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Aller au sommaire du numéro

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Résumé de l'article

Si aucun vaccin ne peut offrir une protection totale, un haut niveau de réglementation en matière de sécurité, d'efficacité et de qualité est fondamental pour la confiance du public et l'adoption des vaccins en tant qu'outils essentiels de la santé publique mondiale. Cet article traite d'une préoccupation croissante au sujet des vaccins sous-optimaux « imparfaits » qui menacent les interventions d'urgence en cas de pandémie, ainsi que les programmes de santé publique habituel. Des normes réglementaires souples permettent aujourd'hui d'approuver plus rapidement des vaccins et des produits thérapeutiques dont l'efficacité n'est peut-être pas optimale. Des normes réglementaires flexibles permettent aujourd›hui d›approuver plus rapidement des vaccins et des produits thérapeutiques dont l›efficacité pourrait être sous-optimale. Les compromis entre les avantages et les inconvénients qui jouent un rôle considérable dans l'évaluation réglementaire, et à tous les stades du développement et de l'administration des vaccins, méritent d'être mieux connus du public, d'être plus transparents et de faire l'objet d'une plus grande responsabilisation. En nous basant sur le cas du premier vaccin antipaludique homologué, le RTS,S Mosquirix™, et à la lumière de l'approbation rapide des vaccins contre la COVID-19, nous examinons les implications socio-techniques des vaccins imparfaits dans les logiques vaccinales mondiales et suggérons des possibilités de renforcement de la légitimité pour informer la prochaine génération de la politique réglementaire en matière de technologie.

# Leaky Vaccines

## A Wicked Problem in Accelerated Vaccine Development

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**Abstract:** While no vaccine can provide 100 percent protection, a high standard of regulatory safety, efficacy and quality is essential for public trust and the uptake of vaccines as essential global public health tools. This article addresses a growing concern that suboptimal "leaky" vaccines threaten emergency response to pandemics as well as routine public health programs. Agile regulatory standards now advance earlier approval of vaccines and therapeutics that may have suboptimal effectiveness. The benefit-harm trade-offs that play an enormous role in regulatory assessment and all stages of vaccine development and delivery deserve better public scrutiny, transparency, and accountability. Drawing on the case of the first licensed malaria vaccine, RTS,S Mosquirix™, in light of the rapid approval of COVID-19 vaccines, we consider the socio-technical implications of leaky vaccines in global vaccine logics and suggest possibilities for building legitimacy to inform the next generation of regulatory technology policy.

**Keywords:** vaccine development; vaccine logics; vaccine acceptance; hesitancy; public trust; regulation; safety; efficacy; malaria

**Résumé** : Si aucun vaccin ne peut offrir une protection totale, un haut niveau de réglementation en matière de sécurité, d'efficacité et de qualité est fondamental pour la confiance du public et l'adoption des vaccins en tant qu'outils essentiels de la santé publique mondiale. Cet article traite d'une préoccupation croissante au sujet des vaccins sous-optimaux « imparfaits » qui menacent les interventions d'urgence en cas de pandémie, ainsi que les programmes de santé publique habituel. Des normes réglementaires souples permettent aujourd'hui d'approuver plus rapidement des vaccins et des produits thérapeutiques dont l'efficacité n'est peut-être pas optimale. Des normes réglementaires flexibles permettent aujourd›hui d›approuver plus rapidement des vaccins et des produits thérapeutiques dont l›efficacité pourrait

être sous-optimale. Les compromis entre les avantages et les inconvénients qui jouent un rôle considérable dans l'évaluation réglementaire, et à tous les stades du développement et de l'administration des vaccins, méritent d'être mieux connus du public, d'être plus transparents et de faire l'objet d'une plus grande responsabilisation. En nous basant sur le cas du premier vaccin antipaludique homologué, le RTS,S Mosquirix™, et à la lumière de l'approbation rapide des vaccins contre la COVID-19, nous examinons les implications socio-techniques des vaccins imparfaits dans les logiques vaccinales mondiales et suggérons des possibilités de renforcement de la légitimité pour informer la prochaine génération de la politique réglementaire en matière de technologie.

**Mots clés :** développement des vaccins ; logique vaccinale ; acceptation des vaccins ; hésitation ; confiance du public ; réglementation ; sécurité ; efficacité ; paludisme

## Introduction

High efficacy and safety standards for vaccines in the late twentieth century that have prevented infectious diseases such as measles, mumps, rubella, tetanus and diphtheria may be weakened by the wide adoption of agile regulations (Azuma 2015; El Zarrad et al. 2022; Morgan et al. 2023, Vural, Herder, Graham 2021). The vaccine industry has long fought for fewer regulatory obstacles and speeding up approval and access to the market. In this paper, we suggest that these agile regulations that allow earlier, conditional approval of vaccines might permit suboptimal *leaky* vaccines into the market that have potential consequences for equitable futures and individual and population health. The scientific evidence for safety and efficacy of more rapidly licensed vaccines may not hold true over time as real-world data surface. Of particular interest to anthropologists and policy communities, approval of and access to these accelerated products may rest as much on the socio-political logics of late capitalism as strictly technical, scientific regulatory factors.

The term *leaky vaccine* is used sparingly in the scientific literature to refer to vaccines that might not sufficiently prevent viral transmission and might bring about more virulent strains (Read et al. 2015). The author [JG] first became aware of the term in 2011 during a conversation with a researcher connected with a World Health Organization (WHO) malaria intervention project. First coined in 1992 by epidemiologists to model the heterogeneity of vaccine efficacy in populations (Halloran, Haber, Longini 1992), the concept of *leaky vaccine* provoked this anthropological inquiry into issues of risk, danger, accountability

and trust attached to such an essential public health tool (Douglas 1970; Douglas and Wildavsky 1982; Haraway 1996; Ryan, Giles-Vernick and Graham 2019).

While in an ideal world, a vaccine would completely protect vaccinees from getting a disease and reduce the probability of transmission to zero, it is widely acknowledged that no vaccine provides 100 percent protection (Haber, Watelet, Halloran 1995; WHO 2021). Many vaccines, however, come very close (for example, polio, measles, mumps, diphtheria, tetanus, hepatitis A). A permittable threshold for vaccine efficacy is dependent on robust randomized clinical trial data collected under careful conditions but is nonetheless subject to the construction of this evidence within the real world of commercial interests and political decision-making. Weighing the benefits and harms of new vaccines involves a careful balance of science, population burden of the disease (which can both charge and be charged by emergencies) and cost. The concept of leaky vaccine recognizes that different (sub)populations have different levels of exposure and frequency of contact (disease burden) and are subject to a multiplicity of indirect population effects. For example, "[a]s a result of feeling protected against infection and disease, vaccinees may increase their exposure to infection" (Haber, Watelet, Halloran 1995, 1259). The routine vaccines used in the late twentieth century against polio, diphtheria, measles mumps, tetanus and pertussis offered high efficacy and significant living memory of the impact of these infectious diseases. The measles vaccine, for example, has 97 percent efficacy, but the highly contagious nature of that disease that requires extremely high vaccine uptake to ensure the general population (including those who have not been vaccinated) will remain uninfected has been largely forgotten, resulting in a decline in measles vaccination and increase of infections. Social factors, from perceived risk of infertility to weakened immune systems, come into play when public health messaging is not sufficiently supported by trust in both government and scientific evidence.

Rather than focus on the public communication aspect of vaccines, however, in this paper, we explore a concerning global trend towards regulatory approval of less efficacious, *leaky* vaccines. In 2020 at the start of the COVID-19 pandemic, for example, just as development began on vaccine candidates, a relatively low 50 percent efficacy threshold for a COVID-19 vaccine was mused acceptable given the disease's anticipated seriousness (Zimmer and Collins 2021). Statistical modellers' predictions of billions of deaths later proved faulty (Ioannidis, Cripps and Tanner 2022), but the urgency for a vaccine now was unambiguous.

Vaccines of low efficacy can be considered leaky when they do not sufficiently prevent viral transmission and have the potential to bring about more virulent strains (Read et al. 2015). In the legal and policy literature, Edmonds and colleagues (2020) and Vural, Herder, Graham (2022) caution on agile regulations that loosen previous standards (El Zarrad et al. 2022). Agile regulation advances leaky products that have undergone fewer clinical trials and have incomplete risk data. In so doing, it has paved the way to "fast-track unproven medication and divert funds from other health needs" (Morgan et al. 2023). We adopt the concept of leaky vaccine to interrogate suboptimal vaccines being pushed for market approval before they can meet the efficacy and safety standards of existing routine childhood vaccines that are globally available. As such, leaky vaccines occupy a liminal space between proven safe and highly efficacious vaccines (for example, measles vaccine) and vaccine candidates not ready for population rollout despite marketing hype and the public health endorsement that may accompany them. We acknowledge at the outset that this is a politically sensitive and dangerous ground to tread for anthropologists who are unequivocally *not* anti-vax in a climate when there is heightened awareness that political ideology is one of the potential drivers of the success of vaccination campaigns and researchers who question new products can be cancelled (Agarwal, Dugas, Ramaprasad 2021; Bardosh et al. 2022; Peng 2022).

