown in the results section because relevant clinical information was not completely available for all patients in the control group to allow risk adjustment between groups.

In this study, the ratio of males and average age was comparable with a relevant number of other studies, but the distribution of co-morbidities was not [57]. The latter was expected because outpatients usually have a different distribution of age and especially of co-morbidities than critically ill inpatients. As expected, the prevalence of hypertension, hyperlipidaemia and cardiovascular disease correlated positively with age, while asthma correlated negatively. Approximately 50% of risk-stratified and treated patients presented with SOB, while the parameters breaths per minute and blood oxygen saturation were still within the normal range. These patients would usually not be considered for hospital admission, although SOB might be considered an alarming early sign of disease progression. Based on the implemented risk stratification, these patients were identified and treated immediately.

Indeed, three of four hospitalised patients were in risk stratification group B including patients especially with SOB, and also the

hospitalised patient of group A reported SOB at the time of consultation. This supports the assumption that COVID-19 patients with SOB are at much higher risk for disease progression and need to be monitored closely.

In contrast to many other studies, the most frequent symptom was cough and not fever [58,59]. Changes in smell or taste in one-third of patients and a negative correlation with age were similar to findings from other groups [60]. While mean time from onset of symptoms to treatment was only 4.8 days (median 4 days), previously reported time spans range from 6.3 days [61] to 8 days [16], up to 16.6 days [14], or it was often even not reported [62]. In most of these studies, COVID-19 disease had most likely already progressed at the time of presentation to stages II or even stage III of the disease [6]. In many studies, often only limited information is provided about co-medications and specifically about clinical symptoms at admission [62]. The latter would be very important to better understand the differences in clinical presentation between inpatients and outpatients and thus the urgency for early anti-COVID-19 treatment in the outpatient setting [63]. The potential of zinc to enhance the antiviral efficacy of HCQ was already described in detail elsewhere [22]. This hypothesis was recently confirmed in a study using a similar triple therapy and treatment duration [23]. Zinc added to HCQ and azithromycin resulted in a significantly increased number of patients being discharged, a reduction in mortality, or transfer to hospice. In another study, when a lower dose of 200 mg of HCQ twice daily was added to basic treatment, mortality of even critically ill patients was significantly reduced [64]. These and our findings indicate that proper dosing of HCQ with its long half-life might be key for a favourable outcome of COVID-19 patients. In critical care, drugs with short half-lives are usually preferred. Especially in critically ill COVID-19 patients, higher doses of HCQ may have unforeseeable effects, e.g. on insulin sensitivity in obese patients [65] and on glucose levels in diabetics [66,67]. Besides glucose levels, it is important to closely monitor renal function, which is increasingly affected during progression of COVID-19 [68]. Because HCQ is substantially excreted by the kidneys, the risk of toxic reactions is greater in patients with impaired renal function [69].

4.1. Potential implications for clinicians and policy-makers

Clinical experience from severely ill inpatients with pneumonia who were treated with high-dose HCQ is not readily transferable to the outpatient setting with upper respiratory tract disease only. For outpatients with a median of only 4 days after onset of symptoms, COVID-19 represents a totally different disease and needs to be managed and treated differently [63]. A simple-to-perform outpatient risk stratification, as shown here, allows for rapid treatment decisions and treatment with the triple therapy of zinc, low-dose HCQ and azithromycin and may prevent a large number of hospitalisations and probably deaths during the SARS-CoV-2 pandemic. This might also help to avoid overwhelming of healthcare systems.

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Competing interests

RD is/was at the time of writing an employee of Alexion Pharma Germany GmbH, and his engagement and contribution to this study and publication was private and independent from his employer; MS is/was at the time of writing External Senior Advisor for the company LEUKOCARE (Munich, Germany) and is/was Manging Director at Starts- and -Ups Consulting (Frankfurt, Germany); VZ is/was a general practitioner in New York State (USA).

Ethical approval

This study was approved by the Western Institutional Review Board and was exempt under 45 CFR § 46.104(d)(4). Ref. Number: D4-Exemption-Zelenko (06-16-2020).

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PART 3

COVID-19 VACCINE INFORMATION

SUMMARY

1- The news stories about the vaccine are no based on publically available laboratory, medical, or scientific information, but on corporate press releases.

2- The vaccine may be 90%+ effective *to lessen* the severity of symptoms of COVID-19 infection, like fever, cough, headache, malaise.

The vaccine *does not prevent* viral infection and does not cure it.

3- The studies in the press are touted as if involving tens of thousands of people.

However, in Pfizer's trial only 170 of them were reported as being "diagnosed with COVID-19" during the trial.

Of those, 162 were in the placebo group and 8 were in the vaccine group.

From this, it is inferred that the vaccine prevented 154 or "95%" people from developing the disease.

