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REVIEW ARTICLE

Global Biological Threats: Novel Tools and Multi-Disciplinary Approaches to Sustainable Development

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Abstract | The Covid-19 pandemic has raised awareness of future biological threats, how we can prepare and develop mitigation strategies. Technology has allowed us to quickly identify the pathogen, map its evolution in real time and develop scores of vaccines within months. This review looks at disease threats from a perspective of human development, and the futuristic technologies that may help in the fight. Most importantly, cooperation across political and ideological boundaries would be needed in a highly inter-connected world. A new disease emerging anywhere is a threat everywhere.

1 Introduction

The Global Burden of Disease (GBD) Survey[1] has looked at the status of health at global, national and regional levels since the 1990s to understand evolving health challenges across populations. The 2017 dataset and the Report[1] highlight a slowdown in progress towards health-related Sustainable Development Goals.[2] Infectious disease mortality has decreased largely due to better healthcare, drugs to combat infections and vaccines to prevent disease. However, outbreaks of infectious disease worldwide have also increased steadily for the past 40 years. An analysis of over 10,000 outbreaks showed bacteria and viruses to be the most common causes, with person-to-person and vector-borne transmission, zoonoses and human-specific illnesses on the rise (Fig. 1).[2]

In a landmark paper in 2008, Kate Jones and colleagues in London showed emerging infectious disease (EID) events between 1940 and 2004 to be distributed non-randomly across the globe[3]. The EIDs were dominated by zoonotic pathogens, and have increased over time. The paper also highlighted antimicrobial resistance (AMR) to be a future threat and predicted global emerging disease 'hotspots', which prominently includes India, south and southeast Asia.

Viruses makeup only 14 percent of known human pathogens but comprise 44% of new and emerging pathogens[4]. Some of the biggest public health threats of the twentieth century such as influenza and HIV came from viruses with zoonotic origins. The first two decades of the twenty-first century has already seen two pandemics, the 2009 swine flu[3] and the ongoing Covid-19,[4] and epidemics of SARS, MERS and Ebola that were significant threats but did not have the geographical spread to become pandemics. All of these outbreaks were caused by viruses that spilled over from wild animals into humans,

[1] The Global Burden of Disease (GBD) provides a tool to quantify health loss from hundreds of diseases, injuries, and risk factors. It is led by The Institute for Health Metrics and Evaluation (IHME), an independent global health research centre at the University of Washington, Seattle, USA.

[2] The SDGs were adopted in 2015 as a universal call by all UN Member States to end poverty, protect the planet and ensure that all people enjoy peace and prosperity by 2030.

[3] Swine Flu was caused by a H1N1 strain of influenza virus, which originated in pigs, and the index human case seen in Veracruz, Mexico. The pandemic lasted from January 2009 to August 2010, with 491,382 laboratory confirmed cases. It is thought to have infected an estimated 0.7–1.4 billion people globally with 284,000 deaths.

[4] Covid-19 started in Wuhan, China in December 2019 due to a novel coronavirus that originated in bats. It was named Severe Acute Respiratory Syndrome (SARS) coronavirus type 2, or SARS-Cov-2. By August 6, 2020, there are over 19 million confirmed cases and over 700,000 deaths reported from 215 countries.

