Health Security and Beyond:

A New Paradigm for a Post-Pandemic World

Prepared by Flagship Pioneering and Eurasia Group

June 2021

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About Flagship Pioneering

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Foreword

Health comes first. The experience of the past 18 months has demonstrated that health is the wellspring from which all human experience flows and the foundation upon which our societies and economies are built. The Covid-19 pandemic has been a shared global experience, if not an equal one. But just as it has reminded us of our human fragility, it has also revealed our ingenuity and near-limitless capacity for innovation.

We know that we must learn the lessons. The challenge is to identify the right ones and to bring about profound change so that "never again" is reality, not rhetoric. This report, published ahead of the G7 meeting in the UK, is one contribution to that crucial debate. The pandemic is not over yet; but now is the time to turn an eye to the future and to resolve to build a different world afterward.

The ambition of this report is expansive: to build a world that is freer from disease than at any point in human history, where every individual is as healthy as they can be, so that we each flourish individually, as well as together. That is the opportunity before us as we emerge from this global catastrophe. The first step to reaching that new era is to have the ambition to imagine it and the determination to build it.

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Chairman, Pioneering Health Security Initiative

Executive summary

The coronavirus pandemic has underscored how important our health is to the functioning of our interconnected societies. And it has exposed the devastating consequences of not taking seriously warnings about threats to our health. As developed countries begin to look over the horizon of the pandemic, the world must think about how to "build back better," in the words of US President Joe Biden.

"Better" means learning the right lessons from the pandemic and prioritizing what we call "preemptive medicine." We must increase spending and government attention on preparing for the next pandemic. But early warning systems and rapid vaccine production are not enough. We must reconceptualize our entire approach to focus more on preempting illness than simply treating it when it arrives—whether as a chronic disease or a novel infectious disease.

That requires a major global effort aimed at protecting against, preventing, or postponing the onset of disease through novel interventions. The fields of preventive medicine and public health are well established, and they include behavioral interventions (such as seat-belt requirements, smoking cessation campaigns, nutritional guidance) and advanced diagnostics. We are proposing expanding and broadening these fields by using biological sciences and new digital technologies to understand how to mitigate future threats to health and to prevent or postpone disease before it occurs.

The adoption of a global preemptive medicine agenda would have profoundly positive impacts for individual health and global economic growth. Healthier populations get more schooling, are more productive, and live longer. Better global health would also hasten the demographic transition in emerging markets, leading to greater investment in the futures of individual children.

A preemptive medicine paradigm will require fundamental changes in the relationship among individuals, the private sector, and the state. We are clear-eyed about the potential challenges arising from a predictive, data-driven approach to health. In order to "crowd in" private investment, protect privacy, and bridge inequality, new policy, regulatory, and financial frameworks will need to be developed, and new institutions will have to be built nationally and globally.

The Covid-19 pandemic presented the world with a public health challenge that none of us have known in our lifetimes. But it also has brought a once-in-a-century opportunity to re-imagine our approach to health to be far more than just "sick care." Anything less than profound and lasting change would be an affront to the millions who have lost their lives. We must not let this opportunity go to waste.

A global wake-up call

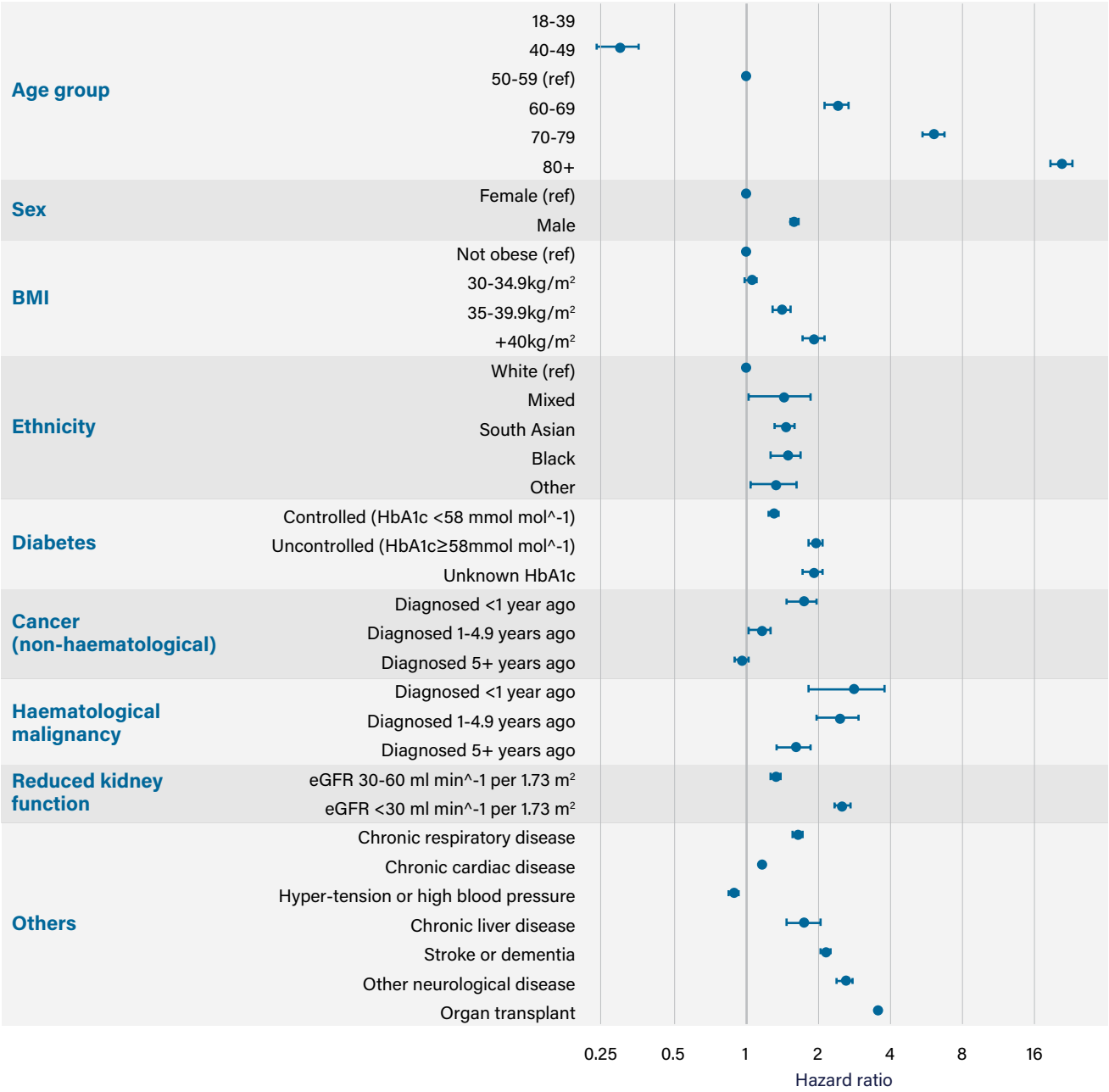
China notified the World Health Organization of 44 cases of pneumonia with an unknown cause on the last day of 2019. One hundred days later, the Covid-19 virus had spread to almost every country and territory on Earth, infected at least 1.5 million people, and caused 88,000 deaths[1]. Governments began to impose stay-at-home orders, causing the greatest peacetime economic shock in history and the severest curbs on liberty in generations. Indeed, the pandemic prompted more than 80 countries to shut down their borders to travelers from affected countries, shutter businesses deemed non-essential, and close schools for around 1.5 billion children[2]. Since then, the global death toll has risen to 3.7 million[3], with the IMF projecting a $28 trillion loss in global output from 2020 to 2025[4]. Covid-19 has been nothing short of a global catastrophe. It is an experience that none of us would wish to repeat.