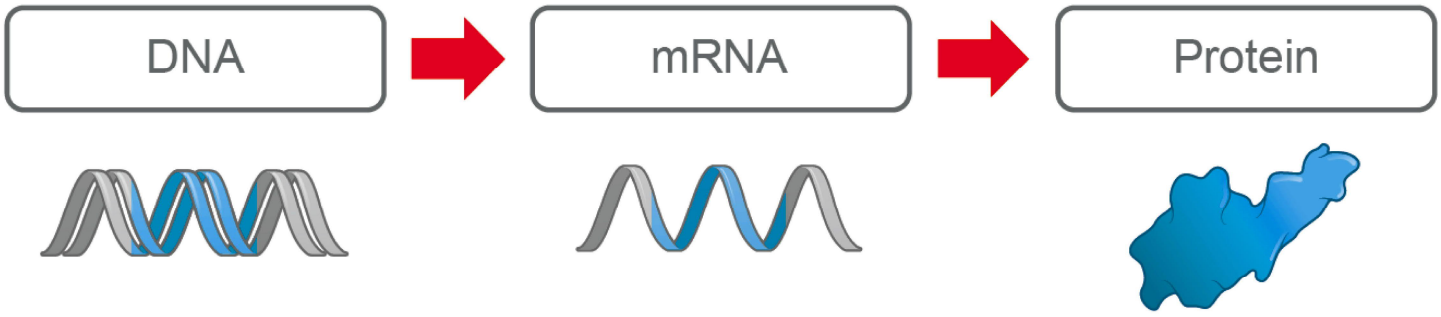
According to the British Medical Journal, "a relative risk reduction is being reported, not absolute risk reduction, which appears to be less than 1%."

4- The safety of the vaccine has not yet been established. Stage III trials are still ongoing. Some data will be collected and studied only 24 months after the injection.

When agricultural GMOs were being developed and were tested in mice, some animals did not develop adverse effects in the first few weeks. Some mice began to show cancerous tumors after 3 months.

The UK's own "Information for UK Healthcare Professionals" pamphlet regarding Pfizer's vaccine points out, "Animal reproductive toxicity studies have not been completed," and, "It is unknown whether COVID-19 mRNA Vaccine BNT162b2 has an impact on fertility."

