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COVID-19

CONTENT

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COVID-19: CONTRADICTIONS, CONFUSION, AND COMPLEXITY

It is mid-July 2020. Some countries are experiencing the peak of the Covid-19 pandemic, while others have loosened their lockdown measures, anticipating a continued slowdown of the epidemic. Meanwhile scientists around the world are working on the development of an effective vaccine.

CONTRADICTIONS

In Japan, the management of a sea aquarium invites visitors to video chat with their 300 sea eels and wave at them as they showed signs of stress because of the absence of the public in the past months. Hundreds of thousands of mainly female garment workers in Bangladesh ignore the nationwide lockdown in order to earn back some of the income loss they experienced over the past months. More than 49 million women are lacking contraceptives, a situation which according to the WHO is likely to result in a baby boom. Donald Trump asks scientists to research the effect of injecting disinfects into a person in order to fight the virus. While the Italian government still provided food rations for the needy, shrewd businessmen developed protective plastic shields for the sunbeds – in anticipation of the tourists that would come as soon as lockdown restrictions in Italy were to be released. State prisons in California are releasing 3,500 inmates to protect them from potential exposure to the virus as a result of the conditions in the prisons. Research from Stanford University shows that, in a country were some 1.6 million people die each year of respiratory diseases, the improved air quality has saved the lives of more than 1,400 children under age 5, and 51,700 adults above 70 years of age. Meanwhile the virus has spread to 188 countries, with more than 13,876,441

confirmed cases of Covid-19 (7.3 million in the Americas), including 593,087 deaths reported to the WHO.[1,2]

CONFUSION

In the absence of a vaccine we have witnessed a wave of containment measures, roughly ranging from total lockdown to the so-called intelligent lockdown (relying on the idea of group or herd immunity and a sense of responsibility on the part of the population) introduced in the Netherlands. The Dutch were accused of lacking solidarity with neighbouring countries' approaches - an interesting observation, given the overall lack of solidarity and coordination at European (and global) levels.[3] With this approach, the Dutch government wanted to 'cushion the social, economic and psychological costs of social isolation and make the eventual return to normality more manageable'.[4] And while social distancing in high-income countries may have saved lives, the question is at what cost? Low-income countries are anticipating counterproductive effects, including a potential rise in other (infectious) diseases and rising morbidity and mortality figures caused by other diseases, as well as a devastating effect on fragile economies and informal sector workers. Adding to the confusion are the many variations in tracking and reporting approaches and misleading or missing data. Reflecting on the past months challenges us to decide on a "new" normal. Can we push a "reset" button, thereby building on some of the (positive) lessons – for example working from home and reducing our ecological footprint by (r)evolutionizing international conferences.[5]

COMPLEXITY

Currently it still feels like a global Catch-22. Without a concrete prospect of a vaccine or treatment, the virus will hold the world in its grip for months and possibly years to come. While some countries seem to have succeeded in containing Covid-19 (China, Taiwan, Vietnam), others are experiencing a peak in infections (countries in Latin America and South Asia). Meanwhile, in some part of the USA the situation is spinning out of control, and African countries are experiencing an early state of the epidemic. Europe seems to be somewhere in between.[6] It feels like we are at a crossroads, and much will depend on the choices that we the public, our governments, and world leaders are making - choices that will have an impact on societies at large, impacting on all aspects of life. The Covid-19 crisis is testing our capacity to deal with the societal consequences of pandemics and to balance economic interests without losing sight of the (health) risks involved.

With this edition of MT*b*, we intend to challenge these three Cs in a constructive manner with articles shedding light on the clinical management of the disease, Covid-19 against a historical perspective of epidemics, field experiences in LMICs, the effect of the pandemic on the refugee crisis in Greece, the role of the WHO, and efforts to counteract vaccine nationalisms. We look forward to your reflections and invite you to react using one of our (social) media channels.

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REVIEW

Management of Covid-19

The Covid-19 (corona virus disease, detected in 2019) pandemic is keeping a firm grip on the world and affects the health of those ill with Covid-19 as well as those with other illnesses; it overburdens health services and causes delays in diagnosis and treatment of other conditions. While there is universal fear of infection, this is especially evident among service providers and people accessing health facilities. Population-based screening programmes to detect breast, cervix and colon cancer have been suspended; the waiting lists for elective surgical procedures are becoming longer. In addition to the impact on health, severe damage to the economy is caused by lockdown measures affecting small and big businesses. Especially in low- and middle-income countries, lockdown and social distancing affect the informal sector and thereby people's livelihoods, resulting in food shortages and malnutrition. Control efforts for various tropical diseases and vaccination programmes have been suspended. The overall morbidity and mortality caused by the pandemic is therefore not restricted to Covid-19. There is no specific treatment for Covid-19 infection, and the pandemic has sparked a flurry of research projects that focus on inhibiting the replication of the virus, on its effects on the human respiratory system and other organs, and on the immune response triggered by Covid-19.

In this paper, current insight into the management of Covid-19 infection as well as the main features of ongoing drug studies are discussed. Lastly, issues in publication including peer review are discussed.

CLINICAL SYNDROME

Covid-19 infection is caused by the SARS-CoV-2 virus; the name refers to the severe acute respiratory syndrome caused by a similar corona virus, SARS-CoV-1. The virus enters the body through person-to-person airborne transmission. There is no proven animal reservoir; in the Netherlands, the infection was detected in mink farms but was thought to originate from humans. The virus is spread in crowded conditions and mass gatherings: the celebration of carnival (province of North Brabant, the Netherlands), winter ski holidays (North Italy, Austria) and (international) football matches like the Champions League match between Atalanta Bergamo vs Valencia on February 19 with 40,000 Italian and Spanish supporters (with subsequent outbreaks in Italy and Spain) are thought to have contributed to major outbreaks in Europe.

The clinical picture is dominated by respiratory symptoms, with fever, shortness of breath, and cough. Fatigue is common and other non-respiratory symptoms include confusion and diarrhoea. Most infections are only mildly symptomatic and self-cure within days or weeks. Other patients require hospitalization and develop pneumonia with so-called ground glass opacities on a CT scan; oxygen administration is needed and other supportive care, including admission to intensive care units with intubation and artificial ventilation, often because of the adult respiratory disease syndrome (ARDS). Severe pneumonia and death occur in 4-5% of admitted patients in a setting with optimal care (*Lancet, Covid-19 clinical research coalition, 25 April 2020*). While in hospital, sudden deterioration may occur caused by thromboembolism in the major lung vessels and the brain, with poor outcome. Viral sepsis has been suggested among explanations causing damage to blood vessels; other organs may be affected as the virus spreads to other parts of the body. An overreaction of the immune system may occur with cytokine release storm (CSR) which may also contribute to organ damage. All this may contribute to development of acute renal failure, viral myocarditis, multi-organ failure and death.

RISK FACTORS AND DIAGNOSIS

Risk factors for a severe course of the disease are co-morbidities such as chronic heart disease, diabetes mellitus, underlying respiratory conditions such as COPD and asthma, malignancy and obesity. In addition, the risk for severe disease increases with advanced age >60 years. In contrast, young children are usually asymptomatic. The diagnosis is made by demonstrating the virus via PCR in a nasal and/or throat swab. Serological tests for IgM and IgG antibodies are currently continually being improved in terms of sensitivity and specificity; these tests only indicate past exposure and are not suitable yet for confirmation of the diagnosis in someone who is symptomatic. Currently, in populations in Europe not more than 5% of people tested have antibodies showing previous infection (asymptomatic or symptomatic); it is not clear whether these antibodies are fully protective and for how long.

INTERVENTIONS

Currently there is no treatment with proven efficacy. A multitude of observational and randomised controlled trials (RCTs) are ongoing, that initially mainly focused on drugs that had been studied for SARS, MERS (Middle East respiratory syndrome) or Ebola disease, but that unfortunately were not developed further when these outbreaks lost their epidemiological importance. Some drugs are still experimental and have not been used or studied in humans, and therefore existing drugs (for whatever indication) that can be re-purposed for Covid-19, are clearly preferred. While most studies focus on mitigation of Covid-19 disease, other efforts focus on prophylaxis. The early drugs that are considered for potential benefit in Covid-19 are included in the Solidarity trial of the World Health Organization (WHO) in patients hospitalized for confirmed Covid-19. It has four arms:

- HIV protease inhibitors: lopinavir/ritonavir
- antimalarials: hydroxychloroquine and chloroquine

PHOTO: MOHSEN NABIL / SHUTTERSTOCK.COM

- antiviral (RNA polymerase inhibitor): remdesivir
- immunomodulatory agent: lopinavir/ritonavir with interferon 1a

Other early major studies include the RECOVERY trial (randomised evaluation of Covid-19 therapy) in the United Kingdom in hospitalised patients, primarily studying the effect of hydroxychloroquine, lopinavir/ritonavir, azithromycin, dexamethasone vs no additional treatment. Patients are further randomized to receive tocilizumab (an interleukin-6 blocker) and convalescent plasma.

ANTIMALARIAL DRUGS

Recently published preliminary data on antimalarials are not encouraging. Hydroxy-chloroquine and chloroquine were among the first candidate drugs suggested. The effect of these antimalarials is thought to be a pH-mediated at the level of virus entry in the cell as well as disruption of viral replication.[1] A combination therapy with azithromycin was suggested to have a beneficial effect.[2] This publication was recently criticised and could not stand up to scrutiny. There is increasing evidence that these drugs are of no clinical benefit and severe cardiotoxicity has been reported, which seems aggravated by co-administration of azithromycin.[3] Prophylactic use of hydroxychloroquine after high-risk or moderate risk post exposure to Covid-19 did not prevent illness in a recent study.[4]

ANTIVIRAL DRUGS

Remdesivir is an antiviral drug (RNA polymerase inhibitor) that inhibits SARS-CoV-2 (that causes Covid-19), as well as SARS-CoV-1 (that causes SARS) and MERS-CoV (that causes MERS) in animal models. In a recently published RCT, there was no clinical benefit although early treatment might shorten time to clinical improvement.[5] There is no evidence yet that remdesivir is beneficial in severe Covid-19 infection in a patient on the intensive care. The drug was recently registered by the European Medicines Agency (EMA).

