Economy and Society

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/reso20

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To cite this article: Ann H. Kelly, Javier Lezaun & Alice Street (2022): Global health, accelerated: Rapid diagnostics and the fragile solidarities of 'emergency R&D', Economy and Society, DOI: 10.1080/03085147.2021.2014730

To link to this article: https://doi.org/10.1080/03085147.2021.2014730

Published online: 28 Feb 2022.

Economy and Society
https://doi.org/10.1080/03085147.2021.2014730

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Global health, accelerated: Rapid diagnostics and the fragile solidarities of 'emergency R&D'

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Abstract

A new paradigm of emergency R&D has transformed global health. Beginning with the 2014–2016 Ebola virus disease epidemic in West Africa, experimental product development has been propelled to the frontlines of outbreak response, radically compressing timelines and unsettling regulatory standards, biosecurity strategies and humanitarian protocols. This paper examines these emerging epistemic practices and ethical norms as they played out in the creation of rapid diagnostic tests for Ebola, Zika and COVID-19. In each of these viral public health crises, new platforms for quick detection have been the principal load-bearing pillar of outbreak response, and the effort to speed up their development illuminates the fragile set of accommodations between public health needs and commercial interests that obtain under conditions of emergency. The World Health Organization's role in stimulating and coordinating the development of these tools provides our analytical through-line, and reveals, we argue, the limitations of an *accelerationist* model of global health innovation organized around the concept of 'market failure'. The evolution of this paradigm of

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'emergency R&D' into a permanent feature of pandemic preparedness will further narrow our imagination of how global health goods should be construed and provided.

Keywords: global health; diagnostics; market failure; solidarity; WHO.

Introduction

On 11 February 2020, a group of prominent scientists, government representatives, regulators and research funders convened at the World Health Organization's headquarters in Geneva to identify key 'knowledge gaps' relating to the rapid spread of the new coronavirus. The questions posed during this 'Global Research and Innovation Forum' were many, as so much was still unknown about SARS-CoV-2 – from its origins, virulence and pathways of transmission to its clinical manifestations, pathogenesis and mechanisms of the immune response. 'Harnessing the power of science is critical for bringing this outbreak under control', WHO Director-General Dr Tedros Adhanom Ghebreyesus told the gathered participants. 'There are questions we need answers to, and tools we need to develop as quickly as possible. WHO is playing an important coordinating role by bringing the scientific community together to identify research priorities and accelerate progress' (WHO, 2020a).

Dr Tedros' words were unexceptional, almost formulaic. They expressed a set of widely accepted wisdoms about the function of R&D 'acceleration' during international health emergencies and the role the WHO should play in the process (Brende *et al.*, 2017; Nuffield Council on Bioethics, 2019). Yet, this particular understanding of what we might call 'emergency R&D' had only taken shape a few years earlier, during the 2014–2016 Ebola virus outbreak in West Africa, when the expedited validation of novel diagnostics and the implementation of large-scale drug and vaccine trials had demonstrated the public health potential of 'just in time' research. 'The Ebola experience', the WHO noted, demonstrated that 'it is possible to compress R&D timelines from a decade or longer to less than a single year' (WHO, 2016a, p. 6), thus dramatically expanding the parameters of what was deemed feasible in an emergency timeframe. In the subsequent months and years, new funding streams, data- and sample-sharing protocols, and fast-track regulatory pathways were initiated, leveraging the Ebola experience to set 'new norms and standards' for fast innovation and intervention during public health emergencies (WHO, 2016a; see also Kelly, 2018).

The resulting paradigm of emergency R&D differs in important ways from previous measures to facilitate a rapid investigative response to medical emergencies. The transition from the 'international health' system of the Cold War period towards the 'global health' enterprise as we currently know it implied new articulations of state, commercial and philanthropic interests, including the growing centrality of publicly subsidized but industry-led R&D (Brandt, 2013; King, 2002; Street, 2014). The 2014–2016 Ebola outbreak added to

this a further emphasis on the 'fast-tracked' development of medical countermeasures and consolidated the reliance of emergency response on the capabilities and interests of for-profit actors (Graham, 2019; Kelly *et al.*, 2020; Roemer-Mahler & Elbe, 2016).

The WHO took up a central role in this new landscape. It provided not only a moral framework to expand access to promising yet untested medical products, but also a set of coordination mechanisms to align the calculations of commercial actors with the organization's humanitarian global health mission. Meetings like the 'COVID-19 Global Research and Innovation Forum' (and the resulting document: 'A Coordinated Global Research Roadmap') are examples of how the WHO seeks to pair key gaps in scientific knowledge and technical capacity with opportunities for product development, and reflect a reworking of its health promotion agenda towards the facilitation of innovation in situations of perceived 'market failure' (Lezaun & Montgomery, 2015; WHO, 2020a; Williams, 2012).

Generating new evidence and new tools during a public health emergency is always fraught with difficult trade-offs, and accommodating the interests, practices and standards of commercial development and for-profit manufacturing into outbreak control brings with it a host of ethical and political challenges. Emergency R&D, and the forms of public-private-philanthropic collaboration that it entails, are underwritten by a very specific set of norms: a moral economy of 'acceleration' that unsettles core conventions of public health intervention. This moral economy is expected to enliven traditional demands for universal access to life-saving medical products with the imperative to intensify the *speed* of product development in the face of a novel threat, thus recombining into a single vision the humanitarian and biosecurity logics of global health action (Lakoff, 2010).

Our inquiry into the contours of this emerging regime of global health action unfolds across the experience of diagnostic innovation during the Ebola, Zika and COVID-19 crises, particularly in relation to the creation of novel rapid, point-of-care devices. The effort to develop these highly-mobile platforms under the pressures of a public health emergency quickly brings to the surface crucial decisions about which products should be prioritized, under what circumstances, for whom and to what end, thus exposing the tensions and fissures at the heart of this new configuration of global health knowledge and power.