With the wide introduction of an agile regulatory ecosystem since 2019 and the onslaught of COVID-19 vaccines and other bio- and genetic therapies arising from COVID-19 research, we can expect that more health products will be moving more rapidly through lower regulatory hurdles and why this may not be good for our common health. In this same space, and while no one can view the long history of the RTS,S malaria vaccine development as "fast-track," we consider how candidate vaccines such as RTS,S, which have required many more years of clinical trials, are now achieving approval despite their leaky profile. Drawing particularly upon the case of malaria, we explore how regulatory leniency toward leaky vaccines may be on an upswing and consider the implications for public trust, vaccine hesitancy and population health. We suggest that looser regulations are prematurely pushing leaky vaccines into real world implementation that have potentially negative implications. We also show that some vaccines have been licensed that prove to be leaky and less fit for purpose over time. Finally, engaging beyond the technical into the socio-moral dimension (Good 1993; Wexler 2009) of regulatory assessment, we suggest addressing leaky vaccines via a symmetrical approach (Graham and Jones 2016;

Latour 1993; Stengers 2005) that accommodates social, political, ecological, biological and technical constituents as a "complex, intractable, open-ended … wicked problem" (Head 2018).

## What's the Problem with a Leaky Vaccine and Why is it Important?

There are various considerations regarding what constitutes a safe vaccine. The harm-benefit balance in populations at significant risk of a disease is weighted differently in less at-risk populations. Both different and changing contexts demand different harm-benefit considerations, as was learned with the roll-out of the first-generation rotavirus vaccine. The early rotavirus vaccine resulted in serious adverse events following vaccination (intussusception) when implemented in populations with significantly less risk from the disease (Clark et al 2023; CDC 2023). Highly efficacious against the virus, it was only 30 percent effective against diarrhea, and serious but rare side effects were discovered to have different safety-harm profiles in different populations (O'Ryan 2017).

Just as heterogeneity in population exposure can challenge the metrics of effectiveness and safety of vaccines in specific populations, the impact of replacement effect by a newer variant of the disease on planetary ecosystems is a serious challenge. The disquiet among both parasitic malaria and bacterial meningitis researchers surrounding ecological shift and the evolution of different and more virulent and intense strains (Broutin et al. 2018; Graham 2016; Read et al. 2015) gained wider public awareness as the world witnessed and experienced new COVID-19 variants. In naïve populations with no previous exposure to dengue, clinical trials showed that a condition known as antibody-dependent enhancement prevented the immune system from blocking the virus, which can multiply and trigger hemorrhagic dengue fever (Märzhauser 2018). Like dengue, malaria is a mosquito-vectored disease where poverty and socioeconomics collide against multiple biological and environmental factors (Ashepet et al. 2021; Janssen and Martens 1997; Muurlink and Taylor-Robinson 2020). The collision and collusion of these constituent actors can create chaos in the development of any vaccine.

So, too, driven by consumer demand, new vaccines have emerged with arguably less immunogenicity and a leakier profile than the previous ones they have replaced. The acellular pertussis vaccine, for example, shows rapidly declining effectiveness compared to the whole-cell vaccine (Schwartz et al. 2016; Alghounaim et al. 2022). Despite this, the acellular vaccine has been widely

adopted in the global North largely because of fewer side effects (less pain at the site of injection, less post-vaccination fever, and better healthcare when there are outbreaks). It is worth noticing that COVID-19 vaccines, although praised at the outset for their high efficacy, failed to sufficiently address the continued transmissibility of the virus and its emerging variants (Franco-Paredes 2022). Pandemic urgency and early announcements of what proved later to be an inflated estimate of the effectiveness of the COVID-19 vaccines in reducing transmission catapulted COVID-19 vaccines into early approval given their life-saving potential despite uncertainty about safety (Prugger et al. 2021).

The relationship between the leakiness of the COVID-19 vaccines and community perceptions and acceptance was largely unknown in the early years of the pandemic. Research went on to show that COVID-19 deaths and low vaccination rates that mapped to ideologically Republican states in the US raised awareness that politics, beliefs and attitudes can determine their health activities (Albrecht 2022). As agile regulations arrived to accelerate products to market, a global infodemic of facts and conspiracy theories demanded greater transparency in evidence and decision-making and active engagements to build trustworthiness rather than relying on a generic public's implicit or unconditional acceptance of vaccines. Even before the COVID-19 pandemic, the WHO cited vaccine hesitancy as one of the top ten health threats to the world (WHO 2019), signalling concerns in public health circles about vaccination as highly suspect.

Escalating mistrust and fear that rapid vaccine development may undermine vaccine safety were aggravated by their short-lived effectiveness and the emergence of vaccine nationalism (Goodman et al. 2020), heated public debates on social media and rallies about the need for a vaccine, and proliferating anti-vaccination sentiments related to "post-truth" perceptions such as increased skepticism towards science and authorities in general, as well as towards vaccine safety and effectiveness (Bardosh et al. 2022). This distrust of science and scientists has been linked to multiple concomitant societal changes: the receding role of independent experts and impartial expert knowledge combined with the growing "management" and commercialization of science, proprietary protections and lack of transparency around research procedures and data (Fraiman et al 2022). Moreover, perceived collusion between political elites and so-called experts with conflicts of interest with pharmaceutical companies has contributed to this distrust.

## Some Questions about Malaria Vaccines from a Critical Anthropology Perspective

Meanwhile, in the territory of endemic malaria, concerns about the safety of the GSK RTS,S vaccine slowed its approval for years (RTS,S Clinical Trials Partnership 2014). Licensing arrived only just before the Oxford/Serum Institute of India's malaria vaccine (R21/Matrix-M) appeared on the landscape. Cautionary concern about implementing a leaky malaria vaccine that might be limited in reducing disease or its transmission and/or result in serious adverse events that would increase vaccine hesitancy slowed the approval of RTS,S for a decade. And therein lies the rub in regulating new products with uncertain safety concerns. Is faster better? And does slow but steady come at a cost to equity? Vaccines with low efficacy, such as the GSK RTS/S malaria (Mosquirix™) vaccine, pose particular concern for scientists and public health professionals when vaccinated individuals may have only partial protection (Otto et al. 2021). Some argue that leaky malaria vaccines should be used if proven safe and effective as long as they are used in combination with additional protective measures that reduce transmission (Kupperschmidt 2015). This argument was consistent with that made by the manufacturer GSK and its multilateral advocates promoting the RTS/S malaria vaccine, as a complement to existing well-documented preventive measures for malaria, such as mosquito pesticides, bed nets, and environmental sanitation programs. It was also consistent with the approach taken by the European Medicines Agency (EMA), the regulatory authority for the GSK vaccine and the official scientific opinion of the vaccine. The European Medicines Agency concluded:

> Despite its limited efficacy, the benefits of Mosquirix™ outweigh the risks… Because the studies showed that Mosquirix™ does not offer complete protection, and the protection it provides decreases in the longer term, it is important that established protective measures, for example, insecticide-treated bed nets, continue to be used in addition to the vaccine (EMA 2015).

Although Mosquirix™ is currently deemed "safe" by GSK (2016, 2023a, 2023b), WHO (2021) and CDC (2024), the CDC (2021) had acknowledged "a few safety signals that warranted further study" in 2021 and the assessment of safety remained contested (for example, Björkman and colleagues 2023). Rolling out, from an ecological standpoint, the safety of RTS,S will have to be determined by an entirely different set of measures. That the vaccine's poor showing of efficacy and immunogenicity were widely seen as "inadequate, limited, poor" by

scientific authorities but still approved for wide dissemination in three African countries requires more information than a review of the current scientific literature answers. Why did WHO change direction from their 2013 goal of a malaria vaccine with 80 percent efficacy (WHO 2015) to their acceptance of 39 percent efficacy (WHO 2020)?

To explore why leaky vaccines are acceptable and qualified as efficacious health interventions, we provide comparisons with the rapid development and implementation of the COVID-19 vaccines while focusing on the longer trajectory of the RTS,S malaria vaccine. Despite the downgrading of the COVID-19 pandemic by the International Health Regulations (IHR) Emergency Committee to an "ongoing health issue which no longer constitutes a public health emergency of international concern (PHEIC)" (IPAC 2023), COVID-19 vaccination campaigns continue. We also consider ontological, epistemological and global health assumptions that shape the evidence for the funding and implementation of a malaria vaccine (RTS,S) that has 39 percent efficacy in light of another promising malaria vaccine (R21) with as high as 77 percent efficacy being readied for seasonal malaria in the global South.

Through critical ethnographic insight from a combined 40 years in the anthropological field of global vaccine development and malaria research we pose a series of questions which strike at the heart of the development of what we suggest are less effective, leaky vaccines. More than a decade after Osterholme and colleagues' (2012) critique of the lack of serious advancement of effective influenza vaccines, we consider the implications of leaky vaccines for public trust and population health. At the centre is concern about the moral basis of profit when disease becomes a market opportunity. With the regulatory trend, pushed by industry to commercialize science earlier, who gets to decide whether leaky vaccines trump other public health techniques, what informs such decisions, and whose interests are being served?

We question why and how the adoption of agile regulatory standards has acquiesced towards earlier *conditional* approval and rolling out of leaky vaccines. We consider the extent to which public health emergencies speed up and/or reduce the development of safer and more effective vaccines amidst growing contextual evidence that while faster routes to market flourish, so do inadequate general health systems where people might be better protected from conditions that cause the disease, and where those diseases might be better detected, monitored and treated as well as prevented.

## The Malaria Vaccine

Although malaria is seldom considered in emergency pandemic planning scenarios, its persistence in the global South continues to challenge the scientific practices of vaccinology and regulation as well as WHO principles of "better health for all." The WHO African Region carries a disproportionately high share of the global malaria burden. In 2021, the region was home to 95 percent of malaria cases and 96 percent of malaria deaths. Children under five accounted for about 80 percent of all malaria deaths in Africa (WHO 2023).