Lopinavir/ritonavir, an antiretroviral drug used in HIV/AIDS has so far failed to show a clinical benefit in early reports. In hospitalized adults with severe Covid-19 infection, no clinical benefit was found.[6] Combination treatment with interferon and ribavirin showed better alleviation of clinical symptoms as well as shortening of duration to negative nasal swab and hospital stay in mild to moderate Covid-19.[7] RCTs on other antiviral drugs against SARS-CoV-2, including favipiravir are ongoing as there are mixed reports about their *in vitro* and *in vivo* efficacy.[8]

IMMUNE MODULATION

This is also a subject of study; the evidence on the use of corticosteroids is controversial. While the immunosuppressive effect may be beneficial, there is concern of prolonged viral shedding and secondary infections.[9,10] The timing of such intervention in the course of the disease may be crucial.

The excessive immune response in the cytokine release is characterized by high levels of cytokines such as interleukin (IL)-6. Tocilizumab is an IL-6 blocker that is used for example in rheumatoid arthritis; a small study in 22 patients recently published showed remarkable clinical improvement in Covid-19, and RCTs are eagerly being awaited.[11] Similarly, the effect of inhibition of IL-1 is being studied.

Other immune therapies include the use of immunoglobulins and re-convalescent plasma of patients who have recovered from Covid-19.

ALTERNATIVE DRUGS

Ivermectin and nitazoxanide have shown anti-SARS-CoV-2 activity *in vitro* and are licensed for other conditions, and thus they can be studied directly in Covid-19.

Latest reports: in a webinar on 30 June 2020, the RECOVERY trial showed unpublished data indicating that in admitted patients who are on oxygen or ventilation, mortality was reduced by 1/5 and 1/3, respectively, after administration of low dose (6 mg) dexamethasone for 10 days. In similar patients, hydroxychloroquine or lopinavir/ritonavir did not show an effect on mortality. It should be noted that the latter two drugs were studied for their antiviral effect, whereas dexamethasone in general influences inflammatory damage to the lungs and is already used in severe ARDS caused by other conditions.

CONTROVERSY

The SARS-CoV-2 virus uses receptors to bind to a respiratory cell before being able to enter the cell and replicate. The angiotensin-converting enzyme (ACE) 2 receptor is among these. Patients with high blood pressure have higher levels of these receptors and treatment for hypertension with an ACE inhibitor or angiotensin receptor blocker (ARB) such as losartan may increase expression of the receptor. It has therefore been speculated that these patients are at increased risk of severe Covid-19. However, there is also the possibility that losartan treatment may be beneficial by blocking the binding of the virus. Currently, there is no conclusive evidence and patients on losartan treatment are advised not to discontinue their treatment.

PUBLICATION STRESS

Every week a plethora of reports are published in scientific journals including the authoritative *The Lancet* and the *New England Journal of Medicine (NEJM)*. While publication, often after expedited peer-review, of any useful result in Covid-19 is clearly important, mistakes have been made. Both *The Lancet* and *NEJM* have retracted papers that were criticized for methodological flaws or poor quality of data after publication.[12-16] The above mentioned work on hydroxychloroquine by the French virologist Didier Raoult, who is held in high esteem in France, particularly in his hometown Marseille, was criticised as many of his publications appeared in journals in which he or his co-workers were among the members of the editorial board. (*The Economist*, June 13th, 2020; *NRC Handelsblad*, June 13th, 2020).

CONCLUSION

Covid-19 causes severe and fatal disease, be it in a minority of cases. Currently there is no drug treatment that has been proved effective and safe, in prophylaxis or in mitigation of clinical disease. Management is therefore largely supportive with intervention by administration of potentially effective drugs based on clinical experience and evolving evidence in the scientific literature.

Note of the author: every week new studies are published that change insight on the management of Covid-19; this paper summarized information available up to 30 June 2020.

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A novel virus, a recurring threat: looking at past pandemic threats to understand how SARS-CoV-2 has evaded global control efforts

Shortly after the New Year, the reporting of emerging clusters of pneumonia from an unknown pathogen in Wuhan, China, began to draw the attention of infectious disease experts and public health officials globally. In spite of Chinese control efforts, including what up until that point was the largest population lockdown in human history, it did not take long for the localized viral infection to disperse itself ubiquitously throughout much of the world. As of the end of June, SARS-CoV-2, the once novel coronavirus, has claimed nearly half a million lives and affected roughly 213 countries and territories. SARS-CoV-2 is categorized as an emerging infectious disease, defined by the World Health Organization (WHO) as any disease that has 'appeared in a population for the first time, or that may have existed previously but is rapidly increasing in incidence or geographic range.'[1] Emerging infectious diseases are primarily zoonotic, meaning they are transmitted to humans from animal hosts, and have been the culprits of most pandemic threats in the past decades, like SARS-CoV (SARS), Ebola, Swine influenza and Zika. With emerging infectious diseases now making an appearance on the global stage every few years, it is vital to look at the specific characteristics of SARS-CoV-2 and the coronavirus disease (Covid-19) that have allowed the virus to evade global control efforts and pose such a grave threat to society. Comparing SARS-CoV-2 to disease agents that have caused former pandemics and global health crises helps to contextualize the threat of the current viral outbreak, and also illuminates how response efforts have been shaped in the wake of international disease threats.

TRANSMISSIBILITY

It was late in the year when health care practitioners in Southern China first encountered cases of a mysterious viral illness that manifested as severe pneumonia leading to acute respiratory distress. With variant strains of avian flu starting to become a seasonal norm, Chinese public health officials did not at first sound any global alarm bells. After spreading to Beijing and then Hong Kong, it boarded planes bound for other continents and began to make its way across land. Almost simultaneously, three separate labs in Hong Kong, Germany, and the United States of America, finally identified the pathogen causing this fatal pneumonia as a novel coronavirus. The Global Outbreak Alert and Response Network was activated, and the WHO provided a rapid and measured response helping to advise every affected nation. By July, the virus was controlled. But this was 2003, and the novel coronavirus was SARS.

The international community learned numerous lessons from SARS, namely about the importance of having strong disease surveillance and centralized health systems. The outbreak led to many countries boosting their infectious disease control capacities, which included the creation of the Center for Infectious Disease Control here in the Netherlands, the resources of which have been integral to helping the control efforts for combatting the current outbreak nationally. Global detection systems, however, had evidently not prepared enough for handling the very different transmission dynamics of the SARS coronavirus successor, SARS-CoV-2.

The basic reproductive number, or R0, refers to the average number of cases generated by an infectious person, and is considered an important indicator of transmissibility. Although the R0 of SARS-CoV-2 is estimated to be only slightly higher than that of SARS (3-5.3 and 2-5, respectively), SARS-CoV-2, possesses numerous qualities that make it not only more transmissible, but more able to evade the surveillance measures that had been able to stop SARS.[2] The period of infectiousness in SARS-CoV-2, for example, not only begins before the onset of symptoms, but in many cases peaks days before most people even know they are sick.[3] This makes mitigating the spread of the virus much more challenging than SARS, which during its 2003 outbreak was transmitted primarily when patients were severely ill and clearly symptomatic. Furthermore, there were only a few known documented asymptomatic SARS cases, which differs vastly from SARS-CoV-2, where asymptomatic cases are suspected to climb into the millions globally. Epidemiologist are still seeking to understand the capacity for asymptomatic cases to spread the virus, but like all unknown elements, it presents further challenges in creating control strategies and finding methods to establish normalcy in a world with Covid-19. Additionally, other elements such as longer relative incubation periods for SARS-CoV-2 (most likely 3-10 days, but potentially as long as 14) may have facilitated its spread during the initial outbreak, allowing people to carry the virus far from disease epicenters under the assumption that they had not contracted the virus since they were not yet sick.[2]

PATHOGENICITY

Ten years after the last cases of SARS were treated, a much more virulent threat began lurking in the jungle of Southern Guinea. By the summer of 2014, the Ebola virus disease (EVD), never before seen in Western Africa or able to reach an urban area, had infiltrated the capital cities of Guinea, Sierra Leone and Liberia. For two chaos driven years, the worst Ebola outbreak in

history rocked Western Africa, sending ripples of fear that the epidemic would spread globally.[4] EVD is infamous for its devastating hemorrhagic symptoms and high pathogenicity, with case fatality rates (CFRs) from previous outbreaks being as high as 90%. The CFR for the 2014-2016 West Africa Ebola outbreak was 40%, making early estimates of SARS-CoV-2 appear relatively low at 2.3%.[2] With SARS-CoV-2, however, the virus's capacity to transmit so efficiently, ability to evade control, and prevalence worldwide in addition to its pathogenicity is what makes it so lethal. To understand the true pathogenicity of SARS-CoV-2, one can compare its CFR to another virus that transmits globally, the seasonal influenza. Seasonal influenza, with a CFR of under 0.1%, is over twenty times less likely to cause death than SARS-CoV-2,[5] which would seemingly discredit the minority of people who have claimed that Covid-19 is just 'another flu'.

The Ebola outbreak being primarily contained to three countries in West Africa does not mean that it was not a global threat. Partly due to very late intervention from the WHO – for which they have been vehemently criticized – the virus became unmanageable in West Africa and made appearances in seven other countries.[4] Following the outbreak, the global health community demanded that the WHO improve responsiveness to emerging infectious diseases.[6] In 2019, perhaps with the understanding that the next emerging infectious disease outbreak was merely a matter of time, the WHO did make major adjustments to help them focus on preparedness and improve emergency response - a component that would become useful just months after its implementation.[7]

EPIDEMIOLOGY

As Ebola terrorized West Africa, a mosquito-borne pathogen called Zika virus was making its way through much of Brazil and spreading throughout South and Central America. While Zika virus-associated birth defects rose at incredible rates, the disease strangely began to recede within a couple of years of its initial emergence. Epidemiologists suspect that Zika virus had hit its herd immunity threshold (HIT).[8] Herd immunity occurs when a certain percentage of the population becomes immune to a disease, either through contracting the illness or from getting vaccinated. The herd immunity required to reduce transmission to below epidemic levels varies for every disease, but is in theory easier to achieve in diseases like Zika that are limited to specific geographic boundaries or demographic factors, in this case to areas in which the Zika transmitting mosquito was endemic.