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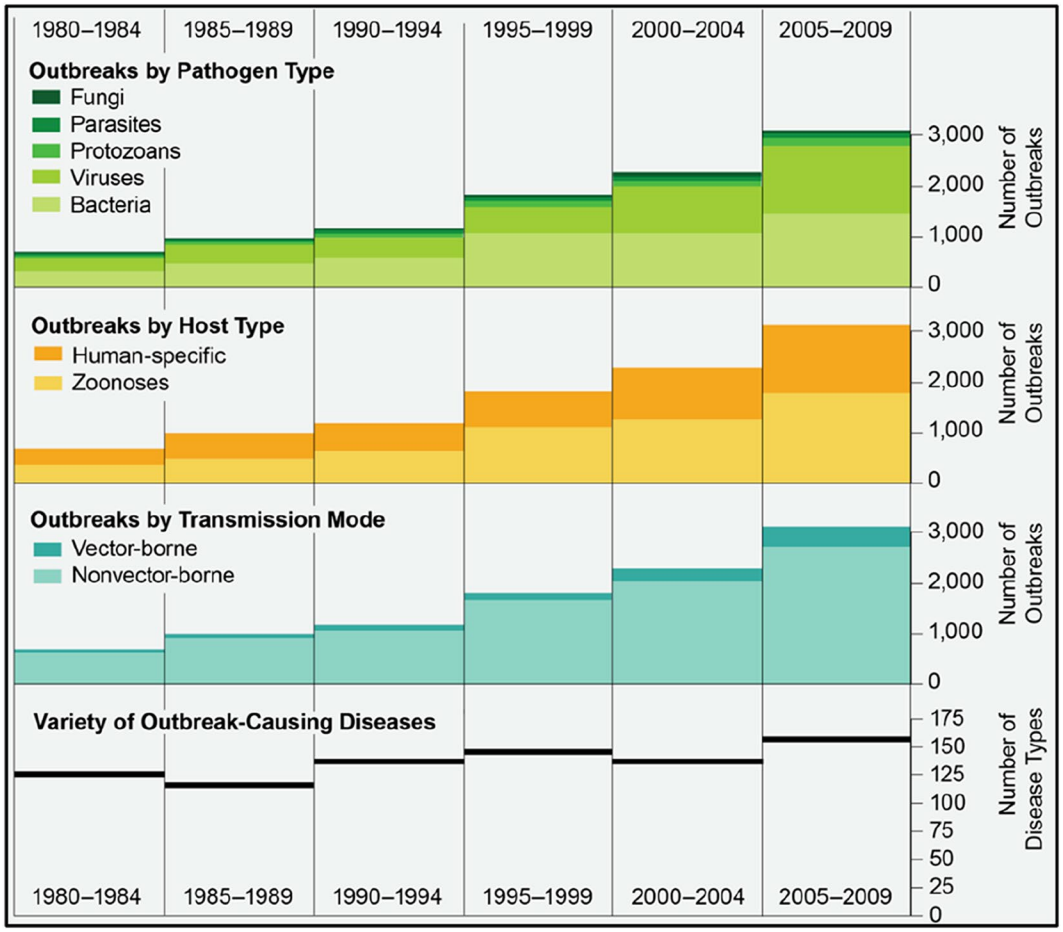

Figure 1: Global infectious disease outbreaks since 1980. Source: www.scientificamerican.com/article/global-infections-by-the-numbers/.

either directly or through an intermediate animal host. The emergence of new viruses has increased in pace over the past 25 years, and the World Health Organization's (WHO) list of 20 pandemic threats include 16 viruses[5].

Each year the WHO, with help from global experts, updates its list of pathogens that pose the biggest threat of causing the next pandemic, and should, therefore, attract topmost priority for research and threat mitigation under the agency's R&D Blueprint[6]. Though not an exhaustive list, it indicates the most likely causes of the next epidemic, which WHO reviews and updates with evolving needs, methodologies and available technologies. Since February 2018, this list always carries "Disease X", a very serious but unknown threat, most likely of viral etiology, but whose nature and timing are not known[6].

Drug-resistant infections and zoonoses are serious threats. Developing better detection, surveillance and environmental monitoring systems, as also prevention (via vaccines) and treatment (via drugs) of disease events, are continually required. Technology, when applied thoughtfully, can improve our ability to recognize and address emerging threats and reduce biological risk.

2 Emerging Pathogens and Threat Mitigation

Pathogens continue to emerge and adapt quickly to new hosts due to high rates of multiplication, mutation and selection. Most experts agree that there will be severe pandemics in the future, but their etiology and timing cannot be predicted. An example is an emergence of a novel coronavirus, SARS-CoV-2, which has changed the way we live and work.

A complex mixture of biological, environmental, socioeconomic and political factors threatens past gains in infectious disease mortality and morbidity. Some of these include pathogen evolution, antimicrobial resistance, climate change,

global warming and deforestation, vaccine hesitancy, increasing pollution and population density, donor fatigue and geopolitical conflicts. At the same time, new tools are being developed in life sciences, nanotechnology, communications, space technologies, etc. that offer science-based solutions to better detect, prevent, cure and control infectious diseases.