A vaccine for malaria has long drawn scientists' interest, with the first promising results published by the Colombian immunologist, Manuel Patarroyo (1988). While Patarroyo's vaccine never attained higher than 28 percent efficacy in his South American studies, it caught the interest of Pedro Alonso (IS Global), the former Director of the WHO Global Malaria Programme responsible for coordinating efforts to control and eliminate malaria and establish norms, technical guidelines and policies to support countries affected by this disease. Invigorated in 2001 by Bill and Melinda Gates Foundation's funding and mobilization of the Malaria Vaccine Initiative, which focused on supporting industry ventures, serious global effort to develop the first malaria vaccine candidate, RTS,S, began in partnership with GSK Bio and the PATH Malaria Vaccine Initiative as well as African and other research organizations. Importantly, in 2013, WHO's Malaria Vaccine Technology Roadmap set the goal for "malaria vaccines with protective efficacy of at least 75 percent against clinical malaria" (WHO 2013). The first studies of the RTS,S Clinical Trials Partnership (2014) found at best 46 percent vaccine efficacy against clinical malaria and acknowledged the important role of other control mechanisms beyond the vaccine alone. Recognizing the importance of other interventions against malaria, the vaccine's partial success was presented as "*an important addition* to current malaria control in Africa" (italics added).

## Combining Existing Preventive Measures to Increase the Efficacy of the GSK RTS,S Malaria Vaccine

RTS,S/AS01 was approved by the EMA in 2015 and rolled out in 2019 in a pilot program in Malawi, Ghana and Kenya. With the engagement of multilateral actors brought by Gates' support in 2001 and WHO SAGE's unilateral endorsement in 2016, the GSK-manufactured vaccine RTS,S/AS01, patented as Mosquirix™, quickly moved from scientific apprehension to financialization for an internationally sanctioned pilot implementation program in Ghana, Kenya

and Malawi in 2019, despite evidence that its efficacy still only ranged between 29 and 39 percent in Phase 2 trials with the age of the immunized and bed net use taken into account.

Those studies estimated that it could reduce 30 percent of severe malaria cases and 21 percent of hospitalization after four doses (WHO 2021). Considerable debate remains in the scientific community on its value, however, given such low efficacy (Björkman et al. 2023). Notably, the vaccine provides protection using other effective malaria prevention and treatment interventions, such as bed nets, antimalarial drugs for disease treatment, indoor residual insecticide spraying to prevent mosquito-borne transmission, and drugs to protect pregnant women and their newborns from malaria. Acknowledging only modest vaccine efficacy, Klein and colleagues (2016) reported safety concerns when RTS,S was associated with higher all-cause mortality in girls and suggested that "the sex differences in all-cause mortality needed rigorous study in both clinical trials and experimental animal models." Chandramohan and colleagues (2021) showed that while RTS,S was non-inferior to chemoprevention in preventing uncomplicated malaria: it was the *combination* of interventions that led to a lower incidence of malaria.

The difference between aspirational and actual achieved ambitions collapses in institutional accounts of the metrics, timelines and contexts needed to prove vaccine safety, efficacy and quality. The World Health Organization's threshold for licensing "[T]o be approved, vaccines are required to have a high efficacy rate of 50% or above" (WHO 2021) was collapsing under the need for pandemic COVID-19 vaccines. The RTS,S vaccine had already gained ground in Phase 3 trials and was the "first, and, to date, the only vaccine to show a protective effect among young children in a Phase 3 trial" (WHO 2020). Early on, WHO had acknowledged that the "RTS,S is only partially effective" and therefore "it will be essential that any vaccinated patients with a fever be tested for malaria, and that all those with a confirmed malaria diagnosis are treated with high quality, effective anti-malarial medicines" (WHO 2016). Accepting those limitations, WHO agreed that the vaccine should not replace other preventive techniques, such as nets or existing medication, and recognized these other preventive techniques as necessary to achieve a desirable standard of effectiveness unattainable by the vaccine alone. Importantly, the RTS,S vaccine would consequently be billed and marketed as a *complementary tool* rather than a replacement (WHO 2020). Surprisingly, considering the emphasis on the complementarity of interventions and the presence of studies in contexts of high

coverage of other control strategies, there is little evidence of the interaction of vaccine introduction with the effectiveness of existing control strategies (Dabira et al 2022). Anthropological work has long shown how social factors are key to the effectiveness of malaria interventions and how the introduction of new tools will change local perceptions of the efficacy of existing tools and impact disease etiology perceptions (Gryseels et al. 2013) and consequent health-seeking itineraries (Fehr et al. 2021; Gryseels et al. 2015, 2019; Jaiteh et al. 2019, 2021a, 2021b; Masungaga et al. 2021; Muela Ribera et al. 2016; Nguyen et al. 2021; Peeters Grietens et al. 2012, 2013, 2015, 2019, 2021). Clearly different prevention, control and elimination strategies will interact, potentially limiting or increasing the success of others. As an example, will general and COVID-19-related vaccine hesitancy limit the uptake of malaria vaccines and diminish adherence to other interventions due to increased distrust in public health programs and hence limit the overall progress towards malaria elimination?

The RTS,S Clinical Trials Partnership (2014) reported early trial results for the GSK and PATH Malaria Vaccine Initiative, later highlighting its "good safety profile" in 2015. While the candidate vaccine's ability to "avert" malaria in children was highlighted, its extremely low efficacy in infants aged six to 12 weeks, or in forest workers received less attention. With the support of the Gates PATH-WHO Malaria Vaccine Initiative, the power and authority of global scientific attention advanced RTS,S development despite acknowledgment of its low efficacy and immunogenicity, never meeting the WHO's required protective efficacy of 70 percent. Studying a different vaccine candidate, Dinga and colleagues (2018) reported that Mosquirix™ at best "has an efficacy of 30% - 60% that wanes rapidly" and insisted that second-generation malaria vaccines would need to be much better than this. Goddard-Borger and Boddey (2018) reported a "sub-optimal" 18 to 31 percent range in efficacy; protection from the GSK vaccine not only waned over time but rebound cases of malaria often followed.

Additionally, caution may be needed in measuring efficacy in non-endemic countries for vaccines intended for endemic countries (Good and Miller 2018). The protective alleles that have immunogenicity for the GSK vaccine that were testing in Phase 2 trials in the UK and US, for instance, have a much lower prevalence in sub-Saharan populations (Nielsen et al 2018). In a Phase 3 RTS,S trial, this difference in immunogenicity resulted in only 26 percent efficacy in the "intention to treat" population in sub-Saharan Africa, despite reporting 36.6 percent efficacy in the "per-protocol" population (RTS,S Clinical Trials Partnership 2012). This problem had already been reported in previous trials

of another malaria vaccine candidate, PfSPZ, where it also resulted in poor immunogenicity (Olotu et al. 2018). Another Phase 3 trial reporting the highest efficacy to date for the GSK vaccine, 45.7 percent, however, notes inconsistent immunogenicity requiring further analysis (Moris, Jongert, van der Most 2018). Like the RTS,S Phase 3 trials, biases inherent in industry-sponsored clinical trials typically favour higher rates of success (Lundh, Lexchin, Mintzes, Schroll, Bero 2017).

For many, there seems little doubt that current tools to address malaria, including the GSK vaccine, are inadequate (Ninwe, Kusi, Adu, Sedegah 2018). To contain and redefine the approval landscape beyond the efficacy rate of the vaccine itself, and thereby qualify the vaccine, researchers thereafter adopted the co-constituent factors that elevated the vaccine's efficacy, while concluding that "the question of malaria vaccines is no longer 'if' but instead, 'when, for which purpose, and with what efficacy' " (Coleho, Doritchamou, Zaidi, Duffy 2017).

## Justifying a Leaky Vaccine

GSK promotes the RTS,S vaccine as *a complementary tool*, building malarial control mechanisms outside of the vaccine itself into their case for efficacy (GSK 2016; GSK 2023a; GSK 2023b). Backstepping from the original goal of high efficacy vaccines, a new narrative gained ground that constructs a case for the approval of the RTS,S malaria vaccine based upon humanitarian response and children's lives saved. One scientist stated "[e]ven a partially effective vaccine could have a significant impact on the health of African children. In this context, I was pleased to see GSK has committed to make the vaccine available on a not-for-profit basis" (GSK 2023b). Sir Brian Greenwood submitted that the

> RTS,S vaccine does not provide complete protection but this decision is testament to the global health community's drive and vision to find a way forward. As part of a tailored approach it has great potential to reduce death and illness in high burden areas, especially when combined with other interventions such as seasonal malaria chemoprevention and bed nets, and be a huge boost to malaria control efforts. (Greenwood 2021).

Introduction of this low efficacy malaria vaccine has not been without criticism (Maxmen 2019; Miura 2016). Calling for a more effective vaccine, Prosper and colleagues (2014) raised concerns that such vaccines can undermine the development of natural immunity while infection remains possible, leading to more severe malaria. Into this gap the R21/Matrix-M™ vaccine appeared, with reports of 77 percent efficacy (Phase 2) for *seasonal* malaria (Datoo et al.

2021), increasing to 80 percent in a two-year follow-up study, a target in line with the original WHO target of 75 percent (Datoo et al. 2022; WHO 2013). The R21/Matrix-M vaccine was licensed in Ghana in May 2023 (University of Oxford 2023) and is being tested in a Phase 3 trial (VAC78) in different malaria transmission settings, including Burkina Faso at time of writing. It took years to build the evidence for the RST,S approval, leaky as it is. Its licensing just before the approval of the at least as effective R21/Matrix-M vaccine that is cheaper and has vastly greater manufacturing capacity, allows GSK to recover some costs of its development. It is not an uncommon tactic to reimburse industry when a more affordable vaccine is near.