SARS-CoV-2, conversely, is ubiquitous and not limited by any geographic area, gender, race, or for the most part, age, although it has shown significantly higher associations of severe disease and mortality with older age groups. The herd immunity needed for reduced transmission of SARS-CoV-2 to below epidemic levels is estimated to be somewhere between 50% and 75% of the population.[9] These estimates take many characteristics of the pathogen into account. There are very few, if any, health care systems in the world capable of handling the volume of Covid-19 patients if a country were to attempt to reach herd immunity as a control measure. Even if that weren't the case, some would suggest that allowing for 75% of the population to get infected with a disease that has such a high case fatality rate (CFR) would result in an unconscionable amount of deaths. Perhaps most significantly, herd immunity is dependent on the population becoming immune. As we still have no conclusive evidence that Covid-19 infection grants lifelong or even long-term immunity, reaching herd immunity and ultimately controlling SARS-CoV-2 will most likely be contingent on the development of a vaccine.

CONCLUSION

The characteristics that make SARS-CoV-2 so transmissible, pathogenic, and widespread have presented extreme challenges to disease control specialists, as well as to a considerable percent of the global population in some form or another. During the 1918 Spanish influenza pandemic that killed between 20 and 40 million people, governing bodies issued public health warnings centered around three components: try to stay inside, socially distance yourself from others whenever possible, and if you must leave your house wear a mask. If it is disheartening to see how little has changed in our individual capacity to control the spread of a pandemic virus, perhaps there is solace in the understanding that remarkable advances have been made in surveillance, diagnostics, and vaccine production, largely informed by previous epidemics of emerging infectious diseases. Learning from the disease specific elements that made SARS-CoV-2 so uncontainable will help shape current control efforts and inform future outbreaks. Every large-scale epidemic should come with numerous lessons not only for containment, but for preparedness, as the arrival of a new pandemic threat is merely just a matter of time.

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Covid-19 in context

The end of my work in a hospital in rural Congo-Brazzaville coincided with the worldwide Covid-19 outbreak. It was painful to leave, knowing that the pandemic would also hit Congo-Brazzaville in the very near future. Luckily, my fellow doctors and I had recently prepared for a possible spread of Ebola virus disease, and we had stockpiled a big container with personal protective equipment just before global demands skyrocketed. When I left, the hospital staff was worried that I would contract Covid-19 in Europe, as the number of new cases was rising quickly. It felt like the world upside down, and leaving amidst all this was difficult as it gave me a sense of letting them down. Many of my fellow global health doctors had to adapt to the pandemic. Everybody was eager to connect professionally, share resources, ask questions and discuss evidence, but there are personal stories as well. Here, we share four experiences of global health doctors around the world during the Covid-19 outbreak in the spring of 2020.

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How Ebola prepared us to fight Covid-19 in the DRC

It was in October 2019 that I received my first patient infected with Ebola. There is a first time for everything, but some things can better be avoided. Within a few days, I found myself alone in our house: my wife and our three children were temporarily elsewhere, as violence against Ebola response teams put the whole village in turmoil. Our 55-bed mission hospital in the Northeast of the DRC became almost empty with no outpatients anymore. Now, eight months later, we have no more Ebola in our area and I gladly use the experience that I acquired and apply it to the Covid-19 outbreak that is threatening us now.

In reality, every epidemic has its own characteristics, and I have learned to see differences and similarities. The mortality of Covid-19 in the DRC (2.2%) is much lower than for Ebola virus disease (EVD) during the epidemic in the area served by our hospital (66%).[1] Contact tracing and isolation of suspect cases, however, seems much easier for EVD than for Covid-19, since EVD hardly occurs without any symptoms. Vaccines are crucial in fighting against an outbreak, and the EVD vaccine possibly saved my life. Some epidemics gain more attention than others. For instance, few people know that the DRC had almost 370,000 measles cases and 6,779 deaths by measles in just the year 2019.[1] However, when I asked the Ebola surveillance team that was visiting our hospital on a daily basis in their 4x4s whether they had seen the measles-epidemic-Landcruisers, they grinned sheepishly.

There are also many similarities. In an outbreak it is crucial to inform all relevant parties and get them on board. If you forget to respect a village chief in the Congolese culture you will struggle to get anything done. Community resistance had massively hindered a thorough uptake of EVD cases, contact tracing and clinical management in our area.[2] So, when we saw the first few cases of Covid-19 in our region, we compiled small information sheets in French and Congolese Swahili about symptoms, prevention and the most important dos and don'ts. When bringing this to chiefs, government officials, church leaders and anyone interested, I found myself directly amidst good conversations, clarifying many things about Covid-19. Outbreaks often negatively impact continuity of care for other conditions, such as malaria and obstetric complications in affected areas, because of closure of health facilities, lack of staff or fear among patients to contract the disease in the facilities.[3] That is what we saw with the Ebola cases in our hospital, and that is what I also feared when Covid-19 would hit us. But luckily, with all Covid-19 measures in place now (borders, schools and churches closed, and meetings >20 people forbidden), hospital visits did not decline and villagers accepted the combined Ebola/Covid-19 triage at the gate knowing that it would help everyone.

I have yet to see the first Covid-19 case in our hospital. We feel at least a bit prepared with a triage and a small isolation unit, but we know that there are many things we cannot control. The Ebola epidemic brought us teams of experts in 4x4s and NGOs with water, sanitation and hygiene (WASH)-projects. Covid-19 brought us a provincial response protocol and many restrictions, but the government's main focus has been on the highly urbanized area of Kinshasa, the country's capital thousands of kilometres away, where cases augment rapidly. Our provincial health authorities designated hospitals without even an oxygen concentrator

as Covid-19 treatment centres. Not a single hospital in our area can provide advanced respiratory support. We feel blessed with two oxygen concentrators powered by our hospital generator, but we are certainly highly underequipped compared to high- or middle-income settings. Unfortunately, most WHO and NGO experts have left the region.

Our area continues to be plagued by insecurity, and outbreaks add to these difficulties. I am learning resilience from my colleagues, some of whom have fled war zones or have been kidnapped or lost relatives and have learned to rebuild their lives after the loss of all their possessions. Our hope and our prayer is that this Covid-19 epidemic will make us stronger, as the Ebola epidemic did.

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EBOLA IS MORE OF AN OPEN WOUND THAN A SCAR

Corona free country?

'My little son has a fever and we will be travelling tomorrow, what shall we do?' January, 2020, a colleague was returning from abroad to Papua, Indonesia. Something was going on in China, and airport authorities in Thailand started doing prior temperature checks on travellers as part of boarding procedures. Wasn't this just a kind of flu, not too severe? 'Don't worry, just give him some paracetamol so that you can pass that temperature check. They are just a little nervous there.'

A month later this "mild flu" apparently was something more serious. More and more deaths were reported and suddenly two brand new hospitals were built in China. Indonesia has quite strong ties with China, including daily flights to Wuhan, so I expected to hear very soon about cases of this new illness. All countries in Southeast Asia reported rapidly rising numbers, but not Indonesia. Instead, the government invested millions of dollars to advertise Indonesia as a corona-free country: 'Come for holidays to Bali!'

Late February, one of my patients was evacuated from Papua to Jakarta for surgery. He was admitted to one of the best hospitals in Indonesia, which was apparently filled with dengue patients. He got a mattress on the floor. The strange thing was that these patients were coughing persistently; some looked really sick and disappeared secretly during the night. He got his surgery and finally a normal bed on a surgical ward. After a few days, he developed fever and started having a sore throat and a dry cough. What to do? I advised him to ask for a Covid test. His doctor was startled: 'We don't have that illness in Indonesia, and you didn't come from abroad. Furthermore, your blood tests and X-ray were totally fine on admission. No need to test. Your wound might be infected, so I will start antibiotics.' The only thing I could do was to strongly advise self-quarantine after he got back in our little Papuan town. The wounds looked perfectly clean and healing, but the fever persisted for a week. Early March, the first Covid-19 cases were reported. But that was in Jakarta, not on our island, far away to the east of Java. Strangely enough, our expat medical team got more and more questions about people who were coughing with fever and shortness of breath. Really healthy people suddenly got sick - sicker than they ever had been before. An interior village reported that all of the villagers became ill after they had received visitors from Jakarta, and two people died. In the meantime, messages from all over the world came in, from Italy, Iran, and the Netherlands. There were not so many cases in the United States of America (USA) yet. It was interesting to see how we as expats reacted differently to this illness in Papua. I heard messages about the rapid spreading of Covid-19 in the Netherlands and elsewhere in Europe and was advising people who had travelled, especially expats, to go into quarantine so they would not spread the virus to vulnerable people. American doctors and nurses were more laid-back. In the USA it was not a big deal, so why would it be a problem in Indonesia? But it did become a big deal. New cases and deaths rose steeply. Jakarta and other parts of Indonesia went into local self-imposed lockdowns, also in Papua. As a family we had to travel to renew our visa; these plans, however, got thwarted as other countries closed their borders. After a quick Jakarta-Kuala Lumpur-Jakarta trip, we got stuck in Jakarta without a work permit and our kids had fever and a cough. After six years in Indonesia we were suddenly forced to go back to the Netherlands. What we can still do is give advice and moral support to friends and colleagues in interior Papua, and send them patterns for batik-masks, templates to 3D print face shields, and money to make that possible.