MODERNA IS ONE OF SEVERAL VACCINE MANUFACTURING COMPANIES BILL GATES CONTROLS



STORAGE

DNA stores instructions for proteins in the nucleus

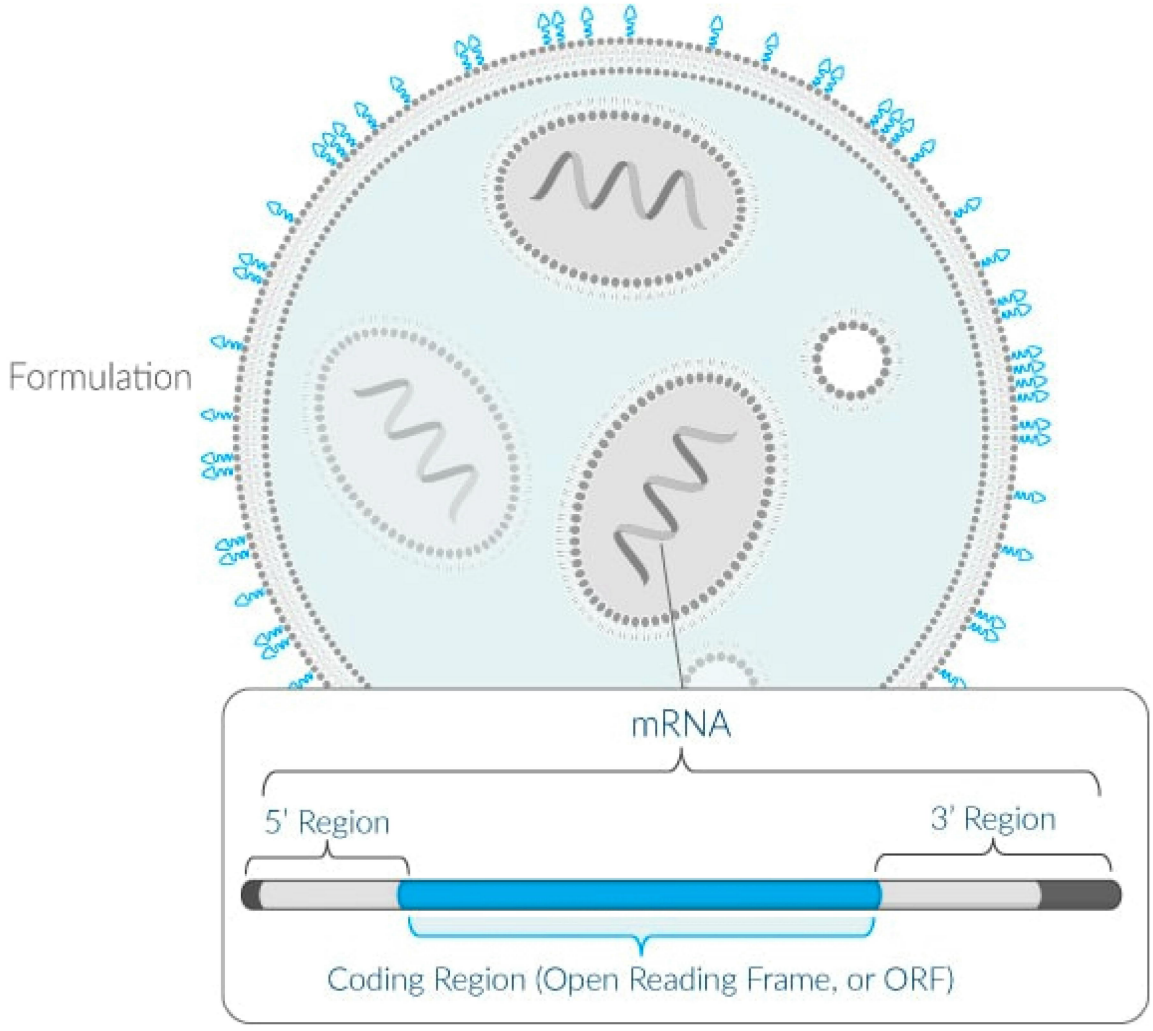
SOFTWARE

mRNA is a temporary set of instructions for cells to make a protein; mRNA is made using DNA

APPLICATIONS

Proteins form the basis of life by performing the functions required by every cell; proteins are made using mRNA

THE GENETIC 'OPERATING SYSTEM'



Within a given modality, the base components are generally identical across development candidates - formulation, 5' region and 3' region. Only the coding region varies based on the protein/s the potential medicine is directing cells to produce.

This is not a vaccine. It is an mRNA INJECTION which causes an IRREVERSIBLE genetic modification. It is experimental genetic engineeringwhich has never been done before. It is extremely dangerous. It is not safe.

The mRNA in the COVID-19 vaccines instruct our DNA to make the viral 'spike' foreign protein FOREVER. It cannot be changed or stopped.

Our immune system will then attacks the foreign spike body to remove it because that's what our immune systems are designed to do. It will attack our own DNA and try to kill and remove the protein because our DNA has been changed into a foreign body. This is the core of all AUTOIMMUNE DISORDERS.

Anticipating and Identifying Collateral Damage in Genome Editing

Trends in Genetics, December 2020, Vol. 36, No. 12, 905-914.

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ABSTRACT

Genome editing has powerful applications in research, healthcare, and agriculture. However, the range of possible molecular events resulting from genome editing has been underestimated and the technology remains unpredictable on, and away from, the target locus. This has considerable impact in providing a safe approach for therapeutic genome editing, agriculture, and other applications.

This opinion article discusses how to anticipate and detect those editing events by a combination of assays to capture all possible genomic changes. It also discusses strategies for preventing unwanted effects, critical to appraise the benefit or risk associated with the use of the technology. Anticipating and verifying the result of genome editing are essential for the success for all applications.

HIGHLIGHTS

Genome editing has a transformative potential in healthcare or to improve crops or livestock. However, the use of Cas9 or other nucleases can yield unpredictable events at the target site or off target.

To overcome these challenge, it is critical to understand and accurately predict the whole range of possible editing outcomes.

The key to success is to combine molecular assays to evaluate the se-quence changes at the target site and to quantify the number of copies of segments deleted/inserted across the genome.

For all applications, thorough evaluation of these outcomes is essential to identify all collateral damage from nuclease activity and for a real appraisal of the benefits and risks associated with applying this technology.

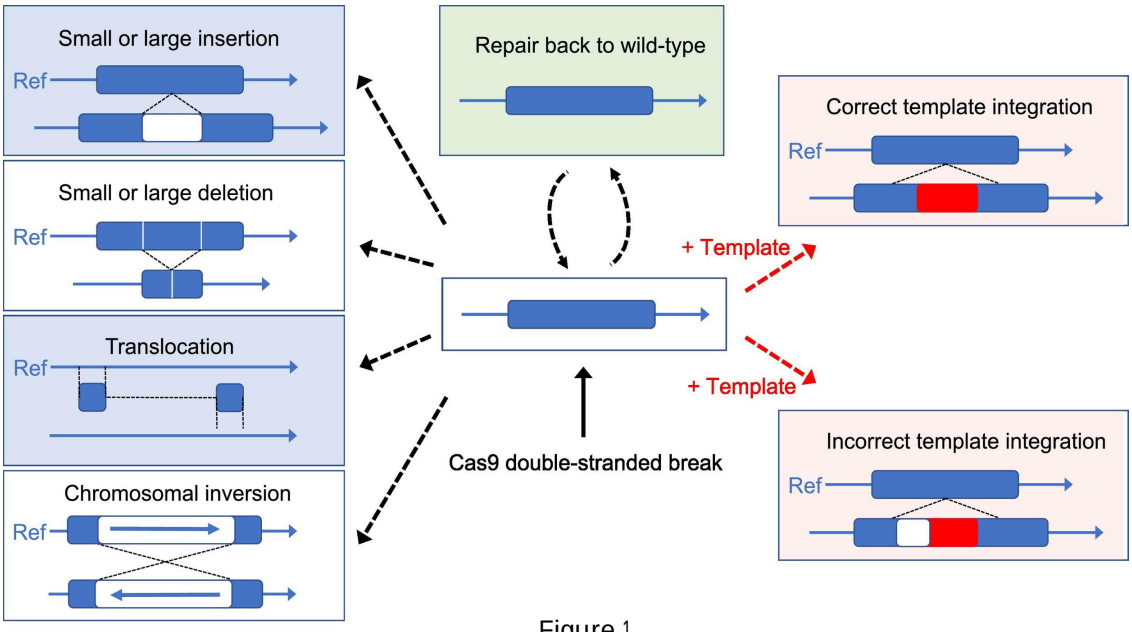

Figure 1

https://www.webmd.com/a-to-z-guides/autoimmune-diseases

WebMD Medical Reference
Jennifer Robinson, MD
June 22, 2020

What Are Autoimmune Disorders?