Emerging infectious diseases predictably gain priority, diverting research funding from time-worn diseases such as malaria. Well before the COVID-19 pandemic, Andrew Lakoff (2007) wrote of preparedness for the emergence of a global health catastrophe as the "new paradigm of emerging infectious diseases." The inevitability of a Pathogen/Epidemic X has been acknowledged for decades; the SARS-CoV-1 outbreak of 2003 spurred on UN member states to endorse pandemic preparedness in the International Health Regulations (WHO 2005). Though both the West African Ebola epidemic and the COVID-19 pandemic showed that very little had been done towards preparedness, heavy financialization of biosecurity by a military industrial enterprise did proceed, and work continued on vaccines against SARS, EVD, zika, chikungunya, dengue, and influenza throughout the first two decades of the twenty-first century. As public health emergencies were declared, funding targeted the most imminent threat. One might expect that their persistence would be a wild card to incentivize further financial capital to improve surveillance and public health preparedness strategies as much, it seems, as to address the root biological causes of these sicknesses. Instead, while market incentives push forward vaccine development, preparedness through strong health systems and other non-pharmaceutical interventions remain relatively neglected.

Despite the constellation of social, biological and environmental factors contributing to both old and new disease outbreaks, hope for a successful response to the next pandemic is typically presented as dependent on the rapid development of new biotechnologies, including vaccines. The cavalcade of announcements for the *Coalition for Epidemic Preparedness Innovations* (CEPI) initiative to develop and stockpile vaccines for future pandemic threats after the West African Ebola epidemic (Bente et al., Butler 2017; Røttingen et al. 2017) in many respects blinded the global response effort from considering more than

vaccine strategies, while paradoxically, the effectiveness of the vaccines becomes increasingly dependent on a plurality of other factors for preparedness and disease response beyond vaccine development (Ross 2017). Complementary malaria control that does not assume the vaccine's intervention alone is an example.

Narratives of single intervention outcomes seldom tell the whole story. As the international community increasingly responds to threats of pandemic infectious disease outbreaks in the Anthropocene where climate, environmental and political pressures, amplified by global migrations, challenge existing models of human behaviour, there is a need to assert caution that the technologies, including vaccines being developed, and the strategies to assure their uptake, meet the highest standards for quality, immunogenicity, efficacy and safety.

As mentioned, the slow progress of malaria vaccines can be contrasted with the exceptionally rapid development of COVID-19 vaccines. Developed in less than one year and marketed worldwide long before data were complete and sufficiently analyzed (Doshi 2020; Fraiman et al. 2022), concerted activities by the global community, and notably, the multilateral ACT-Accelerator partnerships, drove COVID-19 vaccine development (WHO 2023a). While recognizing that parasitic, vector-borne (malaria) and viral (COVID-19) diseases are significantly different, the global vaccine development assemblage is common to both. The time taken to build the evidence base for approval, the kinds of evidence (and information) that are created, and especially the multilateral industry actors involved play significant roles in both. Still, transparent and open-access to the decision-making processes cannot be assumed—data are not widely available and remain protected by intellectual property agreements between governments and industry.

Since 2019, new agile regulations swayed regulators in the global community, easing previous requirements for completed Phase 3 studies and allowing efficacy based upon the "contribution" of other preventative mechanisms beyond the vaccine itself (Edmonds et al. 2020). The prospect for solutions to the radical inequity in access to vaccines may come about through the funding of other manufacturers in the global South that advance different types of public platforms (for example, Health Justice Initiative 2023) beyond private industry solutions such as the Serum Institute of India (SIIL 2023), which was incentivized through technology transfer by the early Gates' initiatives. More and more PHEICs, and global recognition of a next Pandemic X around the

corner will push vaccine development and the international community to respond with equitable solutions. The COVID-19 pandemic taught the world that attention to temporality and context, and to a combination of other factors (for example, community safety measures, sustained and accessible community clinics and treatment centres, manufacturing and sufficient supplies of equipment for hygiene and masking when needed, feasible techniques for social distancing for the poorest and most vulnerable, safe transport to safe workplaces) are needed across the global South and North, and that new technologies inevitably land in the hands of the rich.

Over a decade ago, WHO's Global Vaccine Blueprint expressed concern that the lack of competition in vaccine manufacturing might hinder access to affordable vaccines (Graham et al. 2012). Oxford/SIIL's R21/Matrix-M malaria vaccine is a clear "encouragement" for GSK to lower the high price they have put on their RTS,S vaccine. Insisting on a higher price than the less expensive R21/Matrix-M, GSK will be unlikely to sustain its costs; the R21/Matrix-M malaria vaccine can be manufactured in significantly greater amounts (100 million doses annually compared to six million for RTS,S) (Gavi 2023; SIIL 2023; University of Oxford 2023) guaranteeing a global market at one-quarter of the cost. Furthermore, there is growing acceptance that at least three and likely four doses of the RTS,S vaccine will be needed for ongoing seasonal campaigns. Non-inferiority studies are anticipated to demonstrate comparability between the two vaccines. In both vaccines, public health measures will need to continue to augment the vaccines' modest efficacy.

The history of malaria vaccine development during the first two decades of the twenty-first century point to partnerships and coalitions working on a lead vaccine (for example, GSK's RTS,S and SIIL/Oxford's R21/Matrix-M). Apart from the technical requirements of development, cost and conditions remain a vital ingredient determining a vaccine's adoption. Private manufacturers, such as GSK in the RTS,S vaccine and Pfizer and Moderna in the case of mRNA COVID-19 vaccines preserve the opportunity for significant profits in undisclosed agreements between industry and governments. As was evident with the rVSV-ZEBOV Ebola vaccine, much vaccine development is conducted by public sector government labs and university research teams (Herder, Graham, Gold 2020). Purported not-for-profit agreements take on a life of their own when proprietary rights and access to information limitations prevent disclosure of actual costs. Not-for-profit is not free, and there is a large difference in accessibility and equity when vaccine manufacturers' claims of their cost are not subject to

independent transparency and accountability assessment. After the WHO recommendation of the RTS,S vaccine, the Gavi Vaccine Alliance board decided to fund a malaria vaccination program in Gavi-eligible countries to expand the vaccine's introduction (MVI PATH 2022). Politics and cost configure into technical factors when considering purchasing, in both high- and low-income settings.

Complementary protective measures have been used to clear the efficacy barrier for RTS,S. In a global industry where competition purportedly reigns supreme, the twist with the development of R21/Matrix-M was that a global southern manufacturer (Serum Institute of India) was coming along the inside of GSK'S RTS,S vaccine. Backed by the Gates Foundation since 2003 (Graham 2016), SIIL has grown into the world's largest vaccine manufacturer. The WHO's Global Vaccine Blueprint strategy has long worked to build affordable vaccines into global vaccine pricing, a path that has been paved most particularly by and for the SIIL to corner the market on global vaccines. The early priming of a market by the GSK vaccine allowed Oxford/SIIL a small window into selling the new R21/Matrix-M malaria vaccine, but their capacity to manufacture enough vaccine at an affordable price will predict its success. In comparability studies that will follow, it will be interesting to see to what extent the R21/Matrix-M vaccine will also need to depict its effectiveness as dependent on the combination of other prevention strategies. While GSK initially promoted their vaccine as not-for-profit, the price point is significantly higher than its competition, SIIL's R21/Matrix-M. The RTS,S vaccine's relatively low efficacy has been quieted, diverted by situating its value as a humanitarian act rather than a sleight of hand that challenges scientific efficacy standards. These signs of the WHO Blueprint's success in constraining unfettered profit, however, should not blind regulators or governments to the concerns addressed by leaky vaccines described in this article.

There is no doubt that malaria vaccines hold significant promise for life-saving benefit, especially to children who bear the major burden of malaria mortality. And as we have seen, as the RTS,S/AS01 malaria vaccine continues to be tested in implementation studies, even newer vaccines are catching up (Laurens 2021). Multiple strategies are being advanced to test next-generation malaria vaccines, including other novel approaches that build on principles learned from RTS,S development, vaccination with radiation-attenuated sporozoites, and development of monoclonal antibodies targeting immunogenic peptides. Novel vaccine delivery approaches are also being advanced, including

self-amplifying RNA vaccine delivery, self-assembling protein nanoparticle methods, circumsporozoite protein-based approaches, and whole organism vaccination. New mRNA techniques, sustained release polymer nanoparticle hydrogel vaccination and charge-altering releasable transporters are all in the development pipeline. As vaccine science advances and new approaches optimize knowledge gained, highly effective malaria vaccines that provide sustained protection are within reach. What effect will leaky vaccines have in disrupting both public trust in vaccines and the science that produces them? Our concern remains that leakiness may become a matter of no consequence to a vaccine's market approval. Industry agendas masquerading as humanitarian aid or emergency response cannot allow open season for permeability in the regulatory standards of quality, efficacy and safety of vaccines.

## Conclusion

An anthropological lens helps in challenging the loosening of standards and taken-for-granted assumptions of a global regulatory apparatus. It recognizes that equity, access, trust and effectiveness are in ongoing relationship with safety, efficacy and quality via regimes for reflexive openness, transparency and accountability. Global vaccine logics driven by capitalist concerns of speed to market and industry profits may be undermined by the Global Vaccine Blueprint's intention to incentivize competition in the vaccine industry to lower prices. The Research and Development of vaccines has been driven by global actors who include science, clinics, market fundamentalism, financialization, health and biosecurity threats, economic and ecosystem failures. This global assemblage is often seen and analyzed without the presence of the public among the concerned stakeholders.

The assumption that the same vaccines will work equally well on everyone, that a standardized universal solution works for all bodies in every context, has driven vertical global health programs. The monovalent meningitis A vaccine that works well in a highly endemic Men A landscape offers little solace in the real world of multiple subtypes of meningitis. People vaccinated against Men A need to understand that it is but one subtype of the virus, and that they remain susceptible to others. Four different strains of dengue can lead to a vaccine gap. Should a new strain of malaria develop given a leaky RTS,S vaccine, as has happened with COVID-19 variants, newer vaccines will continually need to be developed to protect against the emerging strains. The ethics of humanitarian response should never be dependent on a universal fix or false assumptions of

biological commensurability (Lock and Nguyen 2011). Premature roll-outs of leaky vaccines will threaten different people differently everywhere.