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The heritage of a highly lethal virus outbreak

I sneezed. Wrong timing. My caretaker flinched. 'I always get a cold from the air-conditioning on the plane', I quickly mumbled. I had just arrived in Sierra Leone amidst the exponential rise

of the pandemic, and any sneezing white person was treated as a potential biohazard. This country knows how to deal with outbreaks. From the very start, Covid-19 was approached the same way as Ebola. While wreaking havoc in Europe and the USA, Covid-19 numbers were still low in Africa. However, Sierra Leone had already closed its airspace and borders for non-essential supplies. A state of emergency was declared, schools were closed and a lockdown put in place until further notice. All this, without a single confirmed case in the country. These decisions do not come without consequences. The country is largely dependent on imports of vital commodities: food, non-consumables and - not least for the hospital

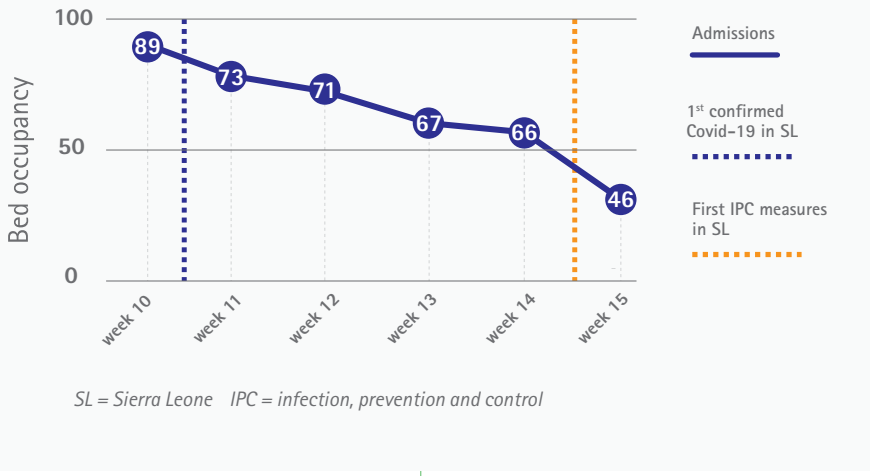

Figure 1. Bed occupancy Masanga Hospital during the Covid-19 pandemic.

- pharmaceuticals. Food prices increased and medicine stocks slowly ran low as most exporting countries kept supplies to themselves. Suddenly some patients had to pay for their medication. Normally in Sierra Leone, health care for children under five years of age and for pregnant women is provided free of charge, but if drug stock runs dry, eventually, patients will have to pay.

Halfway through March, at the general hospital meeting with all employees present, the fear was tangible. Ebola is more of an open wound than a scar. Everyone knows someone, or knows someone who knows someone who died of Ebola. It is hard to explain to people, even the skilled health care workers, that this virus is less fearsome than its highly lethal haemorrhagic counterpart from only five years ago. Not surprisingly, the utter paralysis of the developed world and its crashing economies do not temper the fear. Not only were the personnel scared. A steep decline in hospital admissions followed after downscaling the hospital to just emergency operations [Figure 1]. When I asked my landlord what people's reasoning could be to stay away from the hospital, she told me that they feared to contract corona at the hospital, but more importantly, they feared to be isolated. Logically, suspected corona cases are kept in isolation until the test results become known. The same happened during the Ebola outbreak. Isolation alone had repercussions, regardless of the test

result. Negatively tested Ebola suspects as well as survivors were stigmatised and sometimes excommunicated. Not a surprise then that Sierra Leoneans feared a repetition of this with corona.

Until now, two-and-a-half months after the first case got detected, Sierra Leone has not follow the exponential path that many other countries have, at least if we go by the official numbers. Although the risk factors are limited with fewer old people (life expectancy is 54 years), less obesity, and less smoking, we didn't know how HIV and tuberculosis patients and malnourished patients would be hit. Recently, we had our first case in the hospital. Because the government still anxiously carries out extensive contact tracing (even though clear community spread is present), many mostly asymptomatic staff had to be quarantined. Hence, the hospital was forced to scale down even further as did several other health facilities. It goes

without saying that this has devastating consequences for a country with already dramatically low numbers of health workers. Like in previous disease outbreaks, the provision of routine health care suffers. Many villagers, including our landlord, turned out to suffer from some sort of ailment. With a dry cough, low grade fever, muscle pain and anosmia she insisted she had malaria and sought treatment for it. I let her take her own decision. The fear is clearly still present, and I cannot blame her. I am however comforted that the majority of people will recover from this disease smoothly. Over here, compared to Ebola, corona is a shark without teeth. The real dangers are the repercussions of the governments' containment strategy.

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I FELT LIKE I HAD TO HELP, NOT ONLY BECAUSE I WANTED TO, BUT BECAUSE IT IS MY DUTY AS A GLOBAL HEALTH DOCTOR

Suddenly working in the intensive care unit

It's March 2020, and I'm working in a rural hospital in Ghana, together with four colleagues from the Netherlands. During our two-week stay, we teach (student) nurses and physician assistants at the neonatal and paediatrics unit, and at the same time we learn a lot from them. While I'm working in Ghana, the coronavirus is spreading throughout the world. The first patient in the Netherlands was detected a week before we left, which made us hesitate whether or not we should travel to Ghana. We didn't want to be "patient zero" anywhere, especially not in a country with a poor health care system. However, at that time, a pandemic seemed far away and we concluded travelling to Ghana would not be a big risk. We followed the news about the coronavirus spreading in Europe, and I must confess that we underestimated the crisis and even thought the drastic measures in Europe were a bit farfetched. We had never before stopped shaking hands to prevent a cold or maybe a severe flu, so why now? Was this virus really so harmful?

The Ghanaian medical staff appointed an outbreak management team, which presented guidelines for the hospital. They concluded that the hospital was not prepared for an outbreak, but on the other hand they did not fear a severe outbreak in Ghana, which is generally warm and sunny. They used to fear Ebola, and the corona virus seemed to be less pathogenic. In the weekend of our return home, we finally understood that this virus was a serious threat. We were worried about our flight being cancelled, but everything went well and we arrived home safely.

Home had changed. We had to keep our distance from one another, stop shaking hands and stay inside as much as possible. I drove to the hospital to see what was going on, and to explore at what kind of hospital I had to start working the next day. I saw piles of protection materials; my colleagues were very strict with hand-hygiene rules and I was surprised by my mail box which had exploded and was filled with regularly updated guidelines on procedures and the implementation of rules and regulations. Compared to this, the lack of personal protective equipment and even hand sanitizer in Ghana was confronting.

It's April 2020, and I start working at the ICU. The WHO director has declared Covid-19 a pandemic, something I had only read about in literature and books, or heard about at conferences and seen in movies. I felt like I had to help, not only because I wanted to, but because it is my duty as a global health doctor. I started reading and learning about Covid-19 and about pandemics, checked the news almost every hour, talked about nothing else but corona, and followed webinars about Covid-19 on the ICU, for family doctors, for gynaecologists, from Médecins Sans Frontières and for the national army. At the same time, I prepared myself to work on the ICU, which is something I had never done before. I knew little about mechanical ventilation, and felt insecure about managing the airway in a resuscitation setting. I was working hard, studying a lot and sleeping too little. I even dreamt about patients lying in prone position, family members who became ill and people dying. It felt like a roller coaster ride, together with other health care workers in the world. It felt as if we were working in one big team. The support of so many people was overwhelming for me.

It's May 2020, and I'm driving back home after another shift at the ICU. Eric Clapton's song *Tears in heaven* is on the radio, and the tears stream down my face. He sings about holding hands, and I wonder when we can finally hold hands again.

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In the shadow of the coronavirus: a global rise of infectious diseases due to Covid-19 containment measures

The global outbreak of SARS-CoV-2 has a firm grip on the world. As of mid-June 2020, there have been 8,700,000 confirmed cases and more than 460,000 deaths related to Covid-19. While many high-income countries have overcome the peak of the first wave of infections, the majority of low- and middle-income countries (LMICs) are now awaiting the complete unfolding of the Covid-19 pandemic.
Meanwhile, global efforts to contain the spread of SARS-CoV-2 have indirectly challenged the continuity of many vital infectious disease control interventions for diseases that primarily affect LMICs, such as malaria, tuberculosis (TB) and HIV, as well as numerous vaccine-preventable illnesses. Lockdown measures aimed at mitigating the spread of Covid-19 are subsequently restricting the mobility of health workers, causing disruptions in supply chains due to border closures, and inhibiting the distribution of life-saving supplies and medicine to the community. The result is a ballooning crisis lurking in the shadow of the Covid-19 pandemic, one that will require significant and timely attention to prevent parallel epidemics of other infectious diseases in the months and years to come.

MALARIA

Malaria is one of the world's deadliest diseases, killing over 400,000 people yearly, 90% of whom are in Sub-Saharan Africa (SSA). The progress that has been made in containing malaria in SSA over the past two decades has been largely contingent on sustaining vector control programmes, some of which could be threatened by movement restrictions and the reallocation of resources aimed to slow the spread of SARS-CoV-2.[1] Sudden lapses in the vector control program activities, like the distribution of insecticide-treated-bed nets (ITNs) and indoor residual spraying (IRS) of houses, would put millions of additional people at risk. A modelling study from Imperial College London presented a few potential outcomes that could occur if the distribution of ITNs were to be inhibited by lockdown measures, the worst of which would result in an additional 400,000 people dying of malaria globally within the next year, roughly doubling what was expected in the years prior to Covid.[2] This model does not take into account disruptions that could occur in access to treatment, chemoprophylaxis, or other forms of prevention, which could further precipitate the impact of malaria in SSA. Sustained interruptions in vector control interventions could additionally exacerbate the already growing issue of insecticide resistance in mosquitos across the region, a problem of immense gravity that threatens to reduce the efficacy of the two most prominent malaria control tools available, ITNs and IRS.

VACCINE PREVENTABLE DISEASES

Measures to contain Covid-19 are also impacting current vaccination campaigns and routine vaccination programs across both high- and low-income countries. The global disruption of supply chains and travel restrictions have threatened to impede vaccine supplies, especially in rural areas in low resource settings.[3] Most mass vaccination campaigns have been temporarily suspended in an effort to mitigate the spread of SARS-CoV-2. While the World Health Organization (WHO) recommends that routine vaccination should continue under infection control guidelines, many healthcare workers involved in such vaccination efforts have been re-allocated to the Covid-19 response, leaving health care facilities without sufficient staff to maintain immunisation services. Compounding these issues, fear of the virus has in some areas reduced willingness to seek out health services and contributed to problems of vaccine hesitancy.