Immune system disorders cause abnormally low activity or over activity of the immune system. In cases of immune system overactivity, the body attacks and damages its own tissues (autoimmune diseases). Immune deficiency diseases decrease the body's ability to fight invaders, causing vulnerability to infections.

In response to an unknown trigger, the immune system may begin producing antibodies that instead of fighting infections, attack the body's own tissues. Treatment for autoimmune diseases generally focuses on reducing immune system activity. Examples of autoimmune diseases include:

RHEUMATOID ARTHRITIS. The immune system produces antibodies that attach to the linings of joints. Immune system cells then attack the joints, causing inflammation, swelling, and pain. If untreated, rheumatoid arthritis causes gradually causes permanent joint damage. Treatments for rheumatoid arthritis can include various oral or injectable medications that reduce immune system overactivity. See charts that list rheumatoid arthritis drugs and their side effects.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE). People with lupus develop autoimmune antibodies that can attach to tissues throughout the body. The joints, lungs, blood cells, nerves, and kidneys are commonly affected in lupus. Treatment often requires daily oral prednisone, a steroid that reduces immune system function. Read an overview on lupus symptoms and treatments.

INFLAMMATORY BOWEL DISEASE (IBD). The immune system attacks the lining of the intestines, causing episodes of diarrhea, rectal bleeding, urgent bowel movements, abdominal pain, fever, and weight loss. Ulcerative colitis and Crohn's disease are the two major forms of IBD. Oral and injected immune-suppressing medicines can treat IBD. Learn about the differences between ulcerative colitis and Crohn's disease.

MULTIPLE SCLEROSIS (MS). The immune system attacks nerve cells, causing symptoms that can include pain, blindness, weakness, poor coordination, and muscle spasms. Various medicines that suppress the immune system can be used to treat multiple sclerosis. Read more on multiple sclerosis drugs and their side effects.

TYPE 1 DIABETES MELLITUS. Immune system antibodies attack and destroy insulin-producing cells in the pancreas. At diagnosis, people with type 1 diabetes require insulin injections to survive. Learn about the symptoms to look for in type 1 diabetes.

GUILLAIN-BARRE SYNDROME. The immune system attacks the nerves controlling muscles in the legs and sometimes the arms and upper body. Weakness results, which can sometimes be severe. Filtering the blood with a procedure called plasmapheresis is the main treatment for Guillain-Barre syndrome.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY. Similar to Guillain-Barre, the immune system also attacks the nerves in CIDP, but symptoms last much longer. About 30% of patients can become confined to a wheelchair if not diagnosed and treated early. Treatment for CIDP and GBS are essentially the same. Find out what the treatment options are for CIDP.

PSORIASIS. In psoriasis, immune system blood cells called T-cells collect in the skin. The immune system activity stimulates skin cells to reproduce rapidly, producing silvery, scaly plaques on the skin. See a photo of what psoriasis looks like.

GRAVES' DISEASE. The immune system produces antibodies that stimulate the thyroid gland to release excess amounts of thyroid hormone into the blood (hyperthyroidism). Symptoms of Graves' disease can include bulging eyes as well as weight loss, nervousness, irritability, rapid heart rate, weakness, and brittle hair. Destruction or removal of the thyroid gland, using medicines or surgery, is usually required to treat Graves' disease. Learn more about treatments for Graves' disease.

HASHIMOTO'S THYROIDITIS. Antibodies produced by the immune system attack the thyroid gland, slowly destroying the cells that produce thyroid hormone. Low levels of thyroid hormone develop (hypothyroidism), usually over months to years. Symptoms include fatigue, constipation, weight gain, depression, dry skin, and sensitivity to cold. Taking a daily oral synthetic thyroid hormone pill restores normal body functions. Find out more on treatments for an underactive thyroid.

MYASTHENIA GRAVIS. Antibodies bind to nerves and make them unable to stimulate muscles properly. Weakness that gets worse with activity is the main symptom of myasthenia gravis. Mestinon (pyridostigmine) is the main medicine used to treat myasthenia gravis. Read an overview on the symptoms of myasthenia gravis.

VASCULITIS. The immune system attacks and damages blood vessels in this group of autoimmune diseases. Vasculitis can affect any organ, so symptoms vary widely and can occur almost anywhere in the body. Treatment includes reducing immune system activity, usually with prednisone or another corticosteroid. Learn more about vasculitis symptoms and treatments.