Pandemics and catastrophic biological events are different from the regular health threats we

face periodically. These events are both sudden and severe, and, therefore, a focus on early detection and prevention becomes a priority. Also, as Covid-19 has taught us, the response would have to be global even when many low-income countries may not have the technology or infrastructure. Thus, it becomes imperative for protective equipment, diagnostics, therapeutics, medical equipment and clinical management protocols to be accessible to all in a timely manner. The technologies needed to mitigate the risks are likely to be qualitatively and quantitatively different from those deployed in routine public health and clinical practice. A report from the Center for Health Security at Johns Hopkins University, USA, has outlined technologies that could better prepare the world to prevent infectious disease outbreaks from progressing to catastrophic events[7]. The deployed technologies would require—(1) better sensitivity to facilitate prevention, (2) capacity for early response and decision-making, (3) improved scale and access, (4) ability to be used in diverse settings, and (5) fast development, availability and field deployment.

3 Pathogen-Agnostic Approaches

It is impossible to know the nature of Pathogen X (the causative agent for Disease X) and, therefore, surveillance approaches would have to be ubiquitous and pathogen agnostic. Since its development in the 1980s, DNA sequencing technology has improved in sensitivity, speed, accuracy, automation, cost and field deployment, and is thus a natural choice for pathogen surveillance. Within weeks of the emergence of Covid-19 clusters in Wuhan, scientists in China reported the novel coronavirus sequence[8,9], which spurred the development of diagnostics and vaccines. In the ensuing 7 months, over 80,000 SARS-CoV-2 genome sequences are available in the Global Initiative on Sharing All Influenza Data (GISAID) public database[10], allowing real-time tracking of virus evolution and its movement around the globe, through an open-source project called Nextstrain[11].

Ubiquitous genomic sequencing of microbes can provide insights into pathogen biology, including pathogenicity, transmissibility and resistance profiles. With better computational and analytic tools, this can also lead to advanced genomic sensing systems, which would continually monitor air, water, soil, farms, transportation hubs, sewage systems, mass gatherings, etc. Portable sequencers such as the Oxford Nanopore Technology's MinIon®, have already been used in field settings, such as the Ebola outbreak in West Africa[12] and the Zika outbreak in Latin America[13]. Mass spectrometry has speeded up the detection of proteins and peptides as pathogen-specific biomarkers, and now carbon nanopore technology has the potential to reduce their size and cost[14].

Surveillance is key to mitigation, but its current challenge is surveilling, testing and analyzing diverse and remote ecosystems. Drones are already used to monitor air and water quality and can enable the collection of information from areas difficult for humans to access, but their use in mapping the spread of infection and disease has been very limited[15,16]. In future, drone networks can be used to deploy portable real-time PCR, sequencing and mass spectrometry platforms to sample various microenvironments and carry out onboard analysis. Big Data and Artificial Intelligence solutions would enable the integration of large volumes and diverse data from continuous and real-time surveillance to enable recognition of impending biological threats.

4 Novel Diagnostics

Rapid, accurate and robust diagnostics are critical for early outbreak response, but the development of diagnostics for emerging infections often stalls for lack of financing, viable markets and last-mile delivery. Most existing advanced diagnostic platforms such as genetic sequencing, while more efficient and effective than earlier, still require large investments in equipment, supplies, maintenance, training, and infrastructure.

Microfluidic or "lab-on-chip" devices have the potential to replace traditional laboratory equipment, making diagnostics more accessible, affordable and usable, especially for point-of-care testing and in resource-limited regions[17]. Plastic based microfluidic devices are small—typically the size of a credit card—containing channels lined with diagnostic reagents such as antibodies and other reagents, require low volumes of the analyte, can be read visually and are easy to interpret[18,19]. Paper devices are even cheaper

and disposable but are limited to less complex reactions[20]. These testing devices when teamed with telemedicine or loaded on drones can take clinical care and surveillance to even the remotest of settings. The replacement of microscopes with smartphones for image acquisition also allows better integration of data processing, transfer and storage.

In outbreak situations, especially during pandemics, molecular diagnostics for field use have to be developed quickly, be highly sensitive and specific, low cost, easy to use and interpret results, produced at scale and rapidly deployable to ramp up diagnostic capabilities in low-resource areas. Cell-free diagnostics that use freeze-dried extracts from cells containing engineered synthetic gene networks fulfill these requirements and can be mass-produced at very low cost for field deployment[21]. Currently, it is estimated to take about 1 week from sequence acquisition to manufacturing of cell-free paper-based diagnostic sensors, at a cost of less than 5¢ per sensor, with detection times of under 45 min and a shelf life at room temperature of 1 year[22]. Sensors based on trigger RNA are able to discriminate between strains of Ebola and Zika viruses at single-nucleotide resolution.