More than half of the 129 countries where data is available indicate moderate to severe disruptions of child immunisation services in March and April of 2020, according to the WHO.[3] If the current trend continues, WHO, UNICEF and Gavi, the Vaccine Alliance estimate that more than 80 million children under the age of 1 could be at risk of contracting diseases such as diphtheria, measles and polio globally.[3] These disruptions could also severely impact child mortality, as demonstrated by a modelling study from the London School of Hygiene & Tropical Medicine, which predicts that deaths prevented by sustaining routine childhood immunisation in Africa would highly outweigh the additional Covid related deaths attributed to infections acquired during health care visits.[4]

TUBERCULOSIS AND HIV

With approximately 1.5 million deaths in 2018, TB kills more people yearly than any other infectious disease. Successful treatment of TB requires rigorous case management and often close clinical supervision to provide daily doses of therapeutic drugs for around six months, both of which may prove difficult to maintain amidst movement restrictions and overwhelmed health care facilities. Lockdown measures in high-prevalence countries threaten to interrupt supply chains which would limit the availability of therapeutic drugs to maintain treatment. As with vector control in malaria, sudden cessation and restarting of treatment creates a heightened potential for drug resistance, which could in the future inhibit the last lines of defence against TB. A recent modelling study by the Stop TB Partnership, in collaboration with Imperial College London, predicted that a three-month lockdown could lead to an additional 6.3 million cases in the

coming five years, causing 1.4 million more TB related deaths globally.[5]

The potential interruption of antiretroviral therapy (ART) and the reallocation of facility and community health workers are also major threats for the approximately 37.9 million people living with HIV globally. Modelling of even minor disruptions of ART drug supplies demonstrates the potential for considerable increases in HIV-related deaths and transmission.[6] Both TB and HIV rely heavily on community access to encourage routine testing, and to initiate and ensure the continuation of life-saving treatment. A lack of access for community health workers due to government-imposed lockdowns will cause limitations in condom distribution, peer education and case management that are likely to further contribute to disease progression and mortality in the future.

A NARROW WINDOW OF OPPORTUNITY

If the goal of SARS-CoV-2 containment measures is to reduce mortality and prevent the collapse of health care systems, it will not be achieved by allowing a significant resurgence of other infectious diseases that are in some cases more deadly than Covid-19. As the first principle of medicine states do no harm, it is integral to consider the collateral damage that may be caused by lockdown measures in LMICs.[7] In these settings, many of the restrictions in their current form threaten to undermine decades of progress in combatting malaria, HIV, TB and vaccine preventable diseases. A surge in other infectious diseases on top of the Covid-19 crisis may push many of these already fragile health care systems and economies to their breaking point, limiting their ability to deal with other looming crises like the staggering rise in malnutrition and mass migration.[8]

The WHO has recognized that many nations, particularly in SSA, have a 'window of opportunity' to expand their disease control efforts while they still have a relatively low burden of Covid-19.[9] This could involve large campaigns to distribute insecticide treated bed nets, increase efforts to stockpile and distribute life-saving HIV and TB medication, and ensure that routine vaccinations are sustained during lockdown as an absolute priority. Finding ways to safely reintroduce community health workers could help to ensure the continuity of such programs throughout the duration of the lockdowns.

It is essential for the global health community to also acknowledge another important window of opportunity, the period directly following the lifting of lockdowns. Ensuring the restoration and expansion of program activities during this time period may have significant implications for infectious disease control in the future. This will involve increased active case finding efforts for TB and HIV, vaccine catch up programs, and efforts to improve and re-establish supply chains. With no promise of a Covid vaccine, LMICs cannot afford to wait to address the myriad of infectious diseases that are likely to remain endemic long after the pandemic subsides.

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PHOTO: FIVEPOINTSIX / SHUTTERSTOCK.COM

Moria, 20,000 refugees waiting for a disaster to happen

Interview with Steven van de Vijver, general practitioner and volunteer for Stichting Bootvluchteling (Boat Refugee Foundation)

Moria, a former military site on the Greek island of Lesbos, is seen as an entrance gate to Europe for many refugees. In theory, Moria is equipped to house a maximum of 3,100 refugees, but in March this year the camp was packed with more than 20,000 people in one km^2.[1] About 40% of the residents of the camp are under eighteen and many suffer from serious illnesses, injuries or mental problems.[2-4] In addition to living with ten persons in one tent or box, the refugees also have to queue for consultations at the clinic, to receive food, and for administrative matters.[3] Due to these cramped living conditions, social distancing is an illusion. Furthermore, with lack of water, sanitation, and electricity, the camp is a ticking time bomb for a catastrophic spread of the coronavirus.[5] Since the 17th of March, lockdown measures have been taken in the camp. This means that from 7 a.m. to 7 p.m. only, limited movement within the camp is allowed, there are police checkpoints, and only a maximum of 100 persons a day are permitted to leave the camp. Other than this, no visitors are allowed into the camp, and activities like schooling and sports have been discontinued.[3]
By mid-June 2020, Greece had over 3,000 confirmed cases of Covid-19 with almost 200 deaths.[6] On Lesbos four asylum seekers had been confirmed positive for Covid-19.[3] Fortunately, so far, there have not been any positive cases inside the Moria camp.[3] But one could imagine the disastrous prospect after a first positive case, as it might rapidly cause a high number of cases requiring hospitalization.

We interviewed Steven van de Vijver, a general practitioner in Amsterdam with prior experience as a tropical doctor, who went to camp Moria in March this year to work as a volunteer for the Dutch Stichting Bootvluchteling. Together with gynaecologist Sanne van der Kooij he initiated #SOSMoria: an urgent appeal to all the leaders of the European Union (EU) to take refugees into their countries, in order to tackle the already existent humanitarian crisis and prevent a medical catastrophe.

CAMP MORIA IN TIMES OF THE CORONA CRISIS

According to Van de Vijver, the situation in Moria is extremely problematic: 'When I came to Moria last year, I was already shocked by the living conditions within this camp on European territory. But this year, it was even worse. The number of refugees in Moria has increased from 6,000 in February 2019 to 22,000 at the beginning of this year. Some refugees have been living in the camp for a year instead of a few months, which is the period aimed for by the authorities. Some people have to wait in line for hours to receive their food.' Situated on the edge of the EU, Greece has been functioning as the gateway to other European countries. But in reality the refugees get stuck there as the transfer to other countries has halted.

'Due to the high number of refugees in the camp, it is impossible to treat all diseases and injuries. Time and resources in the medical units are limited, and the lockdown has even aggravated this. Medical aid has to be focused on life-threatening cases, which means that we can't even provide refugees suffering from diseases like scabies with the proper treatment. Moreover, there are many injuries and infections as a consequence of the conditions in the camp itself. The circumstances in the camp are often worse than the conditions that led the people to seek refuge in the first place.'

PHOTOS: TESSA KRAAN

According to Van de Vijver, refugees describe the camp as hell, having regrets of getting there. He is worried about the dilemmas doctors find themselves in, as they may feel that they are violating Hippocrates oath because the circumstances in the camps have a severe damaging effect on refugees' health. To support this last statement, Van de Vijver mentioned that a part of the mental traumas among the refugees, such as hopelessness, are caused by aggression, fires and rape within the camp itself, and are not traumas that the refugees brought from their home countries. The same holds for all sorts of infectious diseases such as scabies.

The corona crisis added an additional strain on the mental health of the

refugees, explains Van de Vijver. 'To some extent, the people are more anxious now than before the corona threat. When a total lockdown in the camp was enacted, the refugees felt as if they were trapped.'

THE SHAPE OF OUTBREAK PREVENTION IN A REFUGEE CAMP

Refugees in the camp are informed about the importance of basic infection prevention measures such as washing hands, coughing in elbows, and maintaining distance. However, all these things are very hard to put into practice in camps such as Moria. People have to wait in line for half an hour to wash their hands, and maintaining distance is even more unfeasible in a place crowded with 20,000 people. Upscaling of testing, as suggested by previously published articles, faces some obstacles as testing of all refugees is difficult to put in practice and could cause further panic and chaos. 'Stichting Bootvluchteling, together with Kitrinos [Greek NGO that provides medical care] and Doctors Without Borders have materials and plans to treat Covid-19 cases, but there is very limited capacity in the nearby hospital. In case of an outbreak in the camp, provision of ventilatory support is essential, but the nearest hospital has only six ICU [intensive care unit] beds, which is not even close to what would be necessary.' According to Van de Vijver, the focus should be on the problem itself rather than finding temporary solutions for Moria: 'In my opinion, the main goal should not be to upgrade Moria with ICU beds and other fancy measures. The goal should be for Moria to disappear. There should not be any camp in the first place.' However, there is disagreement between the NGOs that provide support and local, Greek and other European politicians about which policy would be best: whether to focus on direct measures on site or evacuation of the refugees to other countries.

THE EFFECTS OF THE SOSMORIA DISTRESS CALL

Approximately 7,000 doctors and more than 50,000 other emergency workers have joined the call. According to Van de Vijver, the only solution for the problematic situation in Moria is to evacuate all refugees. Via the SOSMoria call, Stichting Bootvluchteling joined forces with other organisations to evacuate at least 500 children to other European countries (#500kinderen).[7] These children arrived in Moria without their parents or any guardian, traumatised, some suicidal, and they often resort to auto-mutilation. Many countries in Europe have already welcomed some of these children, but the Netherlands is not one of them. In the Netherlands, a lot of municipalities (150) and churches are enthusiastic and willing to welcome these children, but the governing parties in The Hague are not heeding the call. They seem to be afraid to lose voters and instead of welcoming these children in the Netherlands, Ankie Broekers-Knol, the Dutch State Secretary for Justice and Security, drafted a proposal to spend four million dollars to relocate refugees on the island. However, the proposal was criticized by both Dutch and Greek parties for being a naive and useless plan that would not solve anything.