The paper relies on an analysis of qualitative data generated through multiple research projects, including work on the role played by novel diagnostics during the 2014 West Africa Ebola outbreak; a study of experts' efforts to grapple with scientific uncertainty during the 2015–2016 Zika epidemic; and an investigation into the new humanitarian frontiers created by the COVID-19 pandemic.[1] Fieldwork was carried out in Sierra Leone, Brazil, Switzerland, the United Kingdom and the United States, and included interviews with product developers, research scientists, regulators, government officials and representatives from international health organizations centrally involved in epidemic response, such as the WHO and the Foundation for Innovative New Diagnostics (FIND). We reviewed scientific and policy literatures relating to the role of

novel diagnostics in the management of the Ebola, Zika and COVID-19 crises, and undertook close thematic analysis of publicly available documents related to the WHO's Emergency Use Assessment Listing (EUAL, later EUL), including manufacturer applications, independent evaluations and final reports. We also attended multiple public conferences and meetings organized by industry and regulators in Europe, South America, North America and sub-Saharan Africa (following the start of the COVID-19 pandemic, these meetings took place online).

The paper begins by elaborating the role of rapid diagnostic devices in contemporary imaginations of global health. We then turn to the 2014–2016 Ebola virus outbreak in West Africa, and review the efforts carried out to accelerate the development of point-of-care diagnostics in response to a humanitarian crisis that was quickly framed as a global biosecurity threat. The combination of Ebola's devastating impact on vulnerable populations, the perceived belatedness of the international response, and the availability of yet-to-be-tested medical countermeasures developed under the rubric of US biodefence, led to a significant transformation in the WHO's role as a quasi-regulatory agency and R&D accelerator. We go on to describe the efforts to apply this model during the Zika crisis, and in the early weeks and months of the COVID-19 pandemic. Zika's unique socio-legal and political geography presented new challenges to the WHO's vision for emergency R&D, and resulted in a noticeable narrowing of its quasi-regulatory powers. The ongoing COVID-19 pandemic has further shown the limited moral authority of global health accelerationism when the crisis overwhelms powerful states and advanced economies. It has made apparent the limits of rhetorical appeals to international solidarity – pleas for equal while to products were no match for radically uneven geographies of manufacturing and supply.

The experience accumulated while tracking the creation of new diagnostic commodities across these three emergencies suggests that the acceleration of R&D efforts often functions as a poor substitute for comprehensive public health action, and that effective pandemic response requires much more than market-led innovations. It also points to fundamental shortcomings in how we imagine global health goods when the problem is defined as one of 'market failure', and suggests the need for more robust conceptual and institutional frameworks, capable of embedding solidarity in international R&D infrastructures (Lezaun, 2018).

Accelerating diagnosis

Long neglected in R&D funding and policy frameworks, over the last two decades diagnostics have seen a resurgence of interest in global health circles, in tandem with the development of a new generation of rapid, point-of-care tests designed to work in places without well-resourced laboratory infrastructures. Product-development partnerships such as FIND have leveraged

significant funding from global philanthropic actors like the Bill and Melinda Gates Foundation to re-characterize the diagnostic needs of the poor as a demand for novel and portable diagnostic products (Engel *et al.*, 2016; Street, 2017; see also Ehrenstein & Neyland, 2018). The resulting 'testing revolution' has bought with it a proliferation of proprietary devices, effectively decoupling medical diagnosis from local infrastructures and expertise, and enabling diagnostics (and the data they produce) to circulate as commodities (Beisel *et al.*, 2016; Street, 2018).

If scalability is considered an essential ingredient of diagnostic innovation, the urgency associated with outbreak response brings an additional, temporal dimension to the diagnostic global health enterprise. Rapid, accessible and connected diagnostics would enable an epidemic to be mapped in real-time as it spreads through a population and generate the data necessary to calibrate public health interventions. Tools with rapid test-to-result turn-around times are also critical for clinical practice and public safety – delays in diagnosis can have devastating consequences for patients in need of care and multiply opportunities for contagion. Situated at the threshold of humanitarian medicine and biosecurity preparedness, rapid diagnostics are thus expected to close the gap between sentinel device and actuarial tool, merging previously distinct problems and populations into a single sociotechnical project (Lakoff, 2015). The traditional concern of the emergency R&D framework with fast-tracking innovation is compounded in the case of rapid diagnostic tools with the pressure to accelerate the generation of data in the face of a public health crisis.

In the rise of emergency R&D as an authoritative way of framing the global health enterprise we can thus observe the formation of new alignments between humanitarian, scientific and commercial interests, marked by both political exceptionalism and technological utopianism. Emergency R&D plays out, to borrow a formulation of Mitropoulos (2012), across 'the not-yet bounded territory simultaneously figured as the prospect of new markets … and the multiplication of points of exchange' (p. 5). In these circumstances, the 'social contract' that traditionally underpins the license to research and experiment operates across multiple timescales, spaces and jurisdictions, as evidenced by the sharp trade-offs between immediate humanitarian need and future benefit, political contestation over the sharing of biological materials, or rhetorical appeals to 'global solidarity' against a backdrop of national protectionism and stockpiling. In articulating these tensions, the development of rapid diagnostic tools illuminates structural characteristics of global health innovation, and points to the limits that the emergency R&D paradigm places on effective and equitable forms of international emergency response.