The impact has been uneven both within and across countries. The virus has exposed and exacerbated pre-existing health, social, and economic inequalities. Those with chronic conditions and those who are obese have a significantly higher hazard ratio, meaning they are much more likely to be hospitalized or die if they get infected with Covid-19 (see chart below). While age is the single most significant risk factor, it cannot be changed. Our state of health, however, can. It makes sense that individuals who are generally healthy are more resilient to infection than those who are not. This explains why countries with higher rates of chronic disease and obesity have experienced higher mortality rates.

This helps explain why minority and low-income communities in developed countries have suffered higher rates of both infection and mortality during this outbreak. Such communities are more likely to have chronic conditions[5], more likely to be obese[6], more likely to live in multi-generational households[7], and more likely to be employed in occupations where social distancing is difficult[8]. Those in blue collar or manual occupations that cannot be done from home have been less protected by lockdown measures and more exposed to risks[9]. While the pandemic has affected everyone in some way, the nature of that experience has varied significantly.

The longer-term health consequences of Covid-19 are unknown. It is apparent that some people who are infected with the virus experience a collection of enduring symptoms that have been termed "long Covid"[10]. The severity of cases is highly variable; some sufferers are unable to return to work or go about their daily lives, while others experience only mild symptoms. It is currently unclear whether this condition is self-limiting and responsive to vaccines or will require new therapies. Indeed, if long Covid turns out to be a chronic disease, it may be a greater burden on health—and therefore on health systems—than the original acute infection. The health costs of the Covid-19 pandemic may not be fully understood for years to come.

Estimated hazard ratios for each patient characteristic from a multivariable Cox model



Sources: Williamson, E.J. et al. (2020), Eurasia Group

Note 1: The hazard ratios (HR) are the associations between patient-level factors and risk of COVID-19-related death. To measure the HR, the researchers used the primary care records of more than 17 million adults in England and linked to 10,926 deaths from Covid-19. Hazard ratios are shown on a log scale. Error bars represent the limits of the 95% confidence interval for the HR.

Note 2: Groups of people who do not have comorbidities, such as no diabetes, no cancer, no haematological malignancy, and no reduced kidney function, are all treated as reference groups, and therefore, their HR values are 1.

End in sight?

In less than a year since Covid-19 was first identified, multiple vaccines have been invented, proven safe and effective in clinical trials, authorized for emergency use, and begun to be deployed to populations around the world. The rapid development of these vaccines testifies to scientific advancement, human ingenuity, and global cooperation. While some had feared that we would have to learn to live with Covid-19 for the long term, the vaccines mean it is a matter of when, not if, the pandemic will be over. The problem, however, is one of scale: Because the virus has spread across the world, the global population of some eight billion people will need to be vaccinated.

While some countries have been able to deploy vaccines to their populations rapidly, only a handful including Israel, Chile, the US, and the UK have vaccinated more than 50% of adults with at least one dose as of May 2021[11]. Though rollouts are quickly accelerating in countries such as France and Germany, most of the world remains unvaccinated. Vaccine hesitancy rates vary across countries but appear to fall significantly as programs are scaled up[12]. Currently there is significant debate about patent protection for Covid-19 vaccines. This issue is important but is only part of the medium-term discussion. Additional challenges related to global vaccination that must also be considered include manufacturing capacity, raw material production, and human resources. Investment in these areas is necessary in the coming years to minimize the kinds of supply shortfalls and inequitable distribution that we are currently experiencing. Until then, commitments to bolster current manufacturing activity and export excess supply can help bridge the gap.[13]

Even those countries that have rapidly deployed vaccines to their populations will confront significant challenges. The latest studies suggest that up to 5% of recipients register a poor immune response to vaccines and will accordingly remain unprotected despite being vaccinated[14]. While vaccines have proven effective against variants that have emerged so far, there is no guarantee that this will hold true in the future. And there are some early indications that immunity wanes over time, meaning that annual booster shots will be needed for some, if not all people[15].

Despite the progress made in some countries, the world remains in the acute phase of the pandemic: Cases have spiked in populous nations such as India and Brazil, causing more deaths and economic damage and increasing the likelihood that dangerous new variants will emerge that could spread elsewhere. No country will be safe until all countries are safe. It is therefore vitally important that programs such as Covax are scaled up to ensure that the whole world has access to vaccines as quickly as possible. The end of the pandemic may be in sight, but no one should underestimate how tough the journey to getting there will be.

Health security as a human right

Since health is foundational to all human experience, it is logical to consider health security to be a fundamental human right. If health security is a right, then a number of conclusions follow. Rights, by their very nature, are universal. All people, everywhere, deserve and should expect health security for themselves, their families, and their communities. Since health security aims to protect, maintain, and improve health, there is an obligation not only to prepare for future pandemics, but also to take action now to preempt them. Similar to how we expect governments to defend our physical security—our right to life and liberty—we should expect them to defend our health security so our lives are as free as possible from disease.

Never again, all over again?

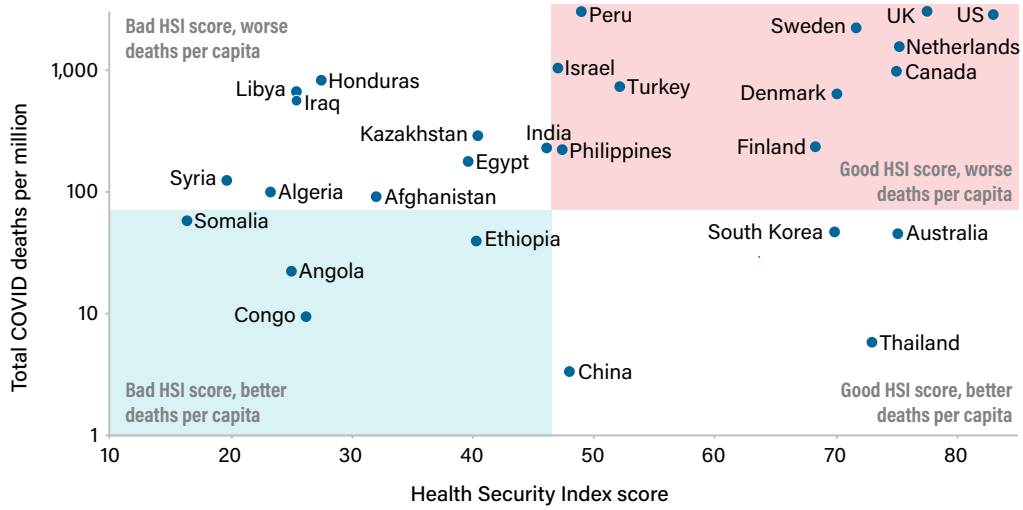
Just as some political leaders dismissed or downplayed the pandemic in its crucial early weeks and months rather than confronting the stark reality of the situation and the hard choices demanded of them[16], it may be tempting to believe that pandemics are once-in-a-century "black swan" events that can neither be predicted nor prevented[17].