Not all markets are the same, and not all vaccines belong in all marketplaces. As we have seen, socio-political-economic and environmental differences can have serious consequences for any vaccine's effectiveness and safety. This paper shows that the same vaccine for all everywhere is not necessarily advantageous. As vaccines and human-vaccine interactions become more complex in a growing number of combinations and multi-valent doses, the preventative and therapeutic contributions of the constellation of vaccines coming down the pipe must consider a more contextualized array of constituent elements towards a common goal, indeed a common good of equitable social and generational justice (Stengers 2005). We have applied a Latourian (1996) symmetrical approach to malaria vaccine development incorporating the biological and social in paving the success of RTS,S vaccines. Our concern remains, however, with the uncertain future of a leaky vaccine subject to the constellation of biological, environmental and cultural factors.

The capitalist logic that commercial drivers are a solution to health for all is misplaced, along with an economic model where partially disclosed advance market commitment agreements are used to counter higher prices at first release of a vaccine favouring the wealthy (Zeng 2018). Forty years of structural adjustment has largely hollowed out public health systems that could detect infectious diseases, monitor vaccine adverse events and treat people in local communities (Graham 2016). Instead, a regulatory science is needed that can address equitable vaccine development and access in the interests of safety, effectiveness, public trust and health for all rather than for corporate profits. Making the data for vaccines open and transparent throughout their development would champion scientific integrity, public trust and industry accountability.

The COVID-19 crisis raised recognition that vaccines (and their failures) are a coproduction of geopolitics and economics. Leaky vaccines most particularly are wicked problems, trying to fix a complex array of neglect and messy details involving bacterial, viral and animal vectors in diverse ecologies that are shaped by any number of intractable cultural, biological, environmental, human and non-human factors. Recognition and wider discussion are needed with all publics that regulatory assessment and vaccine approval and public health decisions may sometimes be based on uncertain evidence. Regulatory assessment is technical, yes, but it is also a political act; vaccine uptake and

hesitancy are driven by ideology as much, perhaps more than by science. Rather than sidelined, the concept of leaky vaccines might be embraced by vaccine research communities and put to use to produce better vaccines, as suggested by Osterholm and colleagues (2012) over a decade ago. Or it can be hushed to silence the real need for better public health systems, access and standards.

The lack of transparency in access to scientific data and all considerations made by closed committees who decide on a vaccine's increasingly conditional approval remains a concern for open data advocates. It is possible that malaria vaccine development as well as other public health responses may have languished, potentially held up by a single vaccine's hegemony over other interventions. The early priming of a market for the GSK leaky vaccine depicts a cooked scenario of the vaccine's partial effectiveness as a positive outcome and GSK's generosity in planning to sell the vaccine at a not-for-profit price point. The vaccine's low efficacy is spun as a benevolent charitable act rather than a sleight of hand that challenges scientific regulatory standards, or at least earlier scientific challenges that were chopped away during the second decade of the twentieth-first century. The endgame of industry is not open science. In the afterworld of the COVID-19 pandemic, mRNA technologies have now arrived on the scene for innumerable forms of vaccine and cancer agents and will be filling the regulatory pipe for years to come, helped along by adaptive clinical trials and agile regulatory modernization. And the profits to industry will roll in, as they benevolently hand out last year's magic bullets to the world's poorest as a tax write-off.

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## References

Agarwal, Ritu, Michelle Dugas, and Jui Ramaprasad. 2021. "Socioeconomic Privilege and Political Ideology are Associated with Racial Disparity in COVID-19 Vaccination." *Proceedings of the National Academy of Sciences* 118 (33) e2107873118. https://doi.org/10.1073/pnas.2107873118.

Albrecht, Don. 2022. "Vaccination, Politics and COVID-19 Impacts." *BMC Public Health* 14 22(1): 96. https://doi.org/10.1186/s12889-021-12432-x.

Alghounaim, Mohammad, Zainab Alsaffar, Abdulla Alfraij, Saadoun Bin-Hasan, and Entesar Hussain. 2022. "Whole-Cell and Acellular Pertussis Vaccine: Reflections on Efficacy." *Medical Principles and Practice* 31 (4): 313–321. https://doi.org/10.1159/000525468.

Ashepet, Mercy G., Liesbet Jacobs, Michiel Van Oudheusden, and Tina Huyse. 2021. "Wicked Solution for Wicked Problems: Citizen Science for Vector-Borne Disease Control in Africa." *Trends in Parasitology* 37(2): 93-96. https://doi.org/10.1016/j.pt.2020.10.004.

Azuma, Kentaro. 2015. "Regulatory Landscape of Regenerative Medicine in Japan." *Current Stem Cell Reports* 1: 118–128. https://doi.org/10.1007/s40778-015-0012-6.

Bardosh K., A. de Figueiredo, R. Gur-Arie, E. Jamrozik, J. Doidge, T. Lemmens, S. Keshavjee, J.E. Graham, and S. Baral. 2022. "The Unintended Consequences of COVID-19 Vaccine Policy: Why Mandates, Passports, and Restrictions May Cause More Harm than Good." *BMJ Global Health*. https://gh.bmj.com/content/bmjgh/7/5/e008684.full.pdf.

Björkman, Anders, Christine Stabell Benn, Pater Aaby, Allan Schapira. 2023. "RTS,S/AS01 Malaria Vaccine -Proven Safe and Effective?" *Lancet Infectious Disease* 23 (8) e318-e322. https://doi.org/10.1016/S1473-3099(23)00126-3.

Bothwell, L.E., J.A. Greene, S.H. Podolsky, and D.S. Jones. 2016. "Assessing the Gold Standard—Lessons from the History of RCTs." *New England Journal of Medicine* 374(22): 2175–2181. https://www.nejm.org/doi/10.1056/NEJMms1604593. (Accessed 29 August 2024).

Brende, B., J. Farrar, D. Gashumba, C. Moedas, T. Mundel, Y. Shiozaki, H. Vardhan, J. Wanka, and J.A. Røttingen. 2017. "CEPI—A New Global R and D Organisation for Epidemic Preparedness and Response." *Lancet* 389(10066): 233–235. https://doi.org/10.1016/S0140-6736(17)30131-9

Broutin, Hélène, O. Thiongane, L. Agier, I. Van-Engelgem, J.-P. Jemmy Ghomsi, A. Ouattara, M. Doutchi, H.B. Manassara, A.T. Dia, and J. E. Graham. 2018. "Fighting Meningitis in Africa: A Call for a Multi-Sectorial Action." *Journal of Tropical Medicine and Health*. JTMH-129. https://www.gavinpublishers.com/article/view/fighting-meningitis-in-africa-a-call-for-a-multi-sectorial-action.

Butler, D. 2017. "Billion-Dollar Project aims to prep Vaccines before Epidemics Hit." *Nature*. 26 January; 541(7638): 444–445. https://doi.org/10.1038/nature.2017.21329.

Centers for Disease Control and Prevention (CDC). 2021. Vaccines. https://web.archive.org/web/20200831141506/https://www.cdc.gov/malaria/malaria_worldwide/reduction/vaccine.html. (Accessed 29 August 2024).

——. 2023. "Rotavirus Vaccine (RotaShield®) and Intussusception." https://www.cdc.gov/vaccines/vpd-vac/rotavirus/vac-rotashield-historical.htm. (accessed 3 June 2023).

——. 2024. Malaria Vaccines. https://www.cdc.gov/malaria/php/public-health-strategy/malaria-vaccines.html (Accessed 29 August 2024).

Chandramohan, Daniel, Issaka Zonga, Issaka Sagara, Matthew Cairms, et al. 2021. "Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention." *The New England Journal of Medicine* 25 August. 385:1005–1017. https://doi.org/10.1056/NEJMoa2026330.

Clark, Andrew, Jacqueline Tate, Umesh Parashar, Mark Jit, M. Hasso-Agopsowicz, N. Henschke, B. Lopman B, K.Van Zandvoort, C. Pecenka, P. Fine, and C. Sanderson. 2019. "Mortality Reduction Benefits and Intussusception Risks of Rotavirus Vaccination in 135 Low-Income and Middle-Income Countries: A Modelling Analysis of Current and Alternative Schedules." *Lancet Global Health*. November 7(11): e1541-e1552. https://doi.org/10.1016/S2214-109X(19)30412-7.

Coleho, C. H., J.Y.A. Doritchamou, I. Zaidi, and P.E. Duffy. 2017. "Advances in Malaria Vaccine Development: Report from the 2017 Malaria Vaccine Symposium." *NPJ Vaccines* 2 (34) https://doi.org/10.1038/s41541-017-0035-3.

Dabira, E. D., H.M. Soumare, H.B. Conteh, F. Ceesay, M.O. Ndiath, J. Bradley, N. Mohammed, B. Kandeh, M. R. Smit, H. Slater, K. Peeters Grietens, H. Broekhuizen, T. Bousema, C. Drakeley, S.W. Lindsay, J. Achan and U. D'Alessandro. 2022. "Mass Drug Administration of Ivermectin and Dihydroartemisinin-Piperaquine against Malaria in Settings with High Coverage of Standard Control Interventions: A Cluster-Randomised Controlled Trial in The Gambia." *Lancet Infectious Diseases*, 22(4): 519–528. https://doi.org/10.1016/S1473-3099(21)00557-0.