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International Journal of Vaccines and Vaccination

New Quality-Control Investigations on Vaccines: Micro- and Nanocontamination

Volume 4 Issue 1 - 2017

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Abstract

Vaccines are being under investigation for the possible side effects they can cause. In order to supply new information, an electron-microscopy investigation method was applied to the study of vaccines, aimed at verifying the presence of solid contaminants by means of an Environmental Scanning Electron Microscope equipped with an X-ray microprobe. The results of this new investigation show the presence of micro- and nanosized particulate matter composed of inorganic elements in vaccines' samples which is not declared among the components and whose unduly presence is, for the time being, inexplicable. A considerable part of those particulate contaminants have already been verified in other matrices and reported in literature as non biodegradable and non biocompatible. The evidence collected is suggestive of some hypotheses correlated to diseases that are mentioned and briefly discussed.

Keywords: Vaccine; Disease; Contamination; Protein corona; Biocompatibility; Toxicity; Nanoparticle; Immunogenicity; Foreign body; Environment; Industrial process; Quality control

Table 1: List of vaccines analyzed, according to their purpose.

N	Name	Brand Name, Country of Distribution	Description
1	Vivotif Berna	Berna Biotech SA, Italy	Anti-Thyphoid Vaccine (Live), group Ty21a
2	Typhim Vi	Aventis Pasteur MSD, Italy	Anti-Salmonella typhi Vaccine
3	Typherix	GlaxoSmithKline S.p.a., Italy	Anti-Thypoid Vaccine (polysaccharide Vi)
4	Anatetall	Chiron (now Novartis) Italy	Adsorbed anti-Tetanus Vaccine
5	Anatetall	Novartis Vaccines and Diagnostics, Italy	Adsorbed anti-Tetanus Vaccine
6	Tetabulin	Baxter AG, Italy	Adsorbed anti-Tetanus Vaccine
7	Dif-Tet-All	Novartis Vaccines and Diagnostics, Italy	Adsorbed anti-Tetanus and diphtheria Vaccine
8	Infanrix	GlaxoSmithKline S.p.a., Italy	Anti-Diphtheria, tetanus and pertussis vaccine
9	Infanrix hexa	GlaxoSmithKline Biologicals s, Italy	Anti-diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and disease caused by Haemophilus influenzae type b
10	Infanrix hexa	GlaxoSmithKline Biologicals s. a. France	Anti-diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and disease caused by Haemophilus influenzae type b
11	M-M-R vaxPro	Sanofi Pasteur MSD, Italy	M-M-R vaxPro (measles, mumps, and rubella) analyzed in Cambridge
12	Repevax	Sanofi Pasteur MSD, France	Anti-diphtheria-tetanus-pertussis-polio-vaccine
13	Repevax	Sanofi Pasteur MSD SNC France	Anti-diphtheria-tetanus-pertussis-polio-vaccine
14	Priorix	GlaxoSmithKline S.p.a., Italy	Anti--measles-mumps, and rubella (MMR) vaccine
15	Morupar	Chiron (now Novartis,), Italy	Anti-measles- mumps, and rubella (MMR) vaccine
16	Varilrix	GlaxoSmithKline S.p.a., Italy	Anti-Chicken pox vaccine (group OKA)
17	Stamaril Pasteur	Sanofi Pasteur MSD, Italy	anti-yellow fever vaccine
18	Allergoid-Adsorbat 6-Graser Starke B.	Allergopharma, Germany	Antiallergic vaccine
19	Engerix-B	GlaxoSmithKline S.p.a., Italy	Adsorbed anti-hepatitis B vaccine
20	Prenevar 13	Pfizer, Italy	Antipneumococcal vaccine
21	Prevenar 13	Pfizer, France	Antipneumococcal vaccine
22	Mencevax Acwy	GlaxoSmithKline, Italy	anti-Neisseria meningococcal group A, C, W135 and Y vaccine
23	Meningitec	Pfizer, Italy	(group C 10) (adsorbed on Al-Phosphate)
24	Meningitec	Pfizer-Italy	Anti-meningococcus (group C 10) vaccine (adsorbed on Al-Phosphate)

Table 2: List of the vaccines according to their manufacturers with the chemical composition of the debris identified in each sample. The elements most represented are reported.