Yet scientists have known for decades that as viruses in animals mutate over time, they will "spill over" into humans. What is unknown is when they will emerge, and how contagious and deadly they may be. Since the "Spanish Flu" pandemic of 1918, influenza pandemics have spread around the world on four different occasions. And in the two decades preceding Covid-19, there were multiple outbreaks of pathogens: Nipah in 2001, SARS in 2002, H1N1 or "swine flu" in 2009, MERS in 2012, H7N9 influenza in 2013, Ebola in 2014, and Zika in 2015. It was only a matter of time before another global pandemic would occur. The warning signs were there for all to see.

The pandemic was not only predictable; it was widely predicted. Leading scientists, physicians, policymakers, and politicians consistently warned of the threat from novel viruses. In 2014, the US and more than 30 other nations signed up to the Global Health Security Agenda—which was endorsed by the G7 that same year—with the explicit aim of reducing the risks from infectious diseases[18]. Pandemics regularly appeared among the top strategic risks identified by government civil contingency planners. In 2013, for example, the UK assessed an influenza pandemic as having a likelihood of between 5% and 50% within five years, rating it as having the severest impact of any foreseeable risk[19].

Despite these predictions, many countries proved poorly prepared. In 2019, the Center for Health Security ranked countries' preparedness for a pandemic. A cursory examination of the rankings reveals them to be almost entirely wrong. Countries that were ranked as best prepared—including the US and the UK—mounted poor public health responses. Many of those whose preparedness was regarded as comparatively weak, by contrast, responded far more effectively. Given the catastrophic global impact, the world was woefully underprepared and overexposed.

How did countries perform relative to pre-pandemic expectations?



Note: The accuracy of the deaths per capita data may vary due to reporting differences; countries included represent a sample of those with high, medium, and low index scores.
Sources: Nuclear Threat Initiative, Johns Hopkins Center for Health Security, Worldmeters, Eurasia Group

Being better prepared is vital because pandemics are more likely to occur in the future than they have in the past. The expansion of global air travel, accelerating urbanization, the climate crisis, increased human-animal contact, and shortages of healthcare workers all elevate risks[20]. Moreover,

there are good reasons to believe that a future pandemic could be far worse than Covid-19. It is sobering to consider that the coronavirus is a comparatively benign pathogen: If it had the infectiousness of measles and the case fatality rate of MERS, hundreds of millions would have died, and national economies would have collapsed.

As the debate now begins about how to prepare for the next pandemic, perhaps the greatest risk is that history repeats itself, that, just as in the past, the wrong lessons will be learned for the future. There is a very real risk that countries will prepare to fight the last war, not the next. From stockpiling personal protective equipment[21] (PPE) that degrades over time to investing in subscale domestic vaccine manufacturing capacity[22] that risks being unused and technologically redundant, there are disturbing signs that the wrong lessons are being learned. But what are the right ones?

The big lessons from the pandemic: We need to preempt threats to our health from contagion and preempt disease to keep people healthy

Learning the lessons

Academics and policymakers will study the pandemic and national and international responses to it for years to come. There are many lessons to be learned about public health measures, economic support, and vaccine development and deployment. The enormous variation in the speed and scope of responses from different governments—together with extensive data captured across countries—will enable comparative analysis about what worked and what did not. The world now knows a great deal more about pandemic management than it did a year ago, so it should be better prepared for a future pandemic. Indeed, pandemic preparedness is the central theme of the G7 meeting taking place in June 2021. Given the scale of Covid-19's impact, the topic will likely dominate international discourse for the foreseeable future.

Preempting the next pandemic

While improving pandemic preparedness is vitally important, there are bigger lessons to be learned. The first is that since the costs of a pandemic are so high, we should be willing to do much more than we presently do to *preempt* future ones. Health security should focus as much on preempting threats before they become full-blown crises as on developing strong crisis management plans to respond to pandemics when they occur. Health security must be a top priority for national governments and multinational institutions.

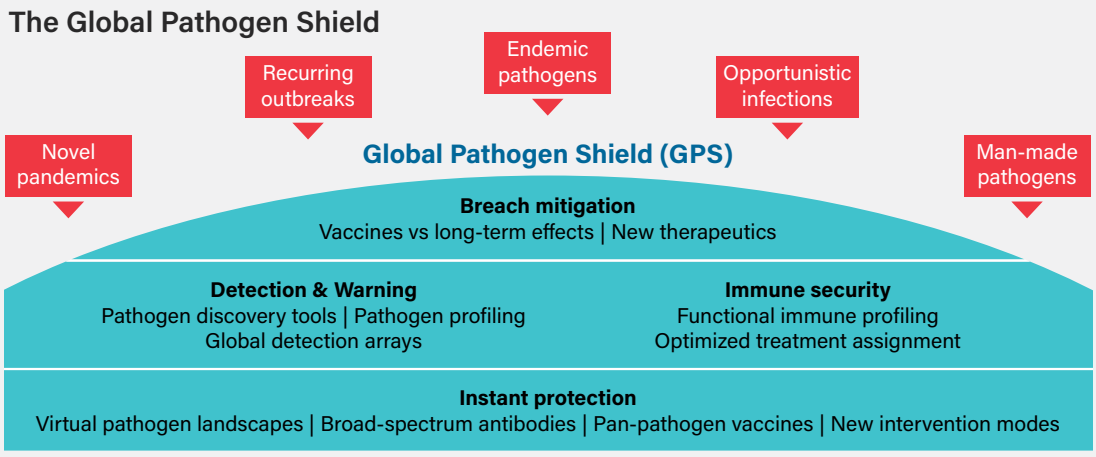
The benefits of acting preemptively against potential pandemic threats, rather than waiting until a pandemic is underway, are significant. The past year has demonstrated the breadth of pandemic-associated costs that preemptive action could have avoided. From the mortality and morbidity caused directly by the coronavirus to the routine healthcare that has been postponed, from children who have missed out on education to families whose living standards have fallen, from businesses that have run up large losses to the permanent scarring of economies, the full costs of the pandemic are nearly incalculable. Since Covid-19 has taken hold in virtually every country and territory worldwide, about 11 billion doses of vaccine will now be required to end the pandemic by achieving "herd immunity" (assuming two shots for 70% of the world's people[23]). With the pandemic expected to cost $28 trillion in lost output between 2020 and 2025[24], the return on investment from interventions that can preempt a future pandemic is enormous.

There is a striking disconnect between government spending on security from violence and spending on health security. More Americans have died from Covid-19 than were killed in the Second World War, Korean War, and Vietnam War combined[25]. More Britons have died from Covid-19 than civilians were killed during the Blitz in World War II[26]. Globally, more people have died from Covid-19 than from all wars in the 21st century put together[27]. The world spent $2 trillion on national defense in 2020[28] , with the US alone spending about $778 billion. Meanwhile, analysis by the World Bank and National Academy of Medicine estimated that between $1.9 and 4.5 billion would need to be invested annually to strengthen health systems against pandemic threats.[29] The World Bank estimated the cost of a severe global pandemic to be $3 trillion—underestimating the actual cost many times over.

Just as every individual has an immune system, the world needs a collective immune system to predict, prevent, and respond to novel pathogens. With nuclear weapons, humankind has stockpiled the means to destroy the world many times over. We accept the idea of massive investment in warheads and missiles that we hope never to use. In sharp contrast, no country possesses the capability to save the world from the current or future pandemics. The costs of building and maintaining a global capability to defend the world from infectious disease are likely to be far lower than the crisis management costs of a future pandemic and a mere fraction of the costs of its wider economic consequences. One such approach to this is Flagship Pioneering's Global Pathogen Shield project (please see box below).