COVID-19 COMPOUNDING THE PLEA FOR SOLIDARITY AND IMMEDIATE ACTION

'I guess you could say that Covid is some kind of catalyst in the Moria refugee crisis. The situation before the outbreak was already completely inhumane, and I wanted to do something about that. I had hoped that in this time of fast decisions, the Dutch government would decide to welcome these refugees from Moria too. I had hoped for solidarity and that people would act faster. I am disappointed with the lack of political action on a national level, even though municipalities are very willing to contribute.'

As Van de Vijver stated clearly, Moria is a ticking time bomb in terms of a Covid-19 outbreak, but also for many other problems. The lives of many refugees are at stake and it is time to act now.

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Read more on the appeal, and the support from European doctors and citizens on the initiative website: https://www.sosmoria.eu/?lang=en

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THE MAIN GOAL SHOULD NOT BE TO PIMP MORIA WITH ICU BEDS AND OTHER FANCY MEASURES. THE GOAL SHOULD BE FOR MORIA TO DISAPPEAR. THERE SHOULDN'T BE A CAMP IN THE FIRST PLACE

Covid-19 and the Trojan horse that eroded the World Health Organization

The Covid-19 pandemic has created havoc around the world since the early days of 2020. My attendance at a civil society meeting in Geneva coincided with the World Health Organization (WHO) declaring the Covid-19 epidemic a public health emergency of international concern (PHEIC).[1,2] Mike Ryan, director of WHO Health Emergencies Programme was worried, yet still optimistic, estimating that the epidemic could be contained at the regional level in Asia. I shared the same sentiment and travelled on after the meeting to Indonesia without real concerns. I returned to the Netherlands just before the epidemic escalated and international borders were closed.

June 2020, we are six months into the pandemic and over 9 million confirmed cases of Covid-19 have now been reported to the WHO, including more than 470,000 deaths.[3] Questions have been raised about the role and capacity of the WHO and other international actors in assisting countries to prepare for and respond to a viral pandemic of this magnitude. According to Dr Tedros, WHO's director general, the main reason for declaring this PHEIC was 'not because of what is happening in China, but because of what is happening in other countries. Our greatest concern is the potential for the virus to spread to countries with weaker health systems, and which are ill-prepared to deal with it.'[1]

The WHO was prepared, in the sense that it was well aware of the emergence of another "Disease-X" – a yet unknown pathogen causing a human disease which eventually would lead to a serious epidemic.[4] The world had witnessed such epidemics before, like the SARS epidemic in 2003, which remained largely contained to China, the Ebola-epidemic which impacted mainly countries in West Africa (2014-2015), as well as other emerging zoonoses such as avian flu, Zika, and Lassa fever. These epidemics all raised global concern (some more than others), and inspired global health actors and national government leaders to underscore the need to strengthen global health security. Sadly, few countries really acted upon their initial commitments and failed to invest in an essential public health function that others have labelled a global public good.[5]

INTERNATIONAL HEALTH REGULATIONS

Following the 2003 SARS epidemic, the World Health Assembly (WHA) adopted a revised version of the international health regulations (IHR), which since their adoption in 1969 had served as the main framework governing the international response and a country's capacity to deal with public health emergencies, including major infectious disease outbreaks.[6,7] Under the IHR, and upon declaration of a PHEIC, the WHO has the power to provide countries with temporary, non-mandatory recommendations on how to deal with the emergency at hand. Countries are not legally obliged to adopt such recommendations, such as in this case testing for Covid-19 virus, tracking possible cases, and identifying risk-groups. However, the IHR obliges countries not to implement policies that would prevent international trade and mobility. For example, WHO member states cannot suddenly make medical examinations, vaccinations or prophylaxis compulsory for travellers in case they are potentially infectious. This did not prevent Austria and other European states from requesting foreign travellers to their countries to provide a certificate of a negative Covid-19 test result. These actions clearly constituted a breach of the IHR,[8] but they could not be followed by any sanctions. Other multilateral organisations perform better in this sense. The World Trade Organization (WTO), for example, uses international dispute settlement mechanisms and a sanction regime when international trade rules are violated. It has become clear that WHO's IHR provides only limited resources, mandate, and legitimacy to direct sovereign countries in addressing their approaches to disease outbreaks and other public health risks. Interestingly though, a hundred years before WHO's establishment, countries already tried to regulate international public health responses.[9] In the words of leading global health lawyers: 'The IHR is no "magic bullet" for global health problems. Previous transformations in international law's relationship with public health have over time atrophied into insignificance.'[7]

POLITICAL TENSIONS BETWEEN THE UNITED STATES OF AMERICA AND CHINA

The recent critique by the Trump administration that WHO has an 'alarming lack of independence from the People's Republic of China' in addressing the Covid-19 pandemic is unfounded.[10] Donald Trump's decision to sever ties with the WHO and his threat to halt funding must be seen as part of a larger geopolitical conflict between the USA and China. A kind of Cold War 2.0 meant to divert attention from the disastrous response and poor performance of the USA's health system itself.[11] China has made errors in dealing with Covid-19, especially in terms of transparency at the beginning of the epidemic. Human rights violations have been an issue in the stringent lockdown and surveillance by the Chinese state.[12] Nevertheless, the rapid public health response by China, and Southeast Asia more generally, has so far proven effective in containing the virus. This has been noted by other low- and middle-income countries (LMICs) and by the WHO. In the report by a WHO evaluation mission to China in February, Dr Tedros hailed the country's swift response and approach.[13] For diplomatic and global

health objectives, it is important that the WHO keeps working closely with the world's most populous country (1.4 billion inhabitants). At the same time, there are informal complaints regarding controlled and restricted access to China for the WHO officials. Meanwhile, China has committed to stepping up multilateral collaboration, pledging US$ 2 billion to the United Nations (UN) for its Covid-19 response, and it has agreed to a full evaluation of the international response once the pandemic is over.[14] In any case, this is a watershed moment in global health, not only for the WHO. In the coming years we are likely to see the USA retreating from international health cooperation in LMICs while China may considerably step up its bilateral health collaboration with African, Asian and Latin American countries.[15]

THE EROSION OF THE WHO

Ironically, the USA, along with some affluent European countries are responsible for WHO's limited capacity to deal with transnational health emergencies. The roots of this problem lie in the governance structure, in which the WHA, composed of all 190+ member states, decides collectively on WHO's programme of work. In the 1980s, high-income countries, in response to the growing influence of LMICs, decided to review their financial contributions to the UN and the WHO in particular, changing to voluntary payments. In the current set-up, eighty percent of WHO's budget is comprised of voluntary contributions by member states, philanthropic organisations (such as the Bill & Melinda Gates Foundation), and private donors. This has led to a situation in which donors no longer provide core funding, but rather support particular programmes, i.e. those that fit their own (domestic) interests. Examples include the USA's financial support for polio eradication, and the Netherlands' targeting of funds to sexual and reproductive health and rights programmes of the WHO. The result has been severe underfunding of certain other programmes, such as emergency preparedness, health systems strengthening (including health workforce strengthening) in LMICs and programmes aimed at achieving universal health coverage. Meanwhile, we have witnessed a surge of global health initiatives for disease-specific approaches, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), Gavi, the Vaccine Alliance, the Global Health Security Agenda (GHSA), and others. They generally deliver short term results, over which the donor countries have more direct control. In the process, the WHO has become hamstrung by its donors, limited in its autonomy, and become relatively neglected in a neoliberal era in which policy objectives such as "value for money" and "enlightened self-interest" received priority over the provision of global public goods, such as the international capacity to respond to pandemics. This trend is also described as "Trojan multilateralism" and has seriously eroded the UN over the last decade.[16]

SOLIDARITY AND SHARED RESPONSIBILITIES

The World Health Report 2007 on health security stated that '57 countries, most of them in Sub-Saharan Africa and Southeast Asia, are struggling to provide even basic health security to their populations.'[17] In response to the 2014-2015 Ebola epidemic, there has been much talk about the need to develop strong and resilient health systems. No less than four international commissions have provided recommendations on how to improve the international response to health emergencies.[18] All of these commissions recommended strengthening WHO's mandate, autonomy and financial basis, as well as reforming the IHR with a view to strengthen its capacity to address global public health risks. The Covid-19 pandemic may provide the "shock momentum" that was needed to stabilize and improve – in a democratic way – the only internationally mandated health organisation in the world.

In his media briefing in late June 2020, Dr Tedros made a plea for global solidarity and urged countries to work together to ensure that supplies (e.g. dexamethasone, oxygen, personal protective equipment) and vaccine development are prioritized for countries with large numbers of critically ill Covid-19 patients. 'The world is learning the hard way that health is not a luxury item; it's the cornerstone of security, stability and prosperity.'[19]

Germany has announced it will make an unprecedented € 500 million pledge to the WHO. This must be seen as a plug for the large funding gap left by the withdrawal of the USA.[20] It can also be seen as a geopolitical signal to the world. Germany prefers in these uncertain times to invest in health security (WHO) rather than military security (NATO). So far, the Dutch government has committed US$ 6.5 million to the WHO for the Covid-19 response.[21] At the same time, it is providing its national airline, KLM, with a € 3.6 billion (!) guarantee to secure its position in international trade and mobility. Will the Netherlands eventually realize that this interconnectedness relies on the peace, wellbeing and health of societies in other parts of the world? Isn't it time to put aside such a frugal attitude and instead invest seriously in global public health? That would be the real call, in the current era of pandemic threats, climate emergency, economic instability and growing disparities.