N	Company	Name	Alluminum	Elements Identified
1	Allergopharma - Germany	Allergoid	yes	Al
2	Aventis Pasteur MSD Lyon - Francie	Typhim Vi	no	BrKP, PbSi, FeCr, PbClSiTi
3	Baxter AG	Tetabulin	no	SiMg, Fe, SiTiAl, SBa, Zn
4	Berna Biotech	Vivotif Berna	no	FeAl, ZrAlHf, SrAl, BiAlCl
5	Berna Biotech	Inflexal V	no	CuSnPbZn, Fe, CaSiAl, SiAl, NaPZn, ZnP, AlSiTi
6	Chiron	Anatetall	$Al(OH)_3$	FeAl, SZnBaAl
7	Chiron	Morupar	no	/
8	GlaxoSmithKline- Belgium	Mencevax ACWY	no	FeCrNi, ZrAl, FeCrNiZrAlSi
9	GlaxoSmithKline	Infanrix	$Al(OH)_3$	Al, AlTi, AlSi
10	GlaxoSmithKline Biologicals	Infanrix hexa	$Al(OH)_3$	SBa, FeCu, SiAl, FeSi, CaMgSi, AlCaSi, Ti, Au, SCa, SiAlFeSnCuCrZn, CaAlSi
11	GlaxoSmithKline Biologicals	Infanrix hexa	$Al(OH)_3$,$AlPO_4$. $2H_2O$	W, FeCrNi, Ti
12	GlaxoSmithKline	Typherix	no	Ti, TiW, AlSiTiWCr, SBa, W, SiAl, AlSiTi
13	GlaxoSmithKline	Priorix	no	WCa, WFeCu, SiAl, SiMg, PbFe, Ti, WNiFe
14	GlaxoSmithKline	Engerix-B	no	Al (precipitates)
15	GlaxoSmithKline	Varilrix	no	FeZn, FeSi, AlSiFe, SiAlTiFe, MgSi, Ti, Zr, Bi
16	GlaxoSmithKline	Fluarix	no	AlCu, Fe, AlBi, Si, SiZn, AlCuFe, SiMg, SBa, AlCuBi, FeCrNi, SPZn
17	GlaxoSmithKline Biologicals	Cervarix	$Al(OH)_3$	AlSi,FeAl, SiMg,CaSiAl, CaZn, FeAlSi, FeCr, CuSnPb
18	Novartis Vaccines and Diagnostics	Anatetall	$Al(OH)_3$	Al, FeCrNi, AlCr, AlFe, BaS, ZnAl
19	Novartis Vaccines and Diagnostics	Dif-Tet-All	$Al(OH)_3$	Fe,SBa, SiSBa, AlZnCu, AlZnFeCr
20	Novartis Vaccines and Diagnostics	Menjugate kit	$Al(OH)_3$	SiAl,Ti,FeZn, Fe, Sb, SiAlFeTi, W, Zr
21	Novartis Vaccines and Diagnostics	Focetria	no	Fe, FeCrNiCu, FeCrNi, SiFeCrNi, Cr, SiAlFe, AlSiTiFe, AlSi, SiMgFe, Si, FeZn

22	Novartis	Agrippal S1	no	Ca, Fe, SBa, SBaZn, Cr, Si, Pb, Bi, e FeSiAlCr, SiAlSBaFe, CaAlSi, Zn, CeFeTiNi, FeCrNi
23	Novartis Vaccines and Diagnostics	Agrippal S1	no	SiAlK, Si, SiMgFe, CaSiAl, SBaZn
24	Novartis vaccines	Agrippal	no	Cr, Ca, SiCaAl, ZrSi, SBa, CuZn, SCa
25	Novartis Vaccines and Diagnostics S	Fluad	no	CaSiAl, FeSiTi,SiMgAlFe, SBa
26	Novartis Vaccines and Diagnostics	Menveo	no	CaSiAl, SiAlFe, FeCrNi, Fe, Al, SBa
27	Pfizer	Prenevar 13	no	FeCr
28	Pfizer	Prevenar 13	no	W, CaAlSi, Al, CaSiAlFe, FeS, FeCr, FeCrNi, Fe, , CaP, FeTiMn, Ba, SiMgAlFe
29	Pfizer	Meningitec - ctrl	no	Cr, Si
30	Pfizer	Meningitec - ctrl	no	FeCrNi, W
31	Pfizer	Meningitec	no	CaSiAl, CaSi, SiAlFeTi, FeCrNi, W, Fe, Pb
32	Pfizer	Meningitec	no	Cr (precipitates), Ca, AlSi
33	Pfizer	Meningitec	no	W, SiCa, CaSi, Pb, FeCrNi, Cr
34	Wyeth Pharmaceutical - UK	Meningitec	no	SiAlFe, SiAlTi, SiMgFe, W, Fe, Zr, Pb, Ca, Zn, FeCrNi
35	Sanofi Pasteur MSD-France	Vaxigrip	no	Fe, FeCrNi, SiAlFe, AlSi, SiAlFeCr
36	Sanofi Pasteur MSD	Stamaril Pasteur	no	CaSiAl, AlSi, Fe, SiMgFe, SiMgAlFe, CrSiFeCr, CrSiCuFe
37	Sanofi Pasteur MSD	Gardasil	$AlPO_4$. $2H_2O$	AlCuFe, PbBi, Pb, Bi, Fe
38	Sanifi Pasteur MSD	Gardasil	$AlPO_4$. $2H_2O$	CaAlSi, AlSi, SiMgFe, Al,Fe, AlCuFe, FeSiAl, BiBaS, Ti, TiAlSi
39	Sanofi Pasteur	Vaxigrip	no	Ca, CrFe, FeCrNi, CaSZn, CaSiAlTiFe, Ag, Fe
40	Sanofi Pasteur	Vaxigrip	no	SiMgFe, CaSiAl, AlSiFe, AlSi,FeCr, FeZn, Fe
41	Sanofi Pasteur MSD	Repevax	$AlPO_4$.$2H_2O$	Bi, Fe, AlSiFe, SiMg, SBa, Ca
42	Sanofi Pasteur MSD S	Repevax	$AlPO_4$.$2H_2O$	Ti, Br, AuCuZn, Ca, SiZn, SiAuAgCu, SiMgFe,FeCrNi. AlSiMgTiMnCrFe, SiFeCrNi, FeAl
43	Sanofi Pasteur MSD	M-M-R vaxPro	no	Si, SiFeCrNi, FeCrNi,FeNi, Fe, SCa, AlSiCa, CaAlSiFeV, SBa, Pt, PtAgBiFeCr
44	Virbac S.A. - Carros - France	Feligen CRP	no	Ca,SiAl

World Health Organization

Coronavirus disease (COVID-19): Serology

9 June 2020 | Q&A

What is herd immunity?