The Global Pathogen Shield[30]

The ongoing Covid-19 crisis has demonstrated that we need to do far more to preempt future pandemics and has opened the door to a much greater focus on innovation to tackle pathogen threats. In a typical year, the seasonal flu kills up to 650,000 people, while malaria and tuberculosis are together responsible for nearly two million deaths per year. Sepsis is involved in up to 20% of annual deaths worldwide, and mosquito-borne malaria is thought to have killed 4%-5% of all humans who have ever lived. What if we could protect humanity against every possible future version of every pathogen threat?



Source: Flagship Pioneering

The major challenge is ultra-diverse biology: increasing numbers of mutations means that the number of possible variants expands exponentially. Indeed, even a limited number of mutations quickly results in over 10^50 theoretically possible mutations—that's about as many atoms as there are on earth.

Broadly, there are three routes to address the problem. The most established approach—employed for seasonal influenza vaccines, for example—is to look at recent and emerging variants and respond as quickly as possible with an intervention that will protect against the nearest-term new version

of that threat. Another strategy is to try and predict the single pathogen variant that will cause an outbreak, in the hopes of being able to develop a targeted, pre-emptive intervention years in advance. A third strategy is to develop a "universal fix" by looking at all known variants and designing a single intervention that will protect against all current and future mutations. These strategies each have important limitations and challenges—including the difficulty of accurately picking out single threats in advance and of predicting escape mutations based on observed pathogen behaviors.

Flagship Pioneering is developing an artificial intelligence engine (known as Octavia[31]) to address the problem. It begins by describing the possible variant sequences through powerful computing and then testing a small selection of representative variants (10^6–10^7) experimentally. Models are then trained on the experimental data to predict the binding and neutralization potential of the full variant space. In a similar manner, it is possible to predict which interventions—for example, mAbs or vaccines—that can neutralize which particular variants. This eliminates the need to pre-identify single pathogen threats in advance; instead, it makes it possible to define a protective antibody repertoire, a basis for variant-proof vaccine design or cross-protective "antibody nets." With sufficient investment, these could be made ready and available to offer instant protection against specific future pathogens as they emerge. The algorithmic basis of Octavia enables constant surveillance of emerging variant sequences to identify and alert the world to novel threats. The Global Pathogen Shield project may herald a future where humankind is protected from future threats, rather than being vulnerable to the next pandemic that will inevitably come.

It's our health, stupid

The next big lesson from the pandemic is that far more should be done to keep people healthy by preventing or postponing disease, since healthier populations are typically more resilient to pandemic threats. In this pandemic, people who were afflicted with chronic disease or obesity were at substantially higher risk of hospitalization and death than those who were generally healthy. While old age and the problems that it brings will always be with us, we can act earlier so people live in good health for longer.

What we have seen over the past two years is the intersection of a contagious disease pandemic with "silent" pandemics of chronic disease and obesity. They are both present in almost every country and territory worldwide, accounting for a large burden of mortality and morbidity. The differences are in the modes of transmission: Whereas contagions such as the coronavirus are typically transmitted by direct contact, by vector (such as mosquito), by vehicle (such as food or water), by droplets (whether touched or inhaled), or by airborne transmission[32], chronic diseases can be understood in part as socially transmitted conditions[33], affected by structural factors (such as urbanization and food systems) and social relationships[34]. That is why a proper response to the experience of the past two years needs to be an integrated effort to tackle both types of pandemic threat, not just one or the other.

Stuck in sickness

The final big lesson of the pandemic is that individuals and societies must invest more in health since it is foundational to all human experience, rather than devoting nearly all their resources to intervention and management once people are already sick.

As individuals, we tend to over-discount our own futures compared to the present, so we do not value our health—until we lose it—and tend to be fatalistic about our health prospects. Most people are incapable unaided of accurately evaluating which factors place their health at greatest risk. As a result, we tend to invest too little in our health.

There is a similar underinvestment in health by governments. Today, more than 95% of OECD resources dedicated to "health" are in fact spent on providing care to those who are already sick, rather than on maintaining or improving health[35]. "Sick care systems," as they might be termed, reward new ways to manage illness rather than innovations that protect, maintain, and improve health.

According to the WHO, public spending on preventive care is a comparatively small component of total health expenditures across countries[36]. In many respects, this reflects the limited suite of measures that have historically been available to policymakers, such as "sin taxes" to depress alcohol and tobacco consumption or regulatory changes such as indoor smoking bans. From the 19th-century focus on measures such as clean water, sanitation, and housing standards to the 20th-century focus on changing population behaviors around diet, exercise, and alcohol and tobacco use, public health measures can be characterized as "broad but blunt." The pandemic calls us to apply leading-edge biological sciences and machine learning technologies in more targeted efforts to keep people healthy.

The lesson from the pandemic is that we need to invest in innovation to achieve escape velocity from a world where we are stuck in sickness to a world where we value and invest in our health.

The preemptive principle and a new paradigm

We have seen stunning new advances in the past year, with novel mRNA vaccines producing terrific results—developed and deployed at a pace that is unprecedented in human history. New advances in biological sciences and machine learning technologies mean that we may be able to predict and *preempt* new Covid-19 variants, offering vaccines that protect against today's variants and those that are most likely to emerge in the future: Imagine getting vaccinated today against this year's *and* next year's variants. That future is nearly here. The same preemptive methods could also be applied to other potential pathogens, identifying which have made—or are likely to make—a species jump and preparing vaccines *before* the first human-to-human transmission occurs.

What if we applied the preemptive principle to disease as well as to contagion? Our health status is too often reduced to a simple but false dichotomy: healthy or sick. The truth is more complex: Our health exists on a healthy-sick spectrum that varies for different physiological systems in our bodies and applies equally to our physical and our mental health. Moreover, there is an important "gray zone" where we may be *seemingly healthy*—we do not feel any symptoms—but in fact are on a trajectory toward having disease, with detectable physiological changes already underway in our bodies or our brains. While people have sometimes been termed "at risk" there have all too often been no interventions available to mitigate or eliminate those risks. Our hypothesis is that this is a new zone for what we term "preemptive medicine"—a window in which disease can either be prevented or postponed, or critically shaped if it occurs. It is the arena of pre-disease and pre-patients. This space for preemptive medicine is not well understood, studied, or described today.

In our view, tomorrow's medicine will be **"preemptive medicine,"** comprising:

- **Health security,** which offers protection from exogenous threats, whether these are infectious diseases, toxins, pollutants, or bioterrorism
- **Preemptive health**, where we *prevent* or *postpone* the onset of disease through novel interventions

Preemptive medicine will be characterized by new methods. There will be a strong element of *prediction*—anticipating who is at risk of disease in the future with novel methods to detect pre-disease states. This will require the identification of novel biomarkers and the application of machine learning technologies. To date, research on characterizing the progression from health to disease has been limited. While not often recognizable in the clinic today, disease etiologies are triggered long before diagnosis and drive progression from an asymptomatic pre-disease condition to a late pre-disease condition comprised of clinically unassigned symptoms, and, ultimately, to disease diagnosis. This applies to both physical and mental health. Indeed, mental health conditions in particular become much more complex when manifested[37].