Ebola and the WHO's EUAL procedure

In August 2014, soon after declaring the Ebola outbreak in West Africa a Public Health Emergency of International Concern (PHEIC), the WHO launched an

'emergency procedure' for the deployment of unproven but promising Ebola diagnostics, medicines and vaccines. What would soon become the WHO's Emergency Use Assessment and Listing Procedure (EUAL) was presented as a risk-based approach to the assessment of 'close-to-market' candidates, addressing those situations where 'the community may be willing to tolerate less certainty about the performance and safety of products, given the morbidity and/or mortality of the disease and the shortfall of options' (WHO, 2015, p. 1). The crisis then unfolding in Guinea, Liberia and Sierra Leone definitely warranted quick action and regulatory innovation. In a context of acute humanitarian need and amidst a rapidly growing outbreak – with no proven treatment or vaccine, and a case fatality rate of 70 per cent – the speedy development of adequate medical countermeasures was an absolute priority (WHO Ebola Response Team, 2014).

The lack of available diagnostics and therapeutics was presented by WHO spokespersons as a situation of 'market failure': the assumption was that companies had the capabilities to create effective tools against Ebola but lacked sufficient incentives to invest in their development. Margaret Chan, WHO Director-General at the time, used this trope several times in her speeches. 'Now people see the reality of this R&D failure, this market failure, on TV screens and in the headline news: the world's empty-handed clinicians in their hazmat suits, trying to help Africa's desperate poor, putting their own lives at risk, and losing them'.[2]

As far as diagnosis was concerned, this understanding failed to capture the deeper infrastructural dimensions of the problem. The three countries at the epicentre of the outbreak suffered from crippling limitations in technical capacity; only one biosafety level 4 facility capable of safely processing Ebola samples existed in the region. Chronically under-resourced and short-staffed, few facilities had the requisite expertise in PCR testing or sample management, while supply systems were unreliable or simply non-existent. Several international research groups and public health agencies deployed mobile laboratories in the early weeks of the crisis – an uncoordinated effort that resulted initially in an uneven and unregulated patchwork of screening and surveillance (Kost, 2018; Vernooij *et al.*, 2020). While some efforts were made to improve and standardize laboratory testing in the region (including the publication by the WHO of guidelines for Ebola testing (WHO, 2014a)), the launch of the emergency procedure suggested a different focus: lost time would be made up by an accelerated development and assessment of rapid, single-use, commercially manufactured testing devices. These diagnostics would allow contact tracing, alleviate pressure on health services, and enhance public acceptance of the exceptional and highly disruptive interventions that were being rolled out under the state of emergency. In contrast to vaccine and therapeutics, which at this point were still in preclinical stages of evaluation, rapid portable tests could be developed quickly and at a lower risk to patient safety.

Through its existing pre-qualification programme, the WHO had long provided *de facto* regulatory oversight for developers and manufacturers hoping to

sell medical products in low- and middle-income-countries ('t Hoen *et al.*, 2014; see also Fuchs, 2018). Similar to this process, emergency listing via the EUAL would authorize a product for procurement by UN agencies, but with a lower evidentiary burden for manufacturers and within the time-limited parameters of the public health emergency. This new emergency procedure was explicitly understood as a way of addressing the problem of market failure – a set of explicit criteria from the WHO guiding the review of experimental products would provide commercial developers with a clear framework for their investment decisions; and an expedited assessment process would incentivize firms to prioritize diagnostic candidates for Ebola already in their pipeline.

The new EUAL procedure was modelled after the 'fast-track' regulatory pathways developed by several national regulatory agencies over the previous two decades. Mechanisms such as the United States Food and Drug Administration's (FDA) Emergency Use Authorization authority and Animal Efficacy Rule, the European Medicines Agency's (EMA) Extraordinary Circumstances and Conditional Marketing Authorization provisions, or Health Canada's Special Access Programme, had created legal frameworks to allow the use of unlicensed medical countermeasures in situations where their potential public health benefit was deemed to outweigh the risks entailed by an evidentiary deficit (Kels, 2015). Many of these mechanisms can be traced back to growing concern in the early 2000s over bioterrorism and biosecurity – the FDA's EUA authority was created as part of the 2004 Project Bioshield Act, which allowed for the stockpiling of experimental medical products that could not, for ethical reasons, be tested prior to a bioterrorist attack (see Kelley & Tilden, 2007).

Through its new EUAL procedure, the WHO sought to extend the normative force and *de facto* regulatory powers of its pre-qualification process into the field of outbreak response. This was not, however, a straightforward expansion of its jurisdiction. As a quasi-regulatory instrument without the backing of sovereign power, the WHO's emergency pathway sat awkwardly alongside the established powers of national authorities. This was particularly true in relation to the FDA, a national agency with an indisputable global reach.[3] In practice, the authority of the EUAL rested on the WHO's customary legitimacy to provide guidance to what one official described as 'countries that do not really have any regulatory system in place' (Sethi, 2018), but outbreak settings presented very specific regulatory challenges, such as deployment procedures, safe disposal, or risk reporting in the absence in many of those countries of effective systems of post-market surveillance. The WHO's EUAL therefore, required additional evaluative steps from those required by the FDA – in the case of diagnostics, independent verification of test accuracy and an assessment of the firm's manufacturing capacity (Meurant, 2015). In essence, the EUAL leveraged the WHO's normative power and culture of technical excellence, while eliding the primacy of national regulatory agencies in setting policy during an emergency – a sleight-of-hand that would come back to haunt the WHO in later pandemics.

One testing technology was seen to hold particular promise for enhancing the speed of epidemic response in West Africa: the rapid antigen test or 'RDT' (rapid diagnostic test). Portable, cassette based, lateral flow RDT devices for infectious diseases including malaria, HIV and sleeping sickness were already widely deployed and championed for their accessibility and scalability. While gold standard PCR tests were confined to laboratory settings, rapid antigen tests, which detected proteins on the surface of the virus, required minimal training and could be used to extend a centrally truncated laboratory system into field settings, advancing the testing frontier to the point of care and allowing patients to be triaged before a confirmatory PCR test was conducted.