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Outbreak of Covid-19 like illness in a remote village in Papua, Indonesia

The Covid-19 pandemic is hitting low- and middle-income countries, where health care resources are already stretched. This article describes the spread of a Covid-19-like illness in M20 (a pseudonym), an isolated village without medical facilities in Indonesia. M20 is situated at an altitude of 6,700 feet in the central mountain range of Indonesia's easternmost province, Papua. It is typically served on request by a small six to eight-seat aircraft, or reached by trekking on foot from other villages. The village consists of seven hamlets of two to six huts, separated by five to ten-minute walks. Villagers are closely related to inhabitants of other villages in the area, and visit each other often. In the villages of the Papuan highland, men and/or families sleep together in one hut, and children sleep with their mothers or families (sometimes up to 30 people in one hut). The closest neighbouring village to M20 is about 1.5 hour by foot, with people visiting multiple times a week. The actual population varies with these interactions and ranges from 150 to 200 people. M20's gender distribution is estimated at 60% women, and 40% men, due to a combination of a higher life expectancy of women (66.8 years compared to 63.0 years for men) and men spending most of their time in towns.[1] Approximately half of the population is under twelve years of age. There are four to six matriarchs, and others are teenagers, young adults and adults in their thirties to fifties. Most men smoke, and most people live in huts with central fire pits, which are used throughout the day for cooking and during the evening and night for heating.[2] The closest government health centre is about three hours by foot, but trained health workers are typically absent, as is common in this region.[3] In M20, lay health workers hold daily clinics where they perform primary health care and dispense medication.

METHODS

This account of an outbreak in a remote village in Papua is compiled from patient care records kept by lay healthcare workers in M20 during and after an outbreak, as well as medical doctors responding to online requests for help. We use a pseudonym to conceal the name of the village and protect its population; patient data were analysed anonymously. Symptoms of villagers seeking medical help were recorded by lay health workers, so initial mild symptoms were not systematically recorded. In most cases with infectious diseases the exact onset of infection is not clear. A major caveat is that polymerase chain reaction (PCR) testing

for Covid-19 was not possible due to the lack of tests and test facilities. Our team repeatedly contacted the government health services, but PCR testing, or testing using reliable antibody tests, was not possible until the time of submission of this report (as of end of June). To collect information on Covid-19 symptoms of all villagers present during the outbreak, the lay medical workers also asked individuals who did not seek medical help about Covid-19 symptoms.

EPIDEMIOLOGIC TIMELINE

On 22 March 2020, the first case of confirmed Covid-19 was reported in Indonesia. However, suspected cases with links to Wuhan China were reported earlier in Jakarta in February 2020. On 20 February 2020, the first suspected Covid-19 patient reported in M20 for care with symptoms of fever, sore throat, cough and stomach complaints although at that time Indonesia had no official Covid-19 cases. Two weeks after the index case in M20, the number of cases rose steeply with 26 patients on one day (Figure 1). Covid-19 had become the top of the differential diagnosis list, as symptoms were in line with the WHO definition of Covid-19, and the index case had been in contact, prior to symptom onset, with a person who had travelled to Jakarta where probable Covid-19 cases were reported.[4] On 3 June 2020, Papua had 862 cases of Covid-19, while all of Indonesia counted 28,233 cases.[5]

Clinic records showed symptoms as summarized in Table 1. Table 2 presents the characteristics of the 101 suspected Covid-19 patients in M20. The illness started with several days of sore throat, followed by stomach complaints, and fever within 24 hours of stomach complaints. Fever and fatigue were constant, lasting 3-5 days. In severe cases (Table 2), fevers above 40°C often accompanied shortness of breath and chest pain, starting after day five of illness. Two villagers died after 48 hours of extreme shortness of breath. Both were male, over 40 years of age, and had underlying chronic illness (most likely chronic kidney disease). The lay healthcare workers treated patients with the limited resources available to them;

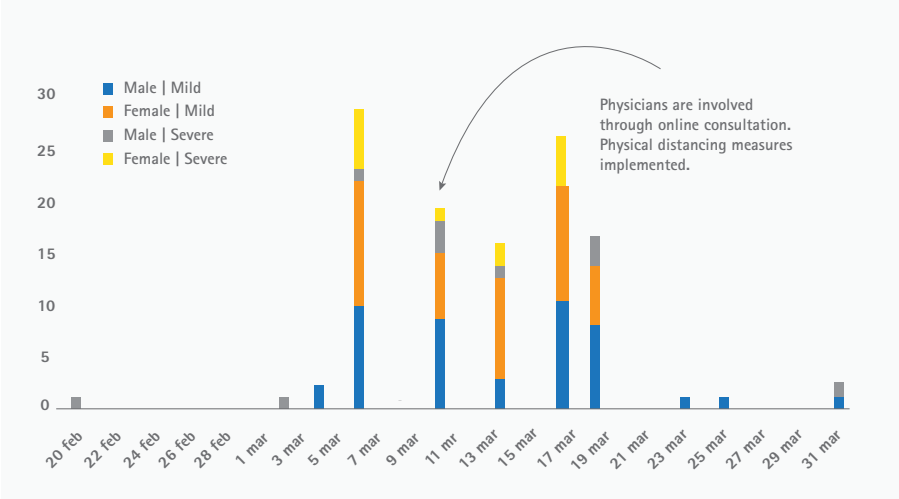

Figure 1: Number of patients with symptoms observed over time.

those with moderate symptoms mainly received paracetamol, up to four times a day. Severely ill patients were given empiric amoxicillin treatment (49% of 101 patients) to prevent and/or treat a possible secondary bacterial pneumonia. Those with fevers over 40°C received a different antibiotic: amoxicillin/clavulanic acid (2% of the patients) or azithromycin (3% of the patients). The actual effect of antibiotics on recovery is not evident. Based upon advice early on in the worldwide epidemic to use chloroquine as a possible treatment

	MILD TO MODERATE SYMPTOMS				SEVERE SYMPTOMS			
AGE	MALE		FEMALE		MALE		FEMALE	
0-5	7	6.9%	5	5.0%	2	2.0%	2	2.0%
6-10	7	6.9%	15	14.9%	1	1.0%	1	1.0%
11-15	2	2.0%	2	2.0%	0		1	1.0%
16-20	8	7.9%	1	1.0%	0		0	
21-25	2	2.0%	2	2.0%	1	1.0%	0	
26-30	4	4.0%	3	3.0%	1	1.0%	3	3.0%
31-35	3	3.0%	6	5.9%	1	1.0%	0	
36-40	3	3.0%	5	5.0%	1	1.0%	0	
41-45	1	1.0%	3	3.0%	0		0	
46-50	2	2.0%	1	1.0%	3	3.0%	1	1.0%
50+	0		0		0		1	1.0%
(median = 17)								
Total	39	38.6%	43	42.6%	10	10.1%	9	8.9%

Table 1. Suspected Covid-19 patients treated in M20.

SEVERE SYMPTOMS	APPROXIMATE PERCENTAGE OF PATIENTS REPORTING
Fever (either mild 37-38.5°C or high <38.5)	80%
Shortness of breath	70%
MILD SYMPTOMS	
Sore or dry throat	90-95% adults. 60-70% children
Coughing (usually at night)	80%
Fatigue	90%
Lethargy (most of the children)	80-90% children
Headache (late in the illness)	60%
Muscle and joint pain	10-20%
Diarrhoea	20-30%
Vomiting	10%

Table 2. Symptoms of patients with suspected Covid-19.

for Covid-19, severely ill and high-risk patients (aged above 40), were given 150 mg chloroquine twice a day for seven days (14% of the patients).[6] Except for the two patients who died, all patients recovered. The effect of chloroquine and antibiotics on recovery is unknown.

As Figure 1 shows, the entire epidemic curve involved 101 patients (about half of the population of the village) over a period of four weeks. Informal questioning in the community revealed that only about ten villagers denied having had any symptoms yielding a presumptive infection rate of 90-95% of all residents. Of the twelve patients over age 40, five were severely sick (41%), and two died (17%). Approximately 50% had mild or no symptoms (Table 2). The median patient age is low (17 years), which might explain the unexpectedly low mortality of 1% given minimal health facilities and no mitigating measures.[7] The high proportion of females in the population may explain that more women (51.5% of the patients) were affected than men. Physical distancing measures were implemented, but their effect was unclear.

CONCLUSION

This outbreak pattern of suspected SARS-CoV-2 in a village in the highlands of Papua (Indonesia) presents a unique report of the course of infection in an entire village population. The dense social structure of the village resulted in the rapid infection of 90-95% of the population within four weeks. Physical distancing and isolation measures were used, but probably not implemented optimally and too late. An effect on the illness course could not be observed.

The M20 population is young, which partially may explain the impact of the suspected Covid-19 outbreak and the relatively low case fatality rate (CFR) and overall death rate (1%), given the scarcity of direct health facilities and the difficulty of complying with mitigating measures like physical distancing. Treatment was provided in the form of chloroquine phosphate and azithromycin for severely ill and high-risk patients. However, no unequivocal conclusions regarding their efficacy can be drawn, something which requires further studies.[8]

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Epidemics and pandemics

By Roel Coutinho
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Roel Coutinho, medical doctor and microbiologist, emeritus professor of Life Sciences at the Utrecht University Medical Center (UMC) and former director of the Centre for Infectious Disease Control (CIb) in the Netherlands, takes us on a journey of discovery to many corners of the globe where epidemics occurred, some of which developed into pandemics. He writes extensively about the spread of HIV from 1980 onwards, the Ebola outbreak in 2014, the cholera epidemic in Haiti after the 2010 earthquake, and the 2009 swine flu pandemic. It is an account of recent epidemics and pandemics that have gripped the world and cost many lives. The author shows how these, as well as age-old infectious diseases such as plague, cholera, and influenza, developed and spread, how professionals and affected populations coped with them, and to what extent they had been anticipated by epidemiologists, microbiologists and virologists. Other potential public health threats include biological warfare and declining vaccination coverage.

The earliest known case of HIV-1 infection was in 1959 in Kinshasa, Democratic Republic of the Congo. However, HIV exploded in the beginning of the 1980s worldwide, especially in Southern Africa where it caused 20% to 25% seropositivity among the general

population with many people succumbing to AIDS and a steep decline in life expectancy as a result. Forty years later, it has become a chronic condition, and there is still no vaccine available. The 2009 Mexican flu and 1918 Spanish flu epidemics, especially the latter, took a huge death toll; probably one hundred million people died, more than in both world wars combined.