Deep insights into the etiologies that ultimately lead to the most prevalent and burdensome chronic diseases are currently being developed through the application of "omics" platforms to map the cellular dysregulations and changes to the cellular interactome that emerge during the continuum from health to disease. These insights make it possible to discover novel, cost-effective approaches and methods to detect the presence of pre-disease conditions, or preemptive medicine zones, in individuals before they become symptomatic and well in advance of progression to disease, as well as to discover safe interventions that specifically target these etiologies to stop or delay progression to disease.

The history of medicine is one of deepening our understanding of disease and creating novel interventions on the one hand and of diagnosing disease at progressively earlier stages on the other (though healthcare expenditure is heavily weighted toward therapeutics rather than diagnostics). Preemptive medicine is the next frontier: It takes the idea of early diagnosis a step further by detecting pre-disease states and creating new interventions to prevent or postpone disease from manifesting. Offering mastectomies to women with high risk BRCA 1&2 mutations prior to a diagnosis of breast cancer is an example of preemptive intervention. Preemptive medicine is therefore best understood as an evolution of the current practice rather than a wholly new departure.

As a starting point, preemptive medicine could involve detection rather than diagnostics, and intervention rather than therapeutics, to extend what is currently offered to people with disease to new offerings for people who are seemingly healthy, but whose biomarkers indicate they are on a trajectory toward disease. Such an approach would deliver greater value to society for investments that have already been made in biomedical research and development. Just as the UK RECOVERY Trial identified that dexamethasone improved outcomes for patients with Covid-19[38], there may be many more clinical uses for existing interventions. By intervening earlier, the same interventions may, in fact, prove more effective than their current applications. Moreover, by repurposing interventions that are already proven to be safe, there is significant potential for the preemptive medicine field to develop rapidly. This mirrors the crossover of technologies originally invented for the military—such as GPS, touch screens, and lithium-ion batteries[39]—into widespread civilian use.

While preemptive medicine may be understood as an evolution of clinical practice, it also represents a radical new departure for many healthcare systems. Regardless of health system structure, many healthcare payers (whether public or private) focus on what is known as "demand management." In some systems, this means rationing access to care by setting high clinical thresholds so that only those with advanced disease are eligible for treatment. A preemptive medicine paradigm turns this approach on its head: Rather than focusing resources on those who are most sick, it aims to intervene far earlier and reduce enormous future expenditures. The financial argument for preemptive medicine is much like that for green technology—significant near-term spending will both reduce long-term costs and improve or save lives. For that reason, preemptive medicine could be a major step toward financial sustainability for health systems, bending the trend of rising costs while delivering much greater value to citizens.

Far superior ways to engage, involve and empower citizens to improve their own health will be central to a preemptive medicine paradigm precisely because the absence of symptoms means that their participation is wholly discretionary. New tools are being developed that will enable individuals to manage their own health by providing them with artificial intelligence-enabled applications to assess their health status and determine if preemptive medicine interventions may be beneficial to avoid progression to a chronic disease. The hope is that these novel disease prediction algorithms, with the appropriate medical and data protection oversight, may allow preemptive and affordable interventions against most non-communicable diseases at a global scale. What's more, early detection will empower people to actively manage and mitigate pre-disease at time when it may well be reversible.

Preemptive medicine is distinct from today's medicine, whether it is proactive or reactive. Today's proactive medicine entails a high standard of care for a population group or care pathway. Providers proactively reach out to patients to ensure that they receive the right package of care. The goal is to prevent the acute exacerbation of chronic conditions (for example, regular eye examinations to prevent retinopathy among people with diabetes). These programs are variously described as "population health management," "chronic disease management," or "integrated care." Reactive medicine deals with the treatment or management of all symptomatic conditions and the acute exacerbation of chronic disease.

With its emphasis on preserving and prolonging health rather than treating or managing sickness, preemptive medicine shares many of the same ambitions as the public health community. Both are based on the same insight that it is better to keep people healthy than to treat them once they are already sick. Yet while they share these attributes in common, there are a number of important differences between the two fields. Public health, as the name suggests, tends to focus on measures that apply to the whole of society: from sanitation to road safety and from smoking bans to nutritional guidance. Its means are typically regulatory, legislative, or financial, and the costs are broadly distributed across society (for example, a small increase in the cost of cars to include seatbelts and airbags). In contrast, preemptive medicine is targeted at tightly defined groups or at individuals, based on a segmentation according to risk and followed by the detection of specific biomarkers. The means of preemptive medicine are novel technologies for detection and intervention made possible by leading-edge biological sciences alongside digital technologies. By being highly targeted, some costs of preemptive medicine interventions could be kept low, which will help it to be globally scalable. Preemptive medicine is, therefore, complementary both to public health and to today's medicine, rather than a competing priority.

The five critical shifts to tomorrow's medicine

1. from focusing on **sickness** to focusing on extending **health**
2. from **reacting** to problems once they happen to **anticipating** problems before they emerge
3. from responding to **symptoms** to responding to **novel biomarkers**
4. from mostly **chaotic** crisis management to mostly **planned** interventions and strong crisis management plans
5. from a **limiting mindset** focused on minimizing illness to a **growth mindset** focused on maximizing health potential

If you're building something new, build it right

"Preemptive medicine" is a reimagining of existing efforts in preventive medicine, with a greater focus on biological sciences and digital technologies. It will need new rules to govern it, rather than simply inheriting the rules of existing healthcare systems. Whereas access to high-quality care is highly variable across and within countries, preemptive medicine should start from the premise that the protection, maintenance, and improvement of health is a human right for all. By its very nature, health security is a form of interdependence: As pandemics do not respect national borders, solutions must be affordable so that they can be scalable on a global basis. It is striking, for example, that many of the diagnostic tests for Covid-19 offered by healthcare providers are more expensive than the vaccines that have been created and provide protection from infection in the first place.

The experience for many patients in healthcare systems today is highly frustrating, characterized by poor information flows, excessive complexity and bureaucracy, and needlessly high costs. Given the tendency of individuals to discount risks to their own future health, the experience of preemptive medicine must be seamless, easy, and satisfying. What people will *put up with* when they are sick is not the same as what they will *expect* when they are seemingly healthy.

At the same time, there are huge new opportunities to engage with people in more meaningful ways. Indeed, individuals could be *highly motivated* to act when they know precisely *how* their health is at risk and there is something *specific* that they can do about it, rather than accepting the fatalistic mindsets that often characterize the experience of sickness. It would be a mistake not to capture this opportunity for far more consumer engagement.

Since preemptive medicine is a new field, there is an unparalleled opportunity to create a fresh "operating system" that features the best of all consumer sectors, not only healthcare, and creates an engaging and enjoyable experience for those who choose to participate in it. But unlocking the full potential of preemptive medicine will require policy innovation in three critical areas: regulation, education and training, and financing. And making those changes happen will require significant commitment from political leaders as well as policymakers.

Regulation

There are important lessons from the vaccine development process during the pandemic. A number of key national regulators were involved from an early stage and acted with a degree of flexibility that was unusual, reflecting the extraordinary circumstances, while patient safety remained paramount. Rather than a return to business as usual, the approach during the pandemic could provide a template for a new normal. Such a change could foster a new generation of vaccines for other infectious diseases by eliminating the prohibitively high costs and time to approval.

Moreover, there will need to be a fundamental reset of the regulatory framework to enable preemptive medicine, while continuing to ensure public safety. The regulatory framework ought to be encouraging innovation rather than preventing it, ushering in preemptive medicine rather than excluding it.