Datoo, MS., H.M. Natama, A. Somé, O. Traoré, T. Rouamba, D. Bellamy, et al. 2021. "Efficacy of a Low-Dose Candidate Malaria Vaccine, R21 in Adjuvant Matrix-M, with Seasonal Administration to Children in Burkina Faso: A Randomized Controlled Trial." *The Lancet* 397 (10287):1809–1818. https://doi.org/10.1016/S0140-6736(21)00943-0.

Datoo, M.S., H.M. Natama, A. Somé, D. Bellamy, O. Traoré, T. Rouamba, et al. 2022. "Efficacy and Immunogenicity of R21/Matrix-M Vaccine Against Clinical Malaria after 2 Years' Follow-up in Children in Burkina Faso: a Phase 1/2b Randomized Controlled Trial." *The Lancet Infectious Diseases* 22(12):1728–1736. https://doi.org/10.1016/S1473-3099(22)00442-X.

Dinga, J.N., S.D. Gamua, S.M. Ghogomu, V.P.K. Titanji. 2018. "Preclinical Efficacy and Immunogenicity Assessment to show that a Chimeric Plasmodium Falciparum UB05-09 Antigen could be a Malaria Vaccine Candidate." *Parasite Immunology* 40(3): e12514. https://doi.org/10.1111/pim.12514.

Doshi, Peter. 2020. "Will COVID-19 Vaccines Save Lives? Current Trials aren't designed to tell us." *British Medical Journal* 371: m4037. https://doi.org/10.1136/bmj.m4037.

Douglas, Mary. 1970. *Natural Symbols: Explorations in Cosmology*. New York: Pantheon Books.

Douglas, Mary and Aaron Wildavsky. 1982. *Risk and Culture: An Essay on the Selection of Technical and Environmental Dangers*. Berkeley: University of California Press.

Edmonds, Sterling, Andrea MacGregor, Agnieszka Doll, Ipek Eren Vural, Janice Graham, Katherine Fierlbeck, Joel Lexchin, Peter Doshi, and Matthew Herder. 2020. "Transparency too little, too late? Why and how Health Canada should make Clinical Data and Regulatory Decision-Making Open to Scrutiny in the Face of COVID-19." *Journal of Law and the Biosciences* 7 (1) January-June 2020, lsaa083, https://doi.org/10.1093/jlb/lsaa083.

El Zarrad, M. Khair, Aaron Y. Lee, Rose Purcell, and Scott J. Steele. 2022. "Advancing an Agile Regulatory Ecosystem to Respond to the Rapid Development of Innovative Technologies." *Clinical and Translational Science* 15(6): 1332–1339. https://doi.org/10.1111/cts.13267.

European Medicines Agency (EMA) 2015. "First Malaria Vaccine Receives Positive Scientific Opinion from EMA." https://www.ema.europa.eu/en/news/first-malaria-vaccine-receives-positive-scientific-opinion-ema. (accessed 3 June 2023).

Fehr, A., C. Nieto-Sanchez, J. Muela, F. Jaiteh, O. Ceesay, E. Maneh, and K. Peeters Grietens. 2021. "From Informed Consent to Adherence: Factors Influencing Involvement in Mass Drug Administration with Ivermectin for in The Gambia." *Malaria Journal* 20(1), [198]. https://doi.org/10.1186/s12936-021-03732-z.

Fraiman, J. J., M. Erviti, S. Jones, P. Greenland, P. Whelan, R.M. Kaplan, P. Doshi. 2022. "Serious Adverse Events of Special Interest Following mRNA COVID-19 Vaccination in Randomized Trials in Adults." *Vaccine* 40 (40):5798–5805. https://doi.org/10.1016/j.vaccine.2022.08.036.

Franco-Paredes, Carlos. 2022. "Transmissibility of SARS-CoV-2 Among Fully Vaccinated Individuals." *Lancet Infectious Diseases* 22(1):16. https://doi.org/10.1016/S1473-3099(21)00768-4.

Gavi. 2023. "Five Things you Need to Know About the New R21 Malaria Vaccine." https://www.gavi.org/vaccineswork/five-things-you-need-know-about-new-r21-malaria-vaccine (accessed 3 June 2023).

Goddard-Borger, Ethan D. and Justin A. Boddey. 2018. "Implications of Plasmodium Glycosylation on Vaccine Efficacy and Design." *Future Microbiology* 13 (6): 609–612. https://doi.org/10.2217/fmb-2017-0284.

Good, Byron. 1993. *Medicine, Rationality and Experience.* Cambridge: Cambridge University Press.

Good, Michael F. and Louis H. Miller. 2018. "Interpreting Challenge Data from Early Phase Malaria Blood Stage Vaccine Trials." *Expert Review of Vaccines* 17 (3):189–196. https://doi.org/10.1080/14760584.2018.1435278.

Goodman, Jesse L, John D. Grabenstein, and M. Miles Braunn. 2020. "Answering Key Questions About COVID-19 Vaccines." *Journal of the American Medical Association* 324 (20): 2027–2028. https://doi.org/10.1001/jama.2020.20590.

Graham, J.E. 2016. "Ambiguous Capture: Collaborative Capitalism and the Meningitis Vaccine Project." *Medical Anthropology: Cross-Cultural Studies in Health and Illness* 35 (5): 419–432. https://doi.org/10.1080/01459740.2016.1167055.

Graham, J.E. 2019. "Ebola vaccine innovation: a Case Study of Pseudoscapes in Global Health." *Critical Public Health* 29 (4):401–412. https://doi.org/10.1080/09581596.2019.1597966.

Graham J.E., A. Borda-Rodrigeuz, F. Huzair, and E. Zinck. 2012. "Capacity for a Global Vaccine Safety System: The Perspective of National Regulatory Authorities." *Vaccine*, 30(33): 4953–4959. https://doi.org/10.1016/j.vaccine.2012.05.045.

Greenwood, Brian. 2021. Vaccine Decision Marks Historic Moment in Malaria Control. https://www.lshtm.ac.uk/newsevents/news/2021/vaccine-decision-marks-historic-moment-malaria-control (accessed 3 June 2023).

Gryseels, C., S. Uk, V. Sluydts, L. Durnez, P. Phoeuk, S. Suon, S. Set, S. Heng, S. Siv, R. Gerrets, S. Tho, M. Coosemans, and K. Peeters. 2015. "Factors Influencing the Use of Topical Repellents: Implications for the Effectiveness of Malaria Elimination Strategies." *Scientific Reports* 5 (16847). https://doi.org/10.1038/srep16847.

Gryseels, C., S. Uk, A. Erhart, R. Gerrets, V. Sluydts, L. Durnez, J. Muela Ribera, S. Hausmann Muela, D. Menard, S. Heng, T. Sochantha, U. D'Alessandro, M. Coosemans, and K. Peeters Grietens. 2013. "Injections, cocktails and diviners: therapeutic flexibility in the context of malaria elimination and drug resistance in northeast Cambodia." *PLOS ONE,* 8 (11): e80343. https://doi.org/10.1371/journal.pone.0080343.

Gryseels, C., M. Bannister-Tyrrell, S. Uk, S. Set, S. Sokha, R. Gerrets, and Peeters Grietens, K. 2019. "A Critical Enquiry into Variability of Insecticidal Net Use in Cambodia: Implications for Assessing Appropriateness of Malaria Elimination Interventions." *American Journal of Tropical Medicine and Hygiene*. 100 (6): 1424–1432. https://doi.org/10.4269/ajtmh.18-0730.

GSK. 2016. "Our Commitment to Fighting Malaria." https://www.gsk.com/media/2534/malaria-factsheet-23-feb-2016.pdf (accessed 3 June 2023).

——. 2023a. "Our 30-year Quest for a Malaria Vaccine." https://www.gsk.com/media/2212/malaria-timeline-full.pdf (accessed 3 June 2023).

——. 2023b. "Behind the science of GSK." https://www.gsk.com/en-gb/behind-the-science/access-to-healthcare/why-are-we-fighting-malaria-in-the-lab-and-on-the-ground/ (accessed 3 June 2023).

Halloran ME, M. Haber, and I.M. Longini. 1992. "Interpretation and estimation of vaccine efficacy under heterogeneity." *American Journal of Epidemiology* 136 (3): 328–343. https://doi.org/10.1093/oxfordjournals.aje.a116498.

Haber, M., L. Watelet, and M.E. Halloran. 1995. "On individual and population effectiveness of vaccination." *International Journal of Epidemiology* 24 (6) :1249–1260. https://doi.org/10.1093/ije/24.6.1249.

Haraway, Donna J. 1996. *Modest_Witness@Second_Millennium.FemaleMan©_Meets_OncoMouse™. Feminism. and Technoscience*. New York and London: Routledge.

Head, B. 2008. "Wicked Problems in Public Policy." *Public Policy* 3(2):110–118.

Health Justice Initiative. 2023. https://healthjusticeinitiative.org.za/. (accessed 3 June 2023).

Iglesias-López, Carolina, Antonia Agustí, Mercè Obach, and Antonio Vallano. 2019. "Regulatory framework for advanced therapy medicinal products in Europe and United States." *Frontiers in Pharmacology* 10: 921. https://doi.org/10.3389/fphar.2019.00921

Infectious Prevention and Control Canada (IPAC). 2023. *Coronavirus (COVID-19) SARS-CoV-2*. https://ipac-canada.org/coronavirus-resources#:~:text=On%20May%204%2C%202023%2C%20the,of%20international%20concern%20(PHEIC). (Accessed 12 June 2023).

Jaiteh, F., Y. Masunaga, J. Okebe, U. D'Alessandro, J. Balen, C. Gryseels, J. Muela Ribera, and K. Peeters Grietens. 2019. "Community Perspectives on Treating Asymptomatic Infections for Malaria Elimination in The Gambia." *Malaria Journal* 18 (39). https://doi.org/10.1186/s12936-019-2672-7.