Of the seven diagnostics that were eventually listed for UN agency procurement by the EUAL, four were rapid antigen tests, with the remainder being automated RT–PCR machines primarily designed to speed up laboratory testing. These automated RT–PCR platforms were effectively deployed in laboratories and Ebola Treatment Centres across the region, but the stalled rollout of rapid antigen tests and persistent ambiguities over their accuracy and public health purpose, revealed the difficulty of aligning commercial and public health logics within the emergency timeframe.

One set of challenges related to the scientific validation of the tests. The lack of common comparative benchmarks for validation of RDTs led to significant variation in the sensitivity and specificity reported in scientific evaluations (Broadhurst *et al.*, 2015). Even when studies were carried out with the same reference assay, patchy infrastructures and unreliable supply chains in the field led to changes in operating protocols (for instance in the reagents or sample preparation method used). Varying degrees of access to samples generated further inconsistencies: some studies used fresh blood, some frozen blood and some (later in the outbreak when samples were becoming scarce) pooled blood samples taken from multiple patients and laboratories (Wonderly *et al.*, 2019). Adjudicating the results of different validation studies became, in the words of an academic researcher involved in the research, like 'comparing apples to oranges'.

At the height of the emergency, the WHO deemed that the immediate need for diagnostics, particularly in rural areas, outweighed the tests' uncertain accuracy. In February 2015, it listed its first RDT, the Corgenix ReEBOV Rapid Antigen Test, with the caveat that it should be used only for screening and triage while awaiting confirmation of results from a laboratory RT–PCR test. Even with these provisos, the value of a less-than-perfect Ebola test remained fluid (Bevan *et al.*, 2018). In fact, as the operational challenges of testing for a highly infectious pathogen in a severely under-resourced health system became even more apparent, the WHO was eventually forced to abandon its plan to use RDTs for screening in primary care facilities. 'The risks', a WHO diagnostics lead explained:

> meant that RDTs could not be used outside the laboratory. If you could create a biosafety environment you could use them, but it became clear this would not be

> able to happen in these countries. You needed people to be dressed properly, in the proper personal protective equipment. And then there is also the disposal of the sample and the kit. Waste disposal was a big issue.

Ostensibly designed for use in health facilities with limited infrastructure, the failure to mitigate the hazards associated with sample extraction and device disposal ultimately made the RDT format unsafe for deployment in primary health facilities. The case for a potential alternative use, as a screening device in the clinical laboratory, was undermined by the increasing availability of highly accurate, automated nucleic acid PCR tests running on high through-put platforms, which obviated the RDT's singular advantage of diagnosing infection quickly in the field.

Once the epidemic began to tail off, the declining prevalence of the virus further diminished the already shaky public health value of RDTs, as their relatively low specificity created the prospect of generating more false positives than true positives – a situation that, according to the WHO, 'will undermine trust in the testing procedures and in the broader public health response' (WHO, 2015). This concern became especially pressing once the effort to achieve zero cases got underway, as a single false positive would keep the region under the shadow of a public health emergency, with dire economic and political consequences.

Rather counter-intuitively, then, a device that had initially been championed for its ability to extend diagnostic capacity to where it was most lacking, was ultimately deemed usable only within a laboratory setting. The shaky utility of rapid diagnostic tests is paradigmatic of the WHO's broader challenge: how to stabilize the value of specific devices in a rapidly developing epidemic scenario long enough to align public health and market logics. The limited use of novel RDTs hinted at the importance of more systemic diagnostic interventions, such as the improvement of specimen referral systems between primary care and central laboratories. These infrastructural improvements may in fact have offered a more scalable epidemic response than highly-portable commercial products.

This gap between the deployment of portable devices and the creation of sustainable public health capacities points to a larger lesson of the Ebola crisis that key actors failed to draw at the time. Even if one accepted the framing of the problem as one of 'market failure', the case of rapid diagnostics suggests that the WHO's emergency use provisions had failed to create a durable set of incentives, let alone a self-sustaining R&D infrastructure (Olliaro *et al.*, 2015). When a new Ebola outbreak was detected in the Democratic Republic of Congo in 2018, none of the rapid tests previously listed by the WHO was commercially available, a fact that several interviewees put down to developers feeling 'burned' by their experience of the EUAL, specifically the failure to establish a viable use-case for rapid tests (see also Cnops *et al.*, 2019; Moran *et al.*, 2020). The fundamental shortcomings of the EUAL framework – the limited role that calculations of future market demand could play in the

context of emergency response – soon became apparent, as a new public health crisis came to monopolize international attention.

The geopolitics of Zika and the WHO's R&D Blueprint

Attempting to solidify its role as the architect of emergency global health research, the WHO issued in the spring of 2016 a new 'R&D Blueprint' for action to prevent epidemics. Building on the experience gathered during the Ebola outbreak in West Africa, the Blueprint laid out a strategic framework for the 'rapid activation of R&D activities' in times of emergency (WHO, 2016a). Among its core areas of concern were the creation of mechanisms to foster collaborations between governmental, humanitarian and commercial stakeholders, the development of new investigative protocols and evidentiary standards for technologies in early development, and the provision of oversight through regulatory and financing mechanisms.