The first change would be to permit, at lower doses or frequencies, the use of already-approved molecules for different indications. Since these uses would not be therapeutic, by definition, a pathway to a different category of approval should be provided for the use of already-approved molecules to biomarker-detected pre-disease states. Given that these molecules are already known to be safe, the rigidity in regulatory frameworks is hard to justify; the original intention of such rules—to encourage innovation—is surely eclipsed by the desirability of preemptive medicine. This will require a reimagining, for example, of the FDA's approach to molecules that have already obtained the designation of generally recognized as safe (GRAS).

Regulators will also need to move away from requirements for clinical claims to be attributed to disease included in the WHO's ICD-10 list of defined diseases. It should be possible—indeed, desirable—to be able to make a clinical claim against preventing or postponing disease rather than treating it once it has manifested. This is a critical step toward enabling a preemptive medicine paradigm.

Finally, given preemptive medicine's lengthy payoff cycles and counterfactual nature—its value being found in the disease that did not occur—there will need to be a different framework for evidence. The field of preemptive medicine will be undercapitalized if it is only possible to make a clinical claim after the fact, since the time horizons may be as long as ten to 20 years. Instead, if it can be proven that particular biomarkers are strongly associated with the successful prevention of future disease, recognition should be given for interventions that show a demonstrable change in those biomarkers.

Education and training

Today's medical schools are focused primarily on sickness rather than on health. A relatively small proportion of medical students will go on to focus on public health, but the overall emphasis reflects the focus and funding of today's healthcare systems. Medical students are taught the art of diagnosing disease based on symptoms and current diagnostic tools that detect disease as well as current practice on how to treat it. If preemptive medicine is to become a reality, there will need to be fundamental reforms to medical education and training for this new field. Changes will need to be made across all countries that decide to pursue a preemptive medicine agenda.

The medical school curriculum will need to change so that all future medical students have a grounding in the principles and opportunities of preemptive medicine and a scientific understanding of pre-disease etiologies as well as biomarkers. Preemptive medicine will need to become an integral part of medical education and training, with all clinical practice grounded in an understanding of the trajectory of cellular and physiological changes from pre-disease through to late-stage disease. It is also likely that some physicians will want to specialize in preemptive medicine, which may require new training pathways to be developed. Tomorrow's doctors may learn how to modify the gut microbiome or when to offer a new cancer vaccine or a program of molecular nutrition that eliminates the progression of dysplasia to carcinoma. The possibilities are limitless.

Financing

More attention will need to be paid to health as an asset that is essential to all wealth creation, whereby investments in health have a measurable return. Government finance officials will need to see preemptive medicine as an investment category rather than merely a cost center.[40] This will rely on a new approach to measurement that focuses on the "stock" of health in a population rather than the flows of activity that are associated with today's healthcare systems. One major change would be to regard all government spending on preemptive medicine as being capital expenditure that gets recognized as such on government balance sheets.

Vaccines provide a highly relevant example. By making forward market commitments, governments and international institutions have de-risked the global market for vaccines, allowing manufacturers to invest in additional capacity and resulting in significant price drops. The approach pioneered by the global vaccines alliance, Gavi, has been adopted by many national government during the Covid-19 pandemic. Governments have a critical role in market shaping for vaccines and other preemptive medicine interventions. Policy decisions will have a crucial impact on whether more vaccines are developed for other infectious diseases and on the wider prospects for preemptive interventions.

There will need to be a fundamental change to the scope and responsibility of the public sector (discussed further below) that aims to mobilize the creativity and ingenuity of the private sector to create valuable innovations in this novel field. Public investment will be required to take risks that the private sector cannot and to "crowd in" private investment. Major changes to innovation policy will be required and new institutions will need to be constructed.

There will need to be a new financial framework that is based on the value created for the individual, economy, society, and payer rather than just the unit cost incurred. Meaningful rewards for innovation will need to be inbuilt and go far beyond the value-based pricing mechanisms piloted in some health systems today. Moreover, given that preemptive medicine interventions will have a cost in the present but a payoff in the future, new frameworks will need to be designed to correct short-termism from healthcare payers who may avoid present costs if they are unlikely to be the recipients of the benefits.

Political, economic, and social implications of the preemptive health paradigm

More productivity, more growth

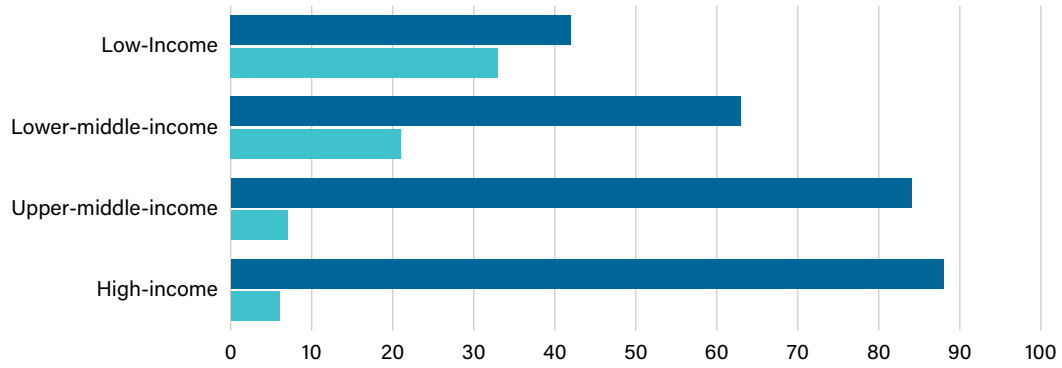
The adoption of a global preemptive medicine agenda would improve the quality of life for the world's population, increasing individuals' ability to contribute to society as people live longer with fewer chronic conditions.[41] Healthy populations tend to reach higher levels of income and enjoy greater economic and social wellbeing, and not only because those living in developed countries tend to experience better health. Improvements in the health stock of a country are broadly linked to increased economic growth and labor force productivity.[42]Most of the economic debate revolves around the magnitude of this impact. A quantification of health improvements in Pakistan between 1980 and 2010, for example, found that following a 1% improvement in health status, workers' productivity rose by 13.4%.[43] Globally, one study found that productivity rose by 6.7% following a 10-percentage point increase in adult survival (the chance of living from 15 to 60).[44] Overall, there is compelling evidence that improved health can promote greater productivity.

Preemptive medicine is an investment with a return. Its positive influences will benefit future generations, as health improvements will heavily affect children—the future labor force. Healthier children attend class more and tend to utilize their education better. On top of that, higher nutrition levels contribute to improved physical and cognitive abilities in children, enhancing the schooling experience and leading to higher literacy levels. In both developed and emerging economies, improvements in health have been linked to subsequent gains in education (which in turn translate to higher income). Following an abrupt decline in worm infections resulting from the successful Rockefeller Sanitary Commission eradication campaign in southern US states in the 1910s, the income gap between north and south was reduced by one-quarter.[45] Indeed, in lower-income countries such as Kenya and Jamaica, deworming has been consistently linked to lower levels of school absenteeism.[46]

While preemptive medicine measures can reduce comorbidity and improve outcomes during infectious disease outbreaks like Covid-19, its most substantial long-term impact could be on the incidence of noncommunicable diseases (NCDs, also known as chronic diseases). According to the WHO's latest data, NCDs are responsible for over 70% of all global deaths (88% in high income countries).[47] The share is lower in low-income countries, but it is still the case that countries of all income levels would see significant gains through a more effective preemptive medicine agenda.