Jaiteh, Fatou, J. M. Ribera, Y. Masunaga, J. Okebe, U. D'Alessandro, J. Balen, and K. Peeters Grietens. 2021a. "Complexities in Defining the Unit of Intervention for Reactive Community-Based Malaria Treatment in the Gambia." *Frontiers in Public Health*, 9 [601152]. https://doi.org/10.3389/fpubh.2021.601152

Jaiteh, F., J. Okebe, Y. Masunaga, U. D'Alessandro, J. Achan, C. Gryseels, and K. Peeters Grietens. 2021b. "Understanding Adherence to Reactive Treatment of Asymptomatic Malaria Infections in The Gambia." *Scientific Reports*, 11(1), [1746]. https://doi.org/10.1038/s41598-021-81468-1.

Janssen M.A., and W. J. M. Martens. 1997. "Modeling Malaria as a Complex Adaptive System." *Artificial Life* 3(3): 213–236. https://doi.org/10.1162/artl.1997.3.3.213.

Ioannidis, John P.A., Sally Cripps and Martin A. Tanner. 2022. "Forecasting for COVID-19 has Failed." *International Journal of Forecasting* 28(2): 423–438. https://doi.org/10.1016/j.ijforecast.2020.08.004.

Klein S. L., F. Shann, W. J. Moss, C. S. Benn, and P. Aaby. 2016. "RTS,S Malaria Vaccine and Increased Mortality in Girls." *mBio* 7(2): e00514– e00516. https://doi.org/10.1128/mBio.00514-16.

Kupperschmidt, Kai. 2015. "Risk of 'Leaky' Vaccines Debated." *Science* 349 (6247): 461–462. https://doi.org/10.1126/science.349.6247.461.

Lakoff, Andrew. 2007. "Are we Prepared for the Next Disaster?" *Contexts* 6(3): 10–12. https://doi.org/10.1525/ctx.2007.6.3.10.

Latour, Bruno. 1993. *We Have Never Been Modern*. Cambridge: Cambridge University Press.

Lauerman, John. 1988. "One Colombian's Quest for a Malaria Vaccine." *The Scientist.* https://www.the-scientist.com/news/one-colombians-quest-for-a-malaria-vaccine-62354 (accessed 3 June 2023).

Laurens, Matthew B. 2021. "Novel Malaria Vaccines." *Human Vaccines and Immunotherapeutics* 17 (11): 4549–4552. https://doi.org/10.1080/21645515.2021.1947762.

Lock, Margaret, et Vinh-Kim Nguyen. 2011. *An Anthropology of Biomedicine*. 2 ed. Oxford: Wiley Blackwell.

Lundh, A., J. Lexchin, B. Mintzes, J.B. Schroll, and L. Bero. 2017. "Industry Sponsorship and Research Outcome." *Cochrane Database Systematic Review*, 2 (2): MR000033. https://doi.org/10.1002/14651858.mr000033.pub3.

Malaria Vaccination Initiative. 2022. "PATH welcomes US$% million grant to expand malaria vaccine access in Ghana, Kenya, and Malawi." *PATH,* 19 April. https://www.path.org/media-center/path-welcomes-us-5-million-grant-expand-malaria-vaccine-access-ghana-kenya-and-malawi/#:~:text=Seattle%2C%20April%2019%2C%202022%E2%80%94,Ghana%2C%20Kenya%2C%20and%20Malawi (accessed 3 June 2023).

Patarroyo, Manuel., R. Amador, R., P. Clavijo, Alberto Moreno, Fanny Guzman, Pedro Romero, Ricardo Tascon, Antonio Franco, Luis A. Murillo, Gabriel Ponton & Gustavo Trujillo. 1988. "A Synthetic Vaccine Protects Humans Against Challenge with Asexual Blood Stages of Plasmodium falciparum malaria." *Nature* 332: 158–161. https://doi.org/10.1038/332158a0.

Märzhauser, Helene. 2018. "Risks of Dengue Vaccination." *Science,* 2 July. http://www.dw.com/en/dengue-risks-and-side-effects-of-the-worlds-first-vaccine/a-42488407 (Accessed 3 June 2023).

Masunaga, Y., J. Muela Ribera, T. T. Nguyen., K. Tesfazghi, and K. Peeters Grietens. 2021. "In Search of the Last Malaria Cases: Ethnographic Methods for Community and private-sector Engagement in Malaria Elimination in Vietnam, Laos, and Cambodia." *Malaria Journal* 20 (1): [370]. https://doi.org/10.1186/s12936-021-03903-y.

Masunaga, Y., F. Jaiteh, E. Manneh, J. Balen, J. Okebe, U. D'Alessandro, C. Nieto-Sanchez, D. H. de Vries, R. Gerrets, K. Peeters Grietens, and J. Muela Ribera. 2021. "The Community Lab of Ideas for Health: Community-Based Transdisciplinary Solutions in a Malaria Elimination Trial in The Gambia." *Frontiers in Public Health* 9: [637714]. https://doi.org/10.3389/fpubh.2021.637714.

Morgan S., A. Hollis, C. McCabe, M. Herder, and M. Paulden. 2023. "Canada's Misguided Changes to Drug Regulation Could Fast-Track Unproven Medications and Divert Funds From Other Health Needs." *The Conversation*, 26 June. https://theconversation.com/canadas-misguided-changes-to-drug-regulation-could-fast-track-unproven-medications-and-divert-funds-from-other-health-needs-207463 (accessed 30 June 2023).

Moris, Philippe, Erik Jongert, and Robbert G. van der Most. 2018. "Characterization of T-cell Immune Responses in Clinical Trials of the Candidate RTS,S Malaria Vaccine." *Human Vaccines and Immunotherapies* 14 (1): 17–27. https://doi.org/10.1080/21645515.2017.1381809.

Muela Ribera, J., S. Hausmann-Muela, C. Gryseels, and K. Peeters Grietens. 2016. "Re-imagining Adherence to Treatment from the 'Other Side': Local Interpretations of Adverse Anti-Malarial Drug Reactions in the Peruvian Amazon." *Malaria Journal*, 15(136). https://api.semanticscholar.org/CorpusID:14703669. (Accessed 30 June 2023).

Muurlink, Olav T., and Andrew W Taylor-Robinson. 2020. "The 'Lifecycle' of Human Beings: A Call to Explore Vector-Borne Diseases from an Ecosystem Perspective." *Infectious Diseases of Poverty* 9(1): 37. https://doi.org/10.1186/s40249-020-00653-y.

Nguyen, T. T., C. Gryseels, D. T. Tran, T. Smekens, R. Gerrets, X. X. Nguyen, and K. Peeters Grietens. 2021. "Understanding Malaria Persistence: A Mixed-Methods Study on the Effectiveness of Malaria Elimination Strategies in South-Central Vietnam." *Frontiers in Public Health,* 9, [742378]. https://doi.org/10.3389/fpubh.2021.742378.

Nielsen CM., J. Vekemans, M. Lievens, K.E. Kester, J.A. Regules, and C.F. Ockenhousee. 2018. "RTS,S Malaria Vaccine Efficacy and Immunogenicity During Plasmodium Falciparum Challenge is Associated with HLA Genotype." *Vaccine* 36(12):1637–1642. https://doi.org/10.1016/j.vaccine.2018.01.069.

Nlinwe, Nfor Omarine, Kwadwo Asamoah Kusi, Bright Adu, and Martha Sedegah. 2018. "T-cell Responses Against Malaria: Effect of Parasite Antigen Diversity and Relevance for Vaccine Development." *Vaccine* 36(17): 2237–2242. https://doi.org/10.1016/j.vaccine.2018.03.023.

Olotu A., V Urbano, A. Hamad, M. Eka, M. Chemba, E. Nyakarungu, Jose Raso, Esther Eburi, Dolores O. Mandumbi, Dianna Hergott, Carl D. Maas, Mitoha O. Ayekaba, Diosdado N. Milang, Matilde R. Rivas, Tobias Schindler, Oscar M. Embon, Adam J. Ruben, Elizabeth Saverino, Yonas Abebe, Natasha KC, Eric R. James, Tooba Murshedkar, Anita Manoj, Sumana Chakravarty, Minglin Li, Matthew Adams, Christopher Schwabe, J. Luis Segura, Claudia Daubenberger, Marcel Tanner, Thomas L. Richie, Peter F. Billingsley, B. Kim Lee Sim, Salim Abdulla, and Stephen L. Hoffman. 2018. "Advancing Global Health through Development and Clinical Trials Partnerships: A Randomized, Placebo-Controlled, Double-Blind Assessment of Safety, Tolerability, and Immunogenicity of PfSPZ Vaccine for Malaria in Healthy Equatoguinean Men." *American Journal of Tropical Medicine and Hygiene* 98 (1): 308–318. https://doi.org/10.4269/ajtmh.17-0449.

O'Ryan, Miguel. 2017. "Rotavirus Vaccines: A Story of Success with Challenges Ahead." *F1000Researc*h 18(6): 1517. https://doi.org/10.12688/f1000research.11912.1.

Osterholm, M. T., N. S. Kelley, J. M. Manske, K. S. Ballering, T. R. Leighton, and K. A. Moore. 2012. *The Compelling Need for Game-Changing Influenza Vaccines: An Analysis of the Influenza Vaccine Enterprise and Recommendations for the Future.* Center for Infectious Diseases Research and Policy (CIDRAP) Report. Minneapolis, MN: University of Minnesota. http://www.cidrap.umn.edu/sites/default/files/public/downloads/ccivi_report.pdf. (Accessed 30 June 2023).