Conceptually, the new agenda expressed yet again a moral economy of preparedness animated by the accelerated development of new medical products. 'While conventional surveillance, contact tracing and containment measures remain cornerstones of a health emergency response', the Blueprint states:

> a repertoire of effective health technologies could be the key to pre-empting full-blown epidemics, and limiting their human, social and economic losses. The Ebola epidemic taught us that we can move faster to try to curb the spread of disease. By acting together based on a coordinated plan, we can accelerate the development of the vaccines, drugs, diagnostics and delivery systems needed to short-circuit emerging health threats. (WHO, 2016a, p. 1)

The Blueprint implicitly characterizes the belatedness of the Ebola response as a matter of technological deficiency – the crisis could have been brought under control earlier if biomedical innovation had advanced at a faster pace. The emphasis on product development drew attention away from chronic gaps in the health systems of the countries at the epicentre of that outbreak. It also helped pass over other aspects of the WHO's response that had come under severe criticism at the time, most notably the delay in declaring a Public Health Emergency of International Concern (Garrett, 2015). Post-mortem analyses of the organization's role had pointed to structural problems, from its ultimate dependence on the financial support and political will of national governments (Piot *et al.*, 2017), to the gap between its vast normative purpose and its narrow operational capacities (Lakoff, 2017). Against the background of these critiques, the WHO's relevance was now being redefined around what the Harvard-LSHTM independent review panel described as its 'key coordinating function in research and development' (Moon *et al.*, 2015, p. 2216). Pulled from the brink of 'an existential crisis of confidence', it was implied, the WHO had proved its capacity to lead, convene and establish

norms among a broad range of public and private actors on research, development and data sharing.

The WHO had an immediate opportunity to exercise this coordinating function again. In February 2016, the organization declared a Public Health Emergency of International Concern (PHEIC) in relation to the outbreak of neonatal microcephaly associated with Zika virus infection during pregnancy. First detected in the northeast of Brazil's in late 2015, the possibility of severe birth abnormalities caused by a little-known mosquito-borne virus immediately grabbed global attention, and offered the WHO, in the words of Assistant Director-General Marie-Paule Kieny, 'an important test case for the R&D Blueprint'.

Scientific research on Zika had been minimal prior to 2015, and the field of diagnostics was essentially non-existent. The US Centers for Disease Control and Prevention (CDC) had developed 'in-house' PCR and ELISA tests in the aftermath of an outbreak on Yap Island in 2007, but there was no commercial diagnostic platform on the market when news of the new disease began to spread. Following the model used during the early months of the Ebola emergency, the WHO convened a series of meetings and invited manufacturers to submit EUAL applications for two test product categories: real-time nucleic acid-based assays for the direct identification of Zika virus genetic material, and assays for the detection of antibodies showing prior infection (WHO, 2014b, 2016b).

The clinical use-cases that should accompany these new Zika tests were not stated in official documents, however; the reports included in the listing of individual products indicated only that the assay was to be used for 'diagnosis or aid for diagnosis' (e.g. WHO, 2018). Diagnostics had obvious value for mapping the spread of the virus and the prevalence of infection-associated microcephaly, but their clinical use-case was less straightforward in the absence of therapeutic or palliative options for those who tested positive. Detection of infection in pregnant women raised the question of early termination, but this option was legally unavailable to most women in many of the countries most directly affected by the outbreak (Diniz, 2017; Wenham *et al.*, 2019). As a result, the definition of a clinical use-case for new diagnostic tools was directly entangled with local struggles over reproductive health and rights, and the politically charged issue of how new diagnostics would be linked to concrete interventions reverberated throughout the WHO-sponsored product development process (Kameda *et al.*, 2021).

In spite of the obvious ambiguity over clinical utility, several commercial developers appeared interested in developing molecular and serological tests. The mosquito vector of the virus is endemic in several affluent countries, including the United States, and increasing reports of sexual transmission were expanding diagnostic demand to virtually all countries in the world, creating a potentially large market for commercial firms (Charrel *et al.*, 2016). In total, 33 applications for new diagnostic tools were submitted to the EUAL while the PHEIC declaration was in force (Chua *et al.*, 2015). By the time the PHEIC was lifted in November 2016, however, only two of those products, both PCR tests for the detection of Zika's genetic material, were listed for procurement.

The reasons for this paucity of products point to flaws in the assumptions that underlaid the WHO's Emergency R&D Blueprint. Many of the applications submitted to the EUAL process were found wanting due to poor assay validation data, lack of standards, reference preparations and samples for validating assays, or questions about the ethical clearance related to the sourcing of biological materials (WHO, 2017b). These issues reflected the lack of pre-existing knowledge and material infrastructures for Zika detection, but also brought into relief the specific geopolitical configuration of the Zika emergency. The crisis had its epicentre in Brazil, a country with significant biomedical research capacity and a track-record of developing innovative products to tackle public health challenges. The difference with the Ebola emergency in West Africa was most evident in the conflicts that immediately ensued over the transfer and sharing of biological samples. During the Ebola outbreak, tens of thousands of biological samples were shipped from the three most affected countries to government laboratories, research institutions and commercial developers in Europe, North America and South Africa (Freudenthal, 2019; Tengbeh *et al.*, 2018). This transfer of biological materials was met with opprobrium from commentators in West Africa and beyond, who pointed out that it often lacked proper consent from individuals or benefit sharing agreements with national institutions, but in the short term it proved hugely advantageous for the rapid development of novel medical products. In contrast, national sovereignty over biological materials was a significant concern in Brazil, and the country had the means to limit their transfer to foreign firms and institutions. Worried that samples from Brazilian citizens could be used to develop commercial products they would not be able to afford, and keen to incentivize the development of 'national' diagnostic tools to meet the country's public health needs, the international flow of public, officially-certified materials remained severely restricted in the early weeks and months of the epidemic (Kameda, 2021).

As a result, several foreign commercial developers acquired clinical samples from private Brazilian laboratories, often for considerable sums, but obtained little information about the sample origins or characterization (Peeling *et al.*, 2020). Many firms and laboratories came to rely on samples collected from international travellers who had been infected while visiting countries where Zika was circulating, but these samples did not provide an adequate benchmark for validation, particularly for antibody tests – high cross-reactivity among different Flaviviruses meant that tests developed with samples from international travellers performed poorly in countries, like Brazil, where dengue was endemic. Several international firms paid in-country laboratories substantial fees to run performance evaluations on their tests, essentially pricing the WHO out of the market for diagnostic evaluations.