Herd immunity is the indirect protection from an infectious disease that happens when a population is immune either through vaccination or immunity developed through previous infection. This means that even people who haven't been infected, or in whom an infection hasn't triggered an immune response, they are protected because people around them who are immune can act as buffers between them and an infected person. The threshold for establishing herd immunity for COVID-19 is not yet clear.

World Health Organization

Coronavirus disease (COVID-19): Serology, antibodies and immunity

13 November 2020 | Q&A

What is herd immunity?

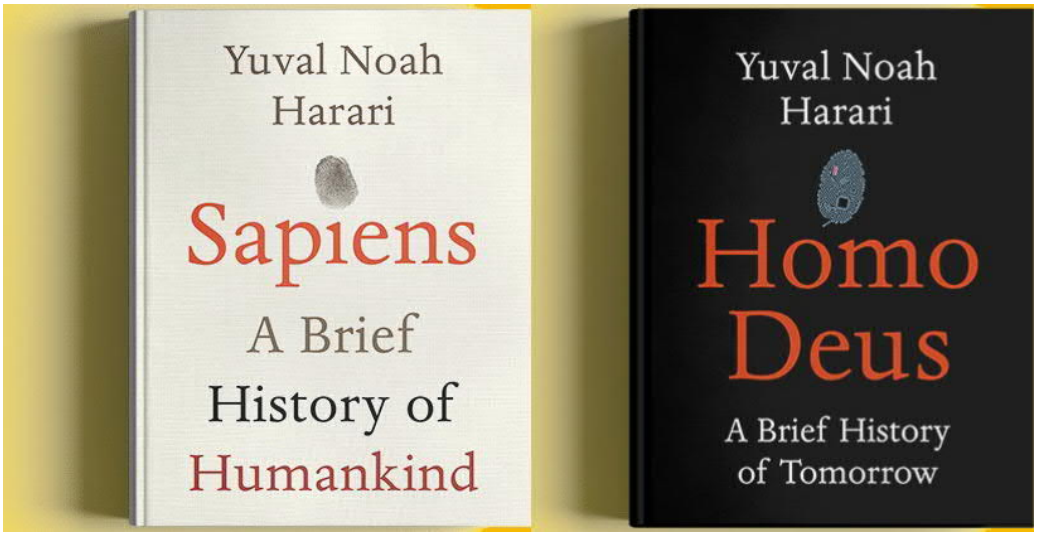
'Herd immunity', also known as 'population immunity', is a concept used for vaccination, in which a population can be protected from a certain virus if a threshold of vaccination is reached.

Herd immunity is achieved by protecting people from a virus, not by exposing them to it. *Read the Director-General's 12 October media briefing speech for more detail.*

TRANSHUMANISM

Episode 3 'Why do we believe lies?' + Exclusive Excerpt from 'Sapiens: A Graphic History'

Posted On November 30, 2020



SAPIENS

You are human but you are not the only species of human. You are Homo Sapiens ("Wise Humans" as we immodestly label ourselves) and just one of a number of different species of human that have roamed the planet together.

It is likely that your Sapiens ancestors killed off the Neanderthal species of humans about 40,000 years ago, and did so because "they were too familiar to ignore, but too different to tolerate" (they also had bigger brains than your ancestors – but perhaps your ancestors had bigger sticks).

Today, Sapiens is the only remaining species of human. However, if you are European or Middle Eastern, then your status as Homo Sapiens is more complicated. You are not pure Homo Sapiens, but probably the result of interspecies breeding between Sapiens and Neanderthal (up to 4% of your genes are probably Neanderthal). So forget mixed race, intersex or other non-binary identities, you are Interspecies. And you are also Trans, but you'll have to read through to insight #10 to find out why.

1. MYTH-MAKERS. The big idea in Sapiens is the thing that sets Sapiens apart from other species. And that difference is that Sapiens are myth-makers; they use imagination and language to create and communicate new worlds, alternatives and possibilities. The importance of shared myths is that they allow Sapiens to cooperate, organise at scale, and dominate the world. Without myths, there is no glue to bind Sapiens together. At an individual level, humans might be memory-makers, but as a species-level they are myth-makers. The genetic mutation that allowed the cognitive powers of speech and Harari calls the Cognitive Revolution.

2. INTERSUBJECTIVITY RULES. The source of human insight is not objective fact nor subjective impression, it lies in 'intersubjective' myths – our shared subjectivity. Powerful intersubjective myths include laws, gods, money, morals, patriarchy and nations that exist neither in the natural world, nor only in unshared imaginations, but in shared intersubjectivity. Understanding humans is not about understanding their differences, it's about understanding.