5 Vaccines

Vaccines are the most efficient and cost-effective tools for disease prevention. In a pandemic situation as with Covid-19 now, it is not the development but clinical testing, manufacture and deployment of vaccines that are bigger challenges. Within 7 months of SARS-CoV-2 being identified, there are more than 165 candidate vaccines in development with 27 vaccines in human clinical trials[23], made possible due to advances in molecular biology, the availability of vaccine platforms, and fast-tracked development and testing pipelines. The challenges of cold chain and efficient delivery often stand in the way of rapid deployment, but these can be addressed through genetic tools and advances in molecular biology and nanotechnology.

A microarray or microneedle patch (MAP) is an emerging technology for mass vaccine administration[24]. It would be useful for rapid needle-free vaccination in outbreak situations as well as for mopping up the last reservoirs of poliovirus that require the injectable killed whole virus vaccine, as opposed to the live attenuated oral polio vaccines used to vaccinate billions around the world. These reliable and pain-free tools would promote compliance through self-administration of vaccines, with little medical training. From an immunological perspective, they deliver the vaccines to intradermal sites from where these are taken up by special antigen-presenting cells (APCs; dendritic cells), processed and presented to B and T cells to give robust protective immune responses[24].

Another transformative idea is that of self-spreading vaccines[25]. It involves vaccinating a small number of people in a target population and letting the vaccine strain circulate in the population much like an infectious virus, except that instead of causing disease it is protective. These have been used to control some viral diseases in animals, but require more work towards engineering these for human use[25]. Covid-19 and other viral vaccines being developed by the US-based biotechnology company Codagenix, which uses a codon deoptimization technology, would be examples of these[26]. Such vaccines could dramatically increase coverage in human or animal populations without requiring each individual to be given the vaccine. Orally ingestible bacteria that are genetically engineered to produce antigens in a human host can also provide for low cost and orally delivered vaccines. There is already proof-of-concept for this using *Salmonella enterica* as the platform for a vaccine against typhoid fever; this is also being used for developing an oral Covid-19 vaccine[27].

Work in 'synthetic vaccinology' has highlighted the utility of self-amplifying mRNA (SAM) vaccines, based on positive-sense RNA viruses, wherein the region coding for viral structural proteins is replaced by a sequence that codes for the vaccine antigen[28]. Enzymatically synthesized mRNA when inserted into cells, is translated into the antigen and a viral replicase. While the former is used to raise immune responses, the latter replicates the RNA and continues to amplify it without producing any viral structural proteins. Consequently, there is amplification without an infectious virus. This technology has been adapted for developing universal flu vaccines[29]. A prototype flu vaccine was made in just 8 days during the 2013 influenza H7N8 outbreak in China[30]. Further research and development to create generic platforms and modes of delivery (e.g. lipid particles) has been utilized in Moderna's mRNA vaccine for Covid-19. Though not a self-amplifying vaccine, it went from virus sequence to human clinical testing in 63 days[31].

6 Next-Generation Antibiotics

In 2018, the World Health Organization called antibiotic resistance as one of the biggest threats to global health, food security and development[32]. It is rising to dangerously high levels in all parts of the world, with newly emerging resistance mechanisms that threaten our ability to treat common infectious diseases such as pneumonia, tuberculosis, blood poisoning, gonorrhoea, and foodborne diseases. Globally about 700,000 people die of resistant infections each year. The Review on Antimicrobial Resistance (AMR), an initiative of the UK government, predicted in its 2016 report[33] that unless action is taken to avert the crisis, within a generation AMR could be responsible for about 10 million deaths every year and an economic loss of US$100 trillion.

Rampant (mis)use of existing frontline antibiotics, especially in developing countries, is a key driver of resistance. On the other hand, very few new antibiotics have been developed over the past decade, and most are slightly different variants of existing drugs, making them easy targets of resistance. Current methods for screening new antibiotics are time consuming, often prohibitively expensive and are usually limited to a narrow spectrum of chemical diversity.