Cause of death, % of total within income group – 2019

Female and male, all age groups NCDs Infectious diseases



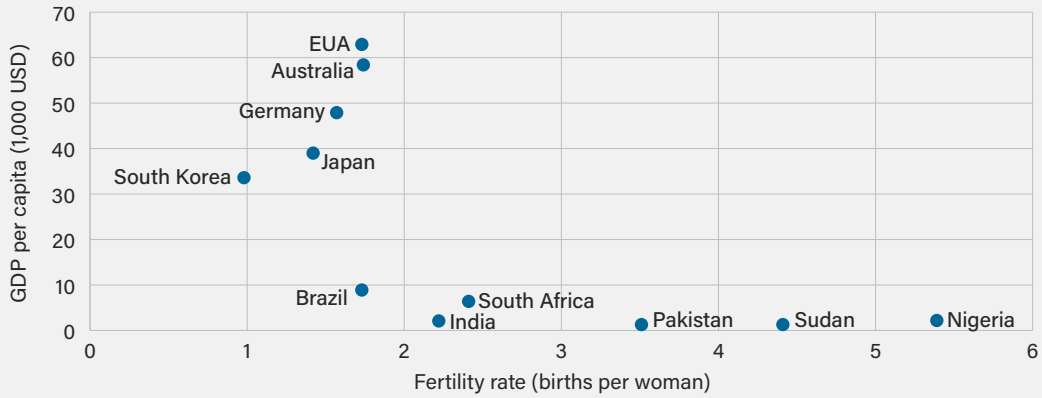
Source: WHO

Leapfrogging to preemptive medicine in emerging markets?

A preemptive medicine agenda could be particularly attractive for low- and middle-income countries as a strategy for accelerating their economic development. A strong preemptive medicine agenda would ultimately slow population growth and hasten the demographic transition in emerging markets over the longer term.[4849] While untangling the myriad factors affecting fertility rates can be tricky, the general long-term trend would be toward families that are healthier and invest more in their children and their futures. As the chart shows, lower fertility and higher incomes tend to go hand in hand.

One reason that improvements in health affect fertility levels is that in places with high infant and child mortality, women tend to give birth to more children than they would like to offset the risk of child mortality[50] If expected deaths in the family fall as a result of longer lives and lower mortality rates, families are likely to have fewer children—and invest more in them. While the long-term effect of health improvements on fertility rates is negative, this demographic transition is not immediate. There is a multi-year lag between improving mortality rates and declines in fertility in low-income countries—populations balloon before fertility rates catch up. Of course, many factors influence fertility rates; female empowerment and labor force participation, healthcare availability, family income levels, literacy levels, and infrastructure also play a role[51]

Fertility rates and GDP per capita, 2018



Sources: WHO and The World Bank

There is considerable potential for lower-income countries to "leapfrog" to preemptive medicine. The absence of well-developed "sick care" systems could provide a "clean slate" for the adoption of a new approach. Low barriers to entry, fewer regulations, and lower costs can help spur technology development outside of developed markets. Outside healthcare, the rapid adoption of mobile technology without investment in fixed lines first in countries such as China, the Philippines, and Vietnam stands as an example of the potential for substantial upgrading capacity.52 This will not always be easy, as there are considerable barriers to technology adoption. Basic infrastructure issues, such as the lack of affordable and reliable electricity, have stymied leapfrogging in sub-Saharan African countries including Kenya and South Africa.53

In some cases, however, healthcare technology developed in lower income countries can be particularly well suited to address specific local challenges, including cost sensitivity and access in more remote areas, and interest in the resulting products can extend well beyond emerging markets. General Electric's ultrasound and portable electrocardiogram machines were developed by subsidiaries in India and later introduced in the US.[54] Other examples include the use of drones to deliver supplies to hospitals, first developed in Rwanda, and of telemedicine kiosks in Kenya.[55] Given the technologies' ability to provide quality care at lower costs across countries, there is ample opportunity to export these innovations to developed markets.

Middle income countries may have the most difficult time adapting to preemptive medicine. Their existing healthcare infrastructure would need to be overhauled in a move to a new model. Lower income countries will have fewer expensive legacy issues to deal with, and higher income countries have more resources to put toward upgraded technologies and treatments.

The international community should work to ensure that low- and middle-income countries have the capacity to take advantage of new technologies. This will not happen automatically, and steps should be taken to ensure that technology is cost-effective. A serious concern is that the US and other developed countries continue to export expensive health technologies and drugs to low- and middle-income countries, where they are considered the gold-standard. This has consequences for the structure of healthcare within the importing country. Rather than developing rural health clinics, countries might import the newest, often expensive, treatments for use in urban hospitals and health centers.

A challenging transition

The adoption of a preemptive medicine paradigm would have profound positive effects on human health, progress, and economic growth. But we are clear-eyed about the potential risks that this new paradigm could pose: complicating innovation, impinging on privacy, and widening inequality among nations. Governments, corporations, and citizens should try to mitigate these risks from the outset, and "build in" mechanisms to ensure that the benefits are maximized and the downsides are minimized. This will likely require creating new national agencies in many countries, developing an international consensus about best practices, and perhaps creating a new international body to regulate compliance and promote equality.

The active state and life sciences innovation

Adoption of a preemptive medicine paradigm would reshape relations between the public and private sectors. A restructuring of the health sector will, in many countries, mean a much more significant government role in the lives of citizens. At the outset, public and private leaders should negotiate and build consensus regarding "public goods" and who should pay for them—that is, how much is socialized and how much remains with the individual. A durable foundation is needed across political parties and interest groups. Governments should be intentional about implementing a strategy to ensure it withstands economic fluctuations. In the event of an economic downturn, the gulf between expectations and state capacity could widen, creating risks to government stability.

Once a consensus is built on the provision of public goods, governments can begin to address areas that the market does not. High risks or long timelines, which are often characteristics of life sciences research, can dissuade private sector investors.[56] Government programs should be designed with an eye toward promoting innovation by taking risks that the private sector cannot and crowding in investment. Patent policies will be central to this effort.[57] Governments should also be aware of potential distortions introduced by the patent system and work to mitigate them.[58]

Effective programs should focus on activities that would not have otherwise been undertaken by private actors. In the case of basic science research, benefits may not be immediately apparent. In other instances, societal benefits may be greater than economic returns. Governments can, and should, provide support alongside private sector actors to spur investment in these areas and fill in the gaps in private sector funding.

Several government programs offer examples of initiatives that have promoted innovation, and investment in basic science research has been shown to pay off in terms of subsequent development of technologies. One recent study found that a $10 million increase in funding from the National

Institute of Health leads to a net increase of 2.7 patents on average.[59] There is also evidence that the introduction of the Medicare program in 1966 stimulated the diffusion of then-new technologies.[60] And, outside of the life sciences field, the Defense Advanced Research Projects Agency (DARPA) has demonstrated the capacity for government to support game-changing innovations, including not only precision weapons and stealth technology, but also significant civil applications such as automated voice recognition, language translation, and GPS technologies.

Research can also guide the design of specific policies that promote innovation while minimizing market distortions. Research and development tax credits have been shown to have a big impact on innovation on a short time horizon in the life sciences industry and beyond.[61]

Another promising model for cost-saving innovation is "demand-pull" funding for a specific treatment, such as the US government's effort to subsidize the Covid-19 vaccines.[62] Operation Warp Speed was successful in part because of the early investment in, and encouragement of, the rapid development of vaccines. But it also worked through advance contracts for purchase and a complementary set of policies that reduced private sector production risks.