Otto S.P., T. Day, J. Arino, C. Colijn, J. Dushoff, M. Li, S. Mechai, G.V. Domselaar, J. Wu, D.J.D. Earn, and N.H. Ogden. 2021. "The Origins and Potential Future of SARS-CoV-2 Variants of Concern in the Evolving COVID-19." *Current Biology* 31 (14): PR918–929. https://doi.org/10.1016/j.cub.2021.06.049.

Patarroyo, M., R. Amador, P. Clavijo, A. Moreno, F. Guzzman, P. Romero, R. Tascon., Antonio Franco, Luis A. Murillo, Gabriel Ponton and Gustavo Trujillo. 1988. "A Synthetic Vaccine Protects Humans Against Challenge with Asexual Blood Stages of *Plasmodium falciparum* malaria." *Nature* 332: 158–161. https://doi.org/10.1038/332158a0.

Peeters Grietens, K., X. Nguyen Xuan, J. Muela Ribera, T. Ngo Duc, W. Van Bortel, N. Truong Ba, K.P. Van, H. Le Xuan, U. D'Alessandro, and A. Erhart. 2012. "Social Determinants of Long-Lasting Insecticidal Hammock-Use Among the Ra-Glai Ethnic Minority in Vietnam: Implications for Forest Malaria Control." *PLOS ONE* 7(1): e29991. https://doi.org/10.1371/journal.pone.0029991.

Peeters Grietens, K., J. Muela Ribera,, V. Soto, A. Tenorio, S. Hoibak, A.R. Aguirre, E. Toomer, H. L. K. Rodriguez., A. Llanos Cuentas, U. D'Alessandro, D. Gamboa, and A. Erhart. 2013. "Traditional Nets Interfere with the Uptake of Long-Lasting Insecticidal Nets in the Peruvian Amazon: The Relevance of Net Preference for Achieving High Coverage and use." *PLOS ONE* 8(1): e50294. https://doi.org/10.1371/journal.pone.0050294.

Peeters Grietens, K., C. Gryseels, S. Dierickx, M. Bannister-Tyrrell, S. Trienekens, S. Uk., P. Phoeuk, S. Suon, S. Set, R. Gerrets, S. Hoibak, J. Muela Ribera S. Hausmann-Muela, S. Tho, L. Durnez, V. Sluydts, U. D'Alessandro, M. Coosemans, and A. Erhart. 2015. "Characterizing Types of Human Mobility to Inform Differential and Targeted Malaria Elimination Strategies in Northeast Cambodia." *Scientific Reports* 5: 16837. https://doi.org/10.1038/srep16837.

Peeters Grietens, K., C. Gryseels, and G. Verschraegen 2019. "Misdirection in the Margins of the Methods of the Malaria Elimination Paradigm." *Critical Public Health.* https://doi.org/10.1080/09581596.2019.1597965.

Peng, Yilang. 2022. "Politics of COVID-19 Vaccine Mandates: Left/right-wing Authoritarianism, Social Dominance Orientation, and Libertarianism." *Personality and Individual Differences* 194: 111661. https://doi.org/10.1016/j.paid.2022.111661.

Proper, Olivia, Nick Ruktanonchai and Maia Martcheva. 2014. "Optimal Vaccination and Bednet Maintenance for the Control of Malaria in a Region with Naturally Acquired Immunity." *Journal of Theoretical Biology* 353(21): 142–156. https://doi.org/10.1016/j.jtbi.2014.03.013.

Prugger, C., A. Spelsberg, U. Keil, J. Erviti, and P. Doshi. 2021. "Evaluating COVID-19 Vaccine Efficacy and Safety in the Post-Authorisation Phase." *British Medical Journal* 375. https://doi.org/10.1136/bmj-2021-067570.

Read, A.F., S.J. Baigent, C. Powers, L.B. Kgosana, L. Blackwell, L.P. Smith, David A. Kennedy, Stephen W. Walkden-Brown, and Venugopal K. Nair. 2015. "Imperfect Vaccination Can Enhance the Transmission of Highly Virulent Pathogens." *PLOS Biology* 13(7): e1002198. https://doi.org/10.1371/journal.pbio.1002198

Ross, A. 2017. "Vaccination Alone will not halt the Next Global Pandemic." *BMJ Opinion*. http://blogs.bmj.com/bmj/2017/06/09/allen-ross-vaccination-alone-will-not-halt-the-next-global-pandemic/(accessed 30 June 2023).

Røttingen J.A, D. Gouglas, M. Feinberg, S. Plotkin, K.V. Raghavan, A. Witty, R. Draghia-Akli, P. Stoffels, and P. Piot. 2017. "New Vaccines Against Epidemic Infectious Diseases." *New England Journal of Medicine* 376 (7): 610–613. https://doi.org/10.1056/NEJMp1613577.

RTS,S Clinical Trials Partnership. 2012. "First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Infants." *New England Journal of Medicine* 365(20): 1863–1875. https://doi.org/10.1056/NEJMoa1102287.

——. 2014. "Efficacy and Safety of the RTS,S/AS01 Malaria Vaccine during 18 Months after Vaccination: A Phase 3 Randomized, Controlled Trial in Children and Young Infants at 11 African Sites." *PLOS Medicine* 29 July. https://doi.org/10.1371/journal.pmed.1001685.

——. 2015. "Efficacy and Safety of the RTS,S/AS01 Malaria Vaccine With or Without a Booster Dose in Infants and Children in Africa: Final Results of a Phase 3, Individually Randomized Clinical Trial. *The Lancet* 386 (9988): 31–45. https://doi.org/10.1016/S0140-6736(15)60721-8.

Ryan, Molly, Tamara Giles-Vernick, and Janice E. Graham. 2019. "Technologies of Trust in Epidemic Response: Openness, Reflexivity and Accountability During the 2014-2016 Ebola Outbreak in West Africa." *BMJ Global Health* 2019(4): e001272 https://gh.bmj.com/content/4/1/e001272.

Schwartz K. L., J. C. Kwong, S. L. Deeks, M.A.Campitelli, F.B. Jamieson, A. Marchand-Austin, T.A. Stukel, L. Rosella, N. Daneman, S. Bolotin, S.J. Drews, H. Rilkoff, and N. S. Crowcroft. 2016. "Effectiveness of Pertussis Vaccination and Duration of Immunity." *Canadian Medical Association Journal* 188(16): E399–E406. https://doi.org/10.1503/cmaj.160193.

Serum Institute of India PVT, Ltd. 2023. "R21/Matrix-M™ Malaria Vaccine Developed by University of Oxford Receives Regulatory Clearance for Use in Ghana." https://www.seruminstitute.com/press_release_sii_130423.php (accessed 3 June 2023).

Stengers, Isabelle. 2005. "The Cosmopolitical Proposal." In *Making Things Public: Atmospheres of Democracy,* Bruno Latour, ed. 994–1003. Cambridge, MA: MIT Press.

University of Oxford. 2023. "R21/Matrix-M™ Malaria Vaccine Developed by University of Oxford Received Regulatory Clearance for use in Ghana." https://www.ox.ac.uk/news/2023-04-13-r21matrix-m-malaria-vaccine-developed-university-oxford-receives-regulatory (accessed 3 June 2023).

Vural, I. E., Matthew Herder and Janice E. Graham. 2021. "From Sandbox to Pandemic: Agile Reform of Canadian Drug Regulation." *Health Policy* 125 (9): 1115–1120. https://doi.org/10.1016/j.healthpol.2021.04.018.

Wexler, Mark K. 2009. "Exploring the Moral Dimension of Wicked Problems." *International Journal of Sociology and Social Policy* 2919(10): 531–542. https://doi.org/10.1108/01443330910986306.

World Health Organization. 2005. "International Health Regulations." *World Health Organization*, 1 January. https://www.who.int/publications/i/item/9789241580410. (accessed 3 June 2023).

——. 2013. "Malaria Vaccine Technology Roadmap." *World Health Organization*, 5 November. https://www.who.int/publications/m/item/malaria-vaccine-technology-roadmap. (accessed 3 June 2023).

——. 2016. "WHO Welcomes Global Health Funding for Malaria Vaccine." *World Health Organization*, 17 November. http://www.who.int/en/news-room/detail/17-11-2016-who-welcomes-global-health-funding-for-malaria-vaccine (accessed 3 June 2023).

——. 2020. Malaria: "The Malaria Vaccine Implementation Program (MVIP)." *World Health Organization*, 2 March. https://www.who.int/news-room/questions-and-answers/item/malaria-vaccine-implementation-programme (accessed 3 June 2023).

——. 2021. "Vaccine Efficacy, Effectiveness and Protection." *World Health Organization*, 14 July. https://www.who.int/news-room/feature-stories/detail/vaccine-efficacy-effectiveness-and-protection (accessed 3 June 2023).

——. 2023a. "The Access to COVID-19 Tools (ACT) Accelerator." *World Health Organization*. https://www.who.int/initiatives/act-accelerator. (accessed 3 June 20230.

——. 2023b. "Malaria.' *World Health Organization*, 4 December. https://www.who.int/news-room/fact-sheets/detail/malaria. (accessed 3 June 2023).

Zeng, Wu, Y.-A. Halasa-Rappel, N. Baurin, L. Coudeville, and D. Shepard. 2018. "Cost-Effectiveness of Dengue Vaccination in Ten Endemic Countries." *Vaccine* 3(3): 413–420. https://doi.org/10.1016/j.vaccine.2017.11.064.

Zimmer, Carl and Keith Collins. 2021. "What do vaccine efficacy numbers actually mean?" *New York Times*, 3 March. https://www.nytimes.com/interactive/2021/03/03/science/vaccine-efficacy-coronavirus.html (accessed 3 June 2023).