In a novel approach, scientists at the Massachusetts Institute of Technology, USA used machine-learning to discover new antibiotics[34]. They trained a deep neural network capable of predicting molecules with antibacterial activity and carried out structure-based predictions on multiple chemical libraries. This led to the discovery of Halicin, which is structurally divergent from conventional antibiotics and displays killing activity against a wide spectrum of pathogenic bacteria, including *Mycobacterium tuberculosis* and carbapenem-resistant Enterobacteria. It also effectively treated *Clostridioides difficile* and multi-drug resistant *Acinetobacter baumannii* infections in mice. The work also identified eight other antibacterial compounds that are structurally distinct from known antibiotics. This pathbreaking approach highlighted the utility of machine learning to expand our antibiotic war chest.

7 Pandemics and Sustainable Development

Sustainable Development Goals (SDGs), also called Global Goals, were adopted by Member States of the United Nations in 2015, as a common set of action points to protect the planet, promote human development, and achieve peace and prosperity for all by 2030 (Fig. 2). According to the United Nations Development Programme (UNDP), "The coronavirus pandemic has shown us a new world; one where the status quo no longer exists. And the reach of Covid-19 is only just beginning to be felt. UNDP estimates global human development—a combination of education, health, and living standards—could fall this year for the first time since 1990"[35]. Though only SDG3 deals with health, the devastating effects of a pandemic like Covid-19 go beyond global health.

7.1 SDG1 (Poverty)

The Covid-19 crisis is estimated to have pushed over 500 million people back into poverty, including an estimated 35.4–178.5 million people in India. An estimated 88% rural and 75% urban households in India suffered a loss of income during the lockdown[36].

7.2 SDG2 (Hunger)

Covid-19 has exposed weaknesses in global food supply chains, especially in fragile economies, pushing millions into further distress. India, with an estimated 19 crores undernourished people and over 50 lakh children under 5 years with severe wasting, has faced a trade-off between hunger and controlling the disease[37].

7.3 SDG3 (Health)

Impressive gains made in infant and maternal mortality, HIV/AIDS and malaria deaths, etc. face setbacks not just due to the disease but also breaks in immunization programmes[38].

7.4 SDG4 (Quality Education)

It is estimated that about 1.25 billion students globally are affected by Covid-19 lockdowns and 86% of primary education is disrupted due to the digital divide in developing countries, including India[39].

7.5 SDG8 (Decent Work)

Over 1.6 billion people work in the global informal economy. The International Labour Organization reports that more than one in six young people have lost their jobs due to the pandemic; others had their hours reduced[40]. In India, about 90% of the workforce, an estimated 450 million people work in the informal sector, and the post-lockdown plight of millions of migrants workers is too well known.

Figure 2: The United Nations Sustainable Development Goals. Source: https://www.undp.org/content/undp/en/home/sustainable-development-goals.html.

Epidemic and pandemic threats are now a global reality. Since the mid-twentieth century, new and often deadly viruses have emerged, mostly spilling over from animal reservoirs into humans. There are an estimated 500,000 animal viruses about which we know very little[41]. Understanding these threats would be a key to developing mitigation strategies to prevent the emergence of new human diseases. As outlined in this review, technology will play an important role in these efforts. But technology can only provide the most sensitive and efficient tools. Equally important is a public health infrastructure that follows good old epidemiology to track diseases before they emerge. International cooperation would also be needed because in a highly connected world a new disease emerging anywhere is a threat everywhere.

8 What Must India Do?

The Covid-19 pandemic has shown poor disease surveillance and surge capacity in India. The Integrated Disease Surveillance Programme, which is housed within the National Centre for Disease Control (NCDC), was set up in 2004 to monitor disease trends and to detect and respond to outbreaks early[42]. This pandemic highlighted the lack of coordination between various agencies in India—Ministry of Health, Indian Council of Medical Research, NCDC and the state health departments. We must convert the challenges posed by Covid-19 into opportunities to improve our public health infrastructure as also strengthen our disease surveillance network, and its capacity and capability. The NCDC and IDSP require technological and programmatic strengthening, and a professional cadre such as the Epidemic Intelligence Service (EIS) of the US Centers for Disease Control and Prevention (CDC)[43]. Importantly, India's disease surveillance network should leverage strengths in engineering, computation, data science and life sciences present in national research labs to adopt and develop new technologies for detection and surveillance.

This is an opportune time to connect all these dots.

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