The prospects for rapid product development diminished further once the epidemic began to wane in Brazil and neighbouring countries. The surprising decline in the incidence of Zika virus infection and associated microcephaly radically reduced the interest of commercial firms, and further complicated

the validation of those tests already in development (Goncalves *et al.*, 2018). The EUAL had faced a similar challenge during the Ebola crisis: when case numbers plummeted, samples became difficult to obtain and the ethical case for relaxing evidentiary requirements unravelled. For Ebola, the Blueprint had concluded, 'emergency development of experimental products came too late to benefit the large majority of affected people' (WHO, 2016a, p. 11). It is difficult to reach a different conclusion for the Zika crisis. Once again, a public health emergency had challenged the premises underlying the WHO's role as broker of public and private interests, and facilitator of last resort for the acceleration of R&D activities. The lack of pre-existing infrastructures for Zika virus detection, robust sovereign claims over biological materials, and fickle interest from commercial developers combined to curb any hopes of creating a 'global pipeline' of products during the emergency. WHO-sponsored efforts to formulate standard target product profiles and the incentive provided by the prospect of emergency listing were not enough to surmount these challenges.

In 2017, an informal WHO consultation identified several lessons from the Ebola and Zika outbreaks. Chief among those was the need to clarify the role of the WHO *vis-a-vis* national regulatory authorities in affected countries (WHO, 2017a). Following this consultation, the EUAL was renamed the Emergency Use Listing (EUL), to dispel the misinterpretation that the 'A' in EUAL stood for 'Authorization'. The revised procedure emphasized the primacy of national regulatory authorities in approving research protocols, signing off on the transportation and export of samples, and authorizing the use of novel products in-country. 'It should be noted', the new EUL guidance now stated, in bold, 'that it is the sole prerogative of WHO Member States whether or not to allow the emergency use of a candidate vaccine/medicine/in vitro diagnostic in their country' (WHO, 2020b, p. 8).

The move from the EUAL to EUL circumscribed the degree of regulatory stewardship the WHO could claim to exercise, but did little to disambiguate the geopolitical constraints that had slowed down the flow of diagnostic materials. The re-assertion of national primacy over the regulation of emergency R&D sat awkwardly with the constant calls to rapid data sharing and 'openness' that tend to follow every declaration of a Public Health Emergency of International Concern. The most recent iteration of the Zika R&D Blueprint emphasizes the need for innovative models 'to support scalable adoption of ZIKV diagnostic tests into national laboratory programs', and notes the importance of clarifying 'the use cases for ZIKV diagnostic testing, taking into consideration regional differences' (WHO, 2021). How those distinct contexts, national interests and biopolitical considerations can find articulation in a 'coordinated response', let alone in business models that allow for a clear return on investment, remains to be seen. COVID-19 exacerbated these tensions, and gave them truly 'global' scope, as the WHO scrambled to reassert its role during a crisis that was throwing even the most powerful states into a state of emergency.

COVID-19: The 'trickle-down' of diagnostics

In the early days of 2020, when reports of an outbreak of pneumonia of 'unknown cause' in the city of Wuhan reached the global health community, the cogs of the emergency R&D system began to whirr. On 11 January, Chinese scientists published the genetic sequence of the SARS-COV-2 virus, the pathogen responsible for the disease that would soon be known as COVID-19. Less than two weeks later, a group at the Institute of Virology in Berlin's Charité University Hospital released details of a laboratory-based RT-PCR nucleic acid detection assay, which was soon published on the WHO website. Between 26 and 30 January – the day when WHO declared the outbreak a Public Health Emergency of International Concern – the Chinese National Medical Products Administration approved five nucleic acid testing kits manufactured in China. On 3 February, the CDC announced the development of a rapid laboratory test kit for use with an existing commercially available RT–PCR platform, and on 9 February, Public Health England announced the development of a test for use in specialist laboratories across the United Kingdom. By September 2021, a website that tracks commercially available COVID-19 diagnostics listed upwards of 600 tests approved for use in US, European and Asian markets.[4] Those tests spanned multiple biological targets, formats and labelled use-cases, from highly accurate PCR based nucleic acid tests intended for use in the diagnosis of symptomatic cases, to rapid antigen tests designed for detection of asymptomatic infection, or rapid antibody tests to enable the testing of contacts for previous exposure.

The unprecedented response of the global diagnostics community was driven by the geographic trajectory of the SARS-COV-2 virus, with rates of infection rising explosively in the high-income countries where the majority of commercial test developers are located. In this diverse, highly active and increasingly crowded research landscape the role of the WHO's EUL was much diminished. Originally motivated by the need to stimulate industry interest in a context of perceived 'market failure', the WHO's emergency procedures had little immediate relevance in the initial phase of the COVID-19 pandemic, as a multitude of firms around the world scrambled for a piece of the enormous COVID-19 testing market. Doubts about the reliability of many of the new testing formats clearly indicated a need for tighter regulatory oversight, but with national authorities in many countries stepping up their own emergency assessment procedures the added value of the EUL was not evident.

In response to these developments, the WHO made several modifications to its procedures. FDA-authorized PCR tests were identified as the benchmark comparison to validate the sensitivity of candidates in the WHO's EUL template. WHO encouraged manufacturers to submit independent performance data with their submissions and offered, with the support of FIND, to validate test sensitivity against samples collected from diverse regions. In a significant departure from previous iterations of the EUL procedure, however,

participation in those assessments was no longer compulsory (WHO, 2020b, 2020c). With requirements for an emergency use listing now pared down to information on quality management systems and the company's own laboratory performance data, most submissions simply replicated the 'instructions for use' already submitted to national regulatory authorities elsewhere.