Another interesting chapter to read is about the cholera epidemic in Haiti, which started in 2010, brought into the country from Asia by Nepalese soldiers who were based on the island because of a devastating earthquake earlier that year. Yersinia pestis and plague are usually considered a problem of the past but plague was not uncommon during the Vietnam War due to acts of violence, and these days the disease is still endemic in Madagascar and in California, United States of America.

Ebola ravaged Western Africa from 2014; Guinea, Sierra Leone and Liberia suffered great losses. Many health personnel died. Following this outbreak, a vaccine was developed with a very high protection rate and formally approved and licensed by the World Health Organization (WHO) in November 2019. Agents that can be used as biological weaponry, such as anthrax, yersinia pestis, cowpox, and salmonella typhimurium, as well as diseases transmitted by mosquitoes, such as chikunkunya and malaria, are described with suggestions on how to deal with them in the future.

The anti-vax movement gets critical comments from the author; there are some 250,000 people in the Netherlands - mostly living in the so-called bible belt - who reject vaccination on religious grounds.

The book concludes with a reflexion on the recent Covid-19 pandemic. It shows that new infections as well as their spread are difficult to contain, resulting in enormous economic losses as well as social implications in our globalised world.

In his vote of thanks at the end of the book, the author emphasises that he himself has gained more insights in epidemics and pandemics while writing the book, and readers may experience the same.

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OPINION

Pooling of knowledge, know-how and intellectual property to counteract vaccine nationalism

Over the past two months, numerous news articles on potential Covid-19 treatments and vaccines have been published. Even though the vast majority of these new medical technologies are still in a development stage, governments are already looking for ways to secure them. This may induce "vaccine nationalism" – countries wanting to skip the queue to be first to access vaccines once they have proven effective and become available. The current system of pharmaceutical development incentivises innovation through patents, leading to monopoly positions for pharmaceutical companies, who then unilaterally decide on the market price for their products. The combination of vaccine nationalism and market monopolies is dangerous for Covid-19 treatments and vaccines because it will hamper equitable access. At Wemos, a Dutch NGO working on various global health topics, we believe that a global crisis requires a global response. Current and future efforts must make sure that they result in maximising both availability and affordability. Creating a pooling mechanism of knowledge, patents and know-how is the best answer to growing vaccine nationalism and monopolies for life-saving medical technologies. The concept of collecting expiring pharmaceutical patents and licensing them non-exclusively to manufacturers of generic products is not new. The Geneva-based Medicines Patent Pool (MPP) has been doing exactly this for almost ten years.[1] With this concept, the organisation is a crucial actor in increasing competition and improving access to medicines against HIV, hepatitis, and tuberculosis.

Non-exclusive licensing will be key for future Covid-19 treatments and vaccines, as it seems very unlikely that a single pharmaceutical company will be able to produce enough vaccines or medicines to satisfy the worldwide demand. Since the desired outcome of such a pool is global access to future pharmaceutical products against Covid-19, Wemos believes the best organisation to manage such an initiative is the World Health Organization (WHO).

The government of Costa Rica was the first to suggest a global database. In an open letter to the WHO, it suggested creating a voluntary pooling mechanism – in line with the MPP – for Covid-19 related knowledge, know-how and intellectual property.[2] The initiative prompted NGOs in various WHO member states to call upon their governments

to support this Costa Rican initative. In the Netherlands, Wemos won the support of many Dutch NGOs and public health experts.[3] Together with follow-up lobbying activities, this resulted in support from the Dutch government for a Covid-19 technology access pool, or C-TAP in short.[4] The Dutch health minister was one of the only country representatives at the World Health Assembly (WHA) to mention C-TAP in his statement to the rest of the WHA. The permanent representative of the Netherlands to the United Nations in Geneva, Switzerland also made a strong statement during the official launch of C-TAP on the 29th of May. Despite the compelling presentations, it is not yet clear how the Dutch government will translate these words into action. At Wemos, we believe that despite the voluntary character of C-TAP, governments are in a good position to negotiate with pharmaceutical companies to contribute to the pool, for instance by attaching conditions to public funding. Such a condition could be that patents of Covid-19 pharmaceutical products that are developed with Dutch public funding are automatically shared with the C-TAP. In order to counter vaccine nationalism and promote global access to new pharmaceutical products, countries around the world should embrace C-TAP. It is likely to be the best way to maximise production and affordability. Now that C-TAP has been formally established, it is essential that countries do their best to make it work. The role of national governments in supporting C-TAP to become a successful global access mechanism for Covid-19 vaccines and treatments is crucial, starting with convincing pharmaceutical companies to contribute to the pool. Considering the large amount of public funding that is currently being spent on research and development, governments have a powerful tool to promote access, namely by attaching conditions to these investments. This is vital: it is in the best interest of the public and would be a strong signal of global solidarity.

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BOOK REVIEW

A constant state of emergency

Paul de Kruif, microbe hunter and health activist

By Jan Peter Verhave
Van Raalte Press
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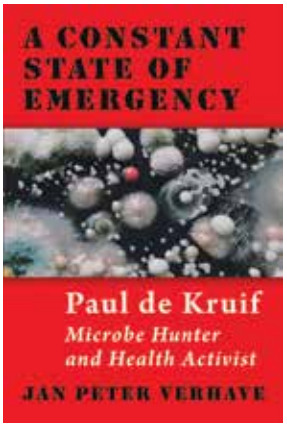
2020, 678 pages

How apt, this title for the biography of Paul de Kruif – microbiologist, journalist, and health activist. Apt, considering the current Covid-19 pandemic sweeping across the world. Also, De Kruif seemed to be in a constant state of emergency himself, considering the rapid speed at which he produced articles and books on medicine and science, his political swinging from progressive during the Great Depression, to eventually more conservative, leaving behind his (in those times) more radical views on socialized medicine and compulsory health insurance. Also, in his final years he converted back to religion, after being a lifelong atheist although born into a conservative Calvinist family in Zeeland, Michigan (USA).



There is no statue for this remarkable person, though one could consider Jan-Peter Verhave's biography as such. The bulky book reads as a tribute to this man who seemed to be overlooked by (medical) historians and policy makers, although some may remember Paul de Kruif (1890-1971) as the author of the *Microbe Hunters* (1926), the book that became an international bestseller, translated into eighteen languages and is still in reprint. Enthusiasts described Microbe Hunters as a most exciting book 'dealing with villains and heroes, blood and thunder', and as a 'war upon pathogenic organisms coming out of the laboratory'. These descriptions make you want to pick up a copy of this book, especially now that the Covid-19 pandemic has many scientists working against the clock to unravel the pathogenic effects of SARS-CoV-2. As in the early decades of the twentieth century, it is a very challenging and arduous task to develop a safe and effective vaccine. De Kruif brought the pioneers of microbiology and biomedicine,

and their discoveries of cures for various infectious diseases to life by telling the fascinating story of the microbes and scientists involved in language everyone could understand.

With this book, the promising microbiologist definitely changed his career path by trading the laboratory for his typewriter. No more experiments, as when in the context of a study on the agents of influenza and the common cold he volunteered to shut himself up naked in an icebox for an hour day after day. Gradually he became a household name and, as a star reporter for *The Reader's Digest* and other magazines, he was able to reach large audiences with his popular writings on medical discoveries, new drugs, causes and cures of diseases, vitamins and hormones, and health insurance. He did so much to the appreciation of the general public, but to a lesser extent of the medical professionals, who rejected him as someone writing about medical matters 'while not even being a medical doctor', expressing their fear that public health systems would take away their patients (and their fees).

Verhave's book is a treat, as it took me on a journey learning about his lifelong mission to popularize medicine and educate people, and getting to know the person behind this public health advocate for policies that take into account the social determinants of health. To do so, he had to leave the "ivory tower" of science, using his typewriter as 'a weapon against medical abuses and a fist to bounce the table'. And it bounced. He rallied the public against tuberculosis in Detroit, unsilenced "the big S" of syphilis (a condition that had become highly prevalent during the economic crisis in the 1920s with one out of ten Americans infected), and steering polio eradication. His quest resulted in more than 200 articles on the common health problems of his time: the dangers of raw milk, maternal deaths, childbed fever, diabetes, parrot fever, health insurance, and the deplorable health situation in Midwestern states and city slums.

Ingeniously, Jan Peter Verhave interweaves Paul de Kruif's work as a catalyst for change with a quite detailed account of his personal life, his flamboyant life style, and his friendship with famous writers, including the poet Ezra Pound, Ernest Hemingway, John Steinbeck, and Sinclair Lewis, with whom he wrote *Arrowsmith* – a novel about a young medical doctor who gradually diverges from caring for patients to focusing on public health and controlling disease outbreaks. As a "champion for the poor" he was on speaking terms with President Franklin D. Roosevelt, and a close friend of Vice-President Henry Wallace and Surgeon General Thomas Parran.

In many ways, he was ahead of his time, as De Kruif fully understood the public benefit of disseminating his work using mass media like theatre, film, radio, and even the new medium of the 1930s, comic books. The staging of one of his plays *Yellow Jack* in the Netherlands in 1934 impressed the audience, though considered a dicey experiment of bringing science to the stage. The play was based on a chapter in *Microbe Hunters* on the tragic death of yellow fever researchers dying in Cuba from experimental exposure to infective mosquitos.

Six hundred words are not enough to cover the wealth of information Verhave presents us in the more than 600 pages of a biography of 'a hard-drinking womanizer with a blasphemous tongue', as Verhave describes De Kruif in his foreword. For Verhave, retired biologist and parasitologist (and author of *The Moses of Malaria* (2011), a biography of the parasitologist Schwellengrebel), it was clear that the man who fought against poverty and horrible diseases deserved more attention. He definitely succeeded in placing De Kruif in the spotlight by taking us along 'a medical history, a history of taking risks in moving doctors, scientists and lay people toward each other and toward a commonly shared healthcare system'. A story to note and to learn from.

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