While working to spur innovation, states should take care to avoid deterring private sector investment in innovation. Poorly conceived state involvement can run the risk of "crowding out" private projects by simply duplicating investment that would have taken place anyway.

Protecting privacy and preventing abuse

An essential component of preemptive medicine is expanding the collection and use of personal health data by the government and private corporations. Empowering citizens to understand the trajectory of their health has clear benefits, but the process of collecting and using this data would exacerbate widespread concerns in democratic governments about data privacy. It could also entrench authoritarian systems by providing them with additional tools to surveil and control citizens. Just as with our physical security, however, there are likely to be some trade-offs between privacy and health security. Striking the wrong balance between privacy and health security has costs in both directions: whether they are invasions of our rights and expectations of privacy or a loss of individual and collective health.

In democratic states, the public and private sectors cannot impose a new preemptive medicine paradigm on citizens without their buy in. In recent years, the climate in most Western democracies has turned hostile toward social media companies accused of amassing too much economic and political power—which is derived from their accumulation of personal data. The accumulation of data of any kind can breed efficiencies but also present opportunities for abuse. For a preemptive medicine paradigm to succeed in a democracy, citizens must not only be assured of the health benefits but also of efforts to limit the prospect of misuse of an individual's most private information.

Many Western countries impose strict safeguards to prevent law enforcement and intelligence agencies from abusing the intentional or incidental collection of citizens' data. The same care should be taken to protect health data. Democracies can protect citizens' health data by creating data protection agencies with independent oversight and enforcement capabilities to bolster existing legislative protections such as the Health Insurance Portability and Accountability Act in the US and the General Data Protection Regulation in Europe.[63] Several European countries have set a standard for how democracies can safeguard health data and build public confidence. The UK's National Health Service uses an independent review process to regulate health data use, and the national health information system allows patients to opt out of sharing health data beyond their own physician.[64] Denmark is also a world leader in protecting collected healthcare data while allowing robust collaboration with research.[65] Governments also have to be wary about data security, given massive thefts of personal data by governments and criminal enterprises over the past decade.[66] Health systems should work closely with security services to ensure adequate protections within the framework of strict safeguards.

Democracies must also be attuned to ways preemptive medicine could evolve in authoritarian states. These states could use preemptive medicine as a pretext to expand surveillance of and discrimination against ethnic minorities or political dissidents, as well as to monitor entire populations.[67] The Covid-19 pandemic has demonstrated new ways that authoritarian states can leverage health data.[68] For example, there have been reports of plans to expand a Covid-19 quarantine app to rate citizens on a health scale from 0 to 100, using inputs including electronic medical records and lifestyle choices.[69] It is not difficult to see how this data could be collected and exploited in the future. Granular knowledge about every citizen's health condition would afford an authoritarian state yet another tool for control, especially if it is paired with other data (such as a "social credit score") to direct all aspects of a person's life.[70] The West cannot compel authoritarian governments to safeguard individual privacy, but it can create costs and downsides for not doing so.

New institutions will be needed

Promoting innovation, protecting privacy, and bridging inequality will require steps at the national and international level. These include creating new national preemptive medicine initiatives in many countries, developing a broad international consensus on preemptive medicine, and establishing an international organization to enforce and promote these norms.

A comprehensive roadmap for implementing a preemptive health agenda will be required. While there is no one-size-fits-all solution, there are a number of potential models that can be followed. And they are not necessarily exclusive; any approach will need to have complementary domestic and international elements.

First, many governments will need to establish a national-level Health Security Agency focused on protecting against exogenous threats like pandemics, bioterrorism, and infectious disease—much as the UK has already done. These challenges cannot be subordinated to existing health infrastructures and require dedicated funding and bureaucratic heft.

Second, there need to be major changes to existing agencies to address the challenge of preemptive health, with a focus on providing better funding for life sciences. There are many possible vehicles that could be helpful. In the US, one way would be to establish a joint venture between a US basic research agency and the National Institutes of Health (NIH), like what has been done in the UK. The gold standard for this approach in the US has been the military's DARPA, which since its creation over 50 years ago has produced an extraordinary range of innovations and invention, spanning the internet, GPS, stealth technologies, and new materials. The agency's innovations have had dramatic implications for the private sector, creating value in health, communication, and even sporting equipment.

Whether DARPA would be the right partner for non-defense research is an open question, but there is little doubt that the model for public-private partnership holds a great deal of promise. Indeed, the Biden administration has proposed the creation of a new agency, modeled on DARPA, that would aim to speed the development of medical treatments by funding risky, innovative projects. Dubbed ARPA-Health, it would be housed at the NIH and have an initial budget of $6.5 billion. It would focus first on cancer and diseases such as Alzheimer's and diabetes, but over the longer run it could serve as an important platform for a broader approach to preemptive medicine.

Ultimately, these approaches can encourage better preemptive care by providing more funding; a partnership through the NIH provides a constructive framework for collaboration and connectivity for the healthcare industry. Alternatively, financing for innovation could be provided by the Centers for Medicare and Medicaid Services and its innovation center, though the center's narrower scope and more limited mandate could constrain its reach. In any of these models, funding can have important knock-on effects by supporting preemptive health both through its encouragement of markets—via "demand pull" and "supply push" dynamics—and by putting the spotlight on critical

gaps in our current system—for example, end stage disease. Beyond funding, a new agency within the FDA, a preemptive medicines division, could help with domestic policy coordination. The Endless Frontier Act provides a template for government intervention in support of basic research and technological innovation, and it could be a model for funding a preemptive medicine initiative. The legislation would fund and facilitate advances in a broad range of healthcare fields, including biotechnology, medical technology, genomics, and synthetic biology.

Third, the international community has a role to play. Countries need to develop common norms and rules of the game pertaining to the use of personal health information, specifically regarding surveillance and inequality. Some countries would object to any new international norms or organizations on sovereignty grounds, but individual country objections cannot stop the pursuit of a basic human right. And as a new architecture is established, reluctant states will witness the benefits of working within it.

A new institutional framework will need to be established at a global level. One option would be to establish an International Health Protection Agency to coordinate national Health Security Agencies, promote technology transfer, and safeguard privacy. The agency could be modeled on the UN's International Atomic Energy Agency.[71] Such a body could be staffed by an independent international team of accredited experts and operate on the basis of majority vote among member states. It could also promote the sharing of best practices among national Health Security Agencies. Countries would submit their preemptive medicine systems to international monitoring, with the goal of ensuring sufficient security and privacy protection and detecting potential abuses, such as discrimination against certain populations. It could also monitor major cases of inequality in access to preemptive medicine technology and recommend remedies. The agency might publicize assessments and perhaps have the power to refer countries that abuse the rights of their citizens to the UN Security Council. Creating a new institution of this type would help fill a gap in the international policy architecture related to data security and privacy, and it would be consistent with other proposals to create a World Data Organization.[72]

Finally, the WHO's traditional powers and responsiveness should be enhanced. Governments should commit to the WHO's mandate for disease outbreak surveillance, the weaknesses of which were revealed during the Covid-19 pandemic, and to a thorough update to its International Health Regulations.

Conclusion

Covid-19 has inflicted the biggest