With much of the WHO's regulatory authority ceded to the FDA and other national regulatory agencies, a new set of concerns about market behaviour moved to centre stage. Despite the oft-repeated mantra that 'nobody is safe until everyone is safe', the cooperative vision for emergency R&D heralded by the WHO was clearly at the mercy of national protectionism. The public health need for diagnostics was arguably most pressing in low- and middle-income countries – limited healthcare and Intensive Care Unit capacity made the humanitarian case for testing, tracing and isolation even more urgent, while the economic impact of lockdowns was intolerable in the absence of state action to compensate firms and employees – but the rush of governments to prioritize the security of their own populations, combined with an intractable scarcity in materials and supplies, led to a concentration of diagnostic capacity in rich countries. In this context, the problem for low-income countries was not one of access to products, but the more fundamental one of access to the market itself. In an editorial in *Nature* in April 2020, John Nkengasong, the Director of the African Centres for Disease Control and Prevention (CDC), appealed to rich countries to 'let Africa into the market for COVID-19 diagnostics':

> The collapse of global cooperation and a failure of international solidarity have shoved Africa out of the diagnostics market … When SARS-CoV-2 was first reported, genome sequences were made available within weeks and several groups in Asia and Europe started producing in-house tests. Africa lacked this capacity and had to wait for the tests to be introduced, a tardy 'trickle-down' of diagnostics. The situation has now become worse: a race is on by the powerful to acquire whatever COVID-19 tests are available. This is not a question of demanding charity. African countries have funds to pay for reagents but cannot buy them. (Nkengasong 2020)

At the end of April 2020, at an event co-hosted by the WHO Director-General, the President of the French Republic, the President of the European Commission, and the Bill and Melinda Gates Foundation, the WHO launched the Access to COVID-19 Tools (ACT) Accelerator. A collaboration between governments, scientists, businesses, civil society and philanthropists, the initiative was intended 'to accelerate the development, production, and equitable access to COVID-19 tests, treatments and vaccines'. While the development of new and accurate tools remained a concern, it was the challenge of large-scale production and distribution that was now given greater priority. 'I just want to make it clear in case there's a misunderstanding', Dr Mike Ryan, Chief Executive Director of the WHO Health Emergencies Programme interjected at the close of the press briefing:

> We're not beginning now with the diagnostic process. The ACT is about scaling up, it's about increasing access, better use and making sure we have the best possible tools in the right quantities, in the right place, using the right kind of innovation for the job we have to do in the next six months. (WHO, 2020d)

The WHO now defined its success not by the number or quality of the products it ushered through development, but on the basis of whether the organization could inspire rich countries and large corporations to take up the issue of access – to 'put aside', in Dr Ryan's words, 'any sense of competition or difference and work together in what has been a broken global market to deliver'.

The ACT-Accelerator had some successes. In the year since its launch, more than 60 million molecular and rapid diagnostic platforms were procured for low-and-middle income countries. Through volume guarantee agreements from the Bill and Melinda Gates Foundation, some novel EUL-approved platforms entered those countries at an affordable price. Yet, a substantial funding gap for diagnostics remained – US$8.7 billion by the end 2020, according to the WHO. With new virus variants cropping up across the world, the issue of diagnostic supply was not merely one of allocating finished products, but rather of creating more distributed infrastructures capable of supporting local manufacture. Neither a new legal organization or a decision-making entity, the ACT-Accelerator was constrained in this regard, as it could not force companies to enter into technology-transfer agreements, nor compel governments to make the considerable investments needed to advance in-country R&D or locate manufacturing infrastructures elsewhere.

In the meantime, what Nkengasong called the tardy 'trickle-down' of diagnostics, the expectation that oversupply in rich countries would eventually help address the needs of poor ones, remained the default model for distributing testing capacity. The mechanisms of 'emergency R&D' created during the West Africa Ebola virus outbreak of 2014–2016 had little traction in a world upended by a public health crisis that was laying bare and intensifying global inequality. Overwhelming economic shocks and a deadly succession of infection waves in affluent countries left little room for the traditional register of humanitarian biomedicine. In practical terms, if not formally, COVID-19 had long ceased to be a Public Health Emergency of International Concern to become a fully-fledged, worldwide crisis, and very few of the mechanisms and institutions of global health preparedness and emergency response were left standing.

Conclusion: Towards new global health solidarities

At the Global Research and Innovation forum in early February 2020, WHO Director-General Dr Tedros Adhanom Ghebreyesus had told the assembled audience: 'This outbreak is a test of solidarity – political, financial and scientific'.[5] Appeals to solidarity have become a common refrain in global health. They are meant to counterbalance state-centric biosecurity agendas and serve

as a bulwark against an increasingly fragmented, multipolar world (e.g. Flahault *et al.*, 2016; Frenk *et al.*, 2014; Harmon, 2006; Prainsack & Buyx, 2017; Prince, 2017). Tracking the evolution of the WHO's role in the development of rapid diagnostics across three recent international public health emergencies, this paper has questioned the extent to which effective forms of solidarity can arise out of the emergency R&D regime as currently constituted (Kelly *et al.*, 2021; Lurie *et al.*, 2021; Wouters *et al.*, 2021). The emphasis on the accelerated design, deployment and commercialization of novel medical tools obviates the radically distinct, if not contradictory, interests and obligations that drive industry investment, scientific inquiry, state action and humanitarian response. Whether or not the WHO can be in a position to mediate those exchanges in a manner that is compatible with the public interest is uncertain. What is clear is that that the formal procedures it has created to speed up the development of medical countermeasures have not functioned as 'solidaristic institutions' (Prainsack, 2020), entrenching instead a political economy of global health R&D with little capacity to generate bonds of mutual obligation.