3. BRANDS ARE POWERFUL INTERSUBJECTIVE MYTHS. Peugeot (Harari's example) is an example of an intersubjective. It doesn't exist in the natural world (you could kill all Peugeot people, buildings and products, and Peugeot would still exist). Instead, Peugeot exists as a shared myth or 'fiction' in our intersubjective imagination that is powerful because it has the power move humans to produce and consume at scale.

4. FICTIONS, NOT FACTS EXPLAIN. The myths Sapiens share define who they are and what they do. Take money, a most powerful shared fiction. Dollar bills are meaningless tokens without the 'shared fiction' that they have value. Endowed with shared meaning, money becomes a unit of exchange, peace of mind, and the measure of our choices. And importantly, it explains behaviour. (For Harari money is also "the apogee of human tolerance" because it is more open-minded than any other shared fiction (language, laws, cultural codes, or religious beliefs) because it does not discriminate on the grounds of ethnicity, religion, age, or sexual orientation.)

5. CHANGE THE MYTH, CHANGE THE WORLD. The intersubjectivemyths that both bind Sapiens together and break them apart is the glue that holds culture together. Break the myth and you break the world, leading to dramatic and rapid social change. Break the myth of monarchy, slavery, patriarchy and you change the pattern of history.

6. BIOLOGY ENABLES, CULTURE FORBIDS. Just as there is nothing so natural as chemicals (they exist in the natural world), anything Sapiens can do is, by definition, natural. Biology opens doors, and it is culture that closes them by proscribing certain behaviours, and labelling them as unnatural. The study of human culture is largely the study of what we prohibit,

7. THE LAW OF THE FEW. History is made by the few, whilst the masses toil at work. For example, the second major revolution in Sapiens' history – the Agricultural Revolution (around 12,000 years ago) – enabled increased food production and massive population growth, but it forced that average farmer into monotonous hard labour. The fruits of the Agricultural Revolution were enjoyed by a few pampered elites, but who were freed up to make history. For Harari, the Agricultural Revolution was history's biggest fraud.

8. THE HOW OF HAPPINESS. Human "happiness does not really depend on objective conditions of wealth, health or even community. Rather, it depends on the correlation between objective conditions and subjective expectations." This means yesterday's luxuries are today's necessities. And by raising expectations further, mass media and advertising may be depleting the human potential for contentment. However, happiness may be a false god ('fiction') inappropriately elevated from its natural status as a fleeting neurochemical response designed to reward adaptive behaviour. For Sapiens, happiness may not be the absence of misery, but the cause of misery driven by the tension, restlessness and dissatisfaction that comes from the pointless, perpetual pursuit of an ephemeral neurochemical response.

9. HUMANS ARE SUPERHUMAN. The third, and possibly final Revolution in human history is underway now and is the Scientific Revolution that began 500 years ago. Though scientific discovery and technological innovation, the Scientific Revolution has empowered Sapiens to transform their environment and themselves, giving them superhuman powers and practically limitless energy. The Scientific Revolution has seen mythical stories replaced by falsifiable theories, certainties replaced by uncertainty, conservatism replaced by curiosity, and perhaps most importantly, words replaced by numbers. But are we any happier?

10. THE FUTURE IS TRANS. The story of Sapiens is coming to an end (in the next century or so), as the species has outgrown its hominid self. Through science and technology they have the power and intelligence to become gods and create new artificial life and recreate themselves. Sapiens are the new gods of 'Intelligent Design' – they are Homo Deus. Their future is not human, it is transhuman as they transition into something new. If they do not destroy themselves first. The problem with Sapiens is that despite their power, they do not know what they want. They do not even know what they want to want. Is there anything more dangerous than dissatisfied and irresponsible gods who don't know what they want?

CONCLUSIONS

Sapiens is perhaps not as impressive as the book that inspired it, Jared Diamond's epic and influential *Guns, Germs and Steel,* but it is more accessible and it perhaps more immediately useful for anyone researching or innovating for humans. The big takeout for us at Brand Genetics is that human-centric insight and innovation is about understanding humans as myth-makers as well as memory-makers. Without these twin insights, very little that humans do, makes any sense at all.

As qualitative researchers, we love the idea of researching 'intersubjectives', the shared myths people use to make sense of the world and guide their action. Similarly, Harari's insight that to understand people, you have to understand not what they want or what they do, but what they are *not allowed to want or do*, opens up interesting avenues of research. Thinking of brands as shared myths is also a useful starting point for investigation. And the idea that people will be happy with innovation only when it beats their expectations is, whilst not new, a powerful reminder of the central role of expectations in insight and innovation.

The narrative of Sapiens is painted with broad brushstrokes with a speculative interpretation that can be and has been, criticised. For the science-minded, Sapiens may seem too interpretivist, whilst for historians, Sapiens may appear too scientised. But for those like us at *Brand Genetics*, working in human-centric insight and innovation, Sapiens provides a wonderful framework and lens for guiding and interpreting what we do.