The Ebola, Zika and COVID-19 emergencies have offered distinct conjugations of accelerated global health research, each one organized around its specific humanitarian, juridical and industrial exigencies. If the Ebola outbreak was defined by the failure of 'incentives' to energize innovation for the world's poor, the Zika emergency clarified the difficulty of aligning the international machinery of emergency R&D with conflicting national priorities and constraints. The story of COVID-19 countermeasures during the initial phase of the pandemic was characterized not by a situation of 'market failure', the problem the WHO architecture for accelerated product development was meant to address, but by the material challenges of large-scale manufacture and supply under conditions of national protectionism. As the virus became a truly global threat, it led to a reassertion of state-centric and often nationalistic framings of solidarity. The huge public investment in R&D that took place in most affluent countries was underpinned by a rhetoric of national security, even of war-time mobilization (Their, 2021). As far as access to medical countermeasures was concerned, global solidarity became contingent on overproduction in well-off countries, the availability of supplies in poor countries the result of a 'trickle down' of commodities manufactured to meet national needs elsewhere.

The failures of WHO-sponsored acceleration to generate effective rapid diagnostic tools for Ebola and Zika had already pointed to some fundamental misalignments, not only between the timescales of global health R&D and infectious disease response, but also in the forms of political authority that underpin each field of practice. Responsible for declaring an international health emergency, the WHO can encourage and orient investments in product development, but ultimately lacks the financial resources, operational scope and legal powers to stabilize markets for public health goods. Its limitations became particularly apparent in the challenges the emergency listing procedure faced in defining clear use-cases for rapid diagnostic tools that offered speed and proximity at the expense of accuracy.

In a context of increasing geopolitical multipolarity, the organization struggled to smooth out the inevitable disjunctures between technological zones and the territorial jurisdictions of nation states (Barry, 2006). Far from creating a unified terrain of humanitarian and commercial innovation, accelerated R&D exposed the frictions between divergent ethical and political norms. Across the three international public health emergencies of the last seven years, rapid diagnostic products failed to give material expression to an ethic of global cooperation and solidarity, instead resurfacing again and again as objects of scientific uncertainty and contested sovereignty. Yet, the outsized role that product development came to play in the management of public health crises has drawn attention away from the structural inequities and power imbalances that lie at the heart of these emergencies and define their scope. When it was discussed in the context of the emergency R&D agenda, solidarity was generally articulated in terms of access to end products – rather than characterizing, from the outset, the concrete costs and obligations of cooperation (Jensen *et al.*, 2021).

Alternative models of global health solidarity have become available during the COVID-19 crisis. They are often modest and fragmentary, but point to alternative configurations of cooperation. The African CDC, for example, is in the process of establishing a biorepository linking country-owned biobanks, which will incorporate reference materials and standardized collection methods to enable the accelerated development of diagnostic platforms. Instead of relying on the 'trickle down' of finished products developed and manufactured elsewhere, these platforms can potentially strengthen a regionalized rapid response – not only to epidemic threats, but to any endemic diseases that might capture scientific attention on the continent. The WHO has played a crucial role in other significant innovations. In November 2021, almost two years into the pandemic, it announced 'the first transparent, global, non-exclusive licence for a COVID-19 technology'. A joint effort with the UN-backed Medicines Patent Pool, the license covers all patents and biological material necessary for the manufacture of tests based on a serological diagnostic technology developed by the Spanish National Research Council (CSIC). The license is royalty-free for low- and middle-income countries, and will remain in force until the relevant intellectual property expires. Commending CSIC 'for its commitment to solidarity', Dr Tedros urged developers of COVID-19 vaccines, treatments and diagnostics 'to follow this example and turn the tide on the pandemic and on the devastating global inequity this pandemic has spotlighted'.[6]

Initiatives like these are suggestive of global health innovation frameworks that move beyond a narrow focus on 'acceleration', and on fixing situations of 'market failure', and seek instead to mitigate chronic deficits in the global bioeconomy by creating new regional capabilities and non-exclusive commodities. Any attempt to forge new global health solidarities, we argue, should start this way, by addressing the radically uneven geographies that define processes of product design, development, manufacturing, regulation and supply.

Acknowledgements

We would like to thank our many collaborators for their contributions to the wider research projects on which this paper has drawn, including Rashid Ansumana, Imogen Bevan, Momoh Gbetuwa, Mohamed Boie Jalloh, Koichi Kameda, Ilana Löwy, Gustavo Matta, Mohammed Hashim Rogers and Eva Vernooij. Any errors or omissions are the sole responsibility of the authors. We are also grateful to our reviewers, whose close reading and astute comments helped sharpen our argument.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

Research for this paper was supported by the European Research Council under the European Union's Horizon 2020 research and innovation programme [grant agreement number: 715450], the Wellcome Trust [Award grant number 204939/Z/16/Z], and a Newton Fund Institutional Links award [grant number 280969145] funded by the Department for Business Energy & Industrial Strategy and the Fundação Oswaldo Cruz, and delivered by the British Council.

Notes

1 See: Investigating the design and use of diagnostic devices in global health (www.diadev.eu); Acting in an uncertain world: Mapping public health responses to the Zika epidemic in Brazil (https://www.insis.ox.ac.uk/zika-virus-epidemic-in-brazil), and the Zika Social Science Network (https://zssn.org/about).

2 Address by Margaret Chan to the Regional Committee for Europe, 16 September 2004.

3 The primacy of the FDA was to some extent written into the WHO's EUAL, which specifies an 'abbreviated' pathway for those products that have already been authorized for emergency use in the United States.

4 https://www.360dx.com/coronavirus-test-tracker-launched-covid-19-tests

5 Dr Tedros Adhanom Ghebreyesus. Media briefing, 5 February 2020. https://www.who.int/news-room/detail/12-02-2020-world-experts-and-funders-set-priorities-for-covid-19-research

6 'WHO and MPP announce the first transparent, global, non-exclusive licence for a COVID-19 technology,' WHO and MPP Joint Press Release, 23 November 2021. https://www.who.int/news/item/23-11-2021-who-and-mpp-announce-the-first-transparent-global-non-exclusive-licence-for-a-covid-19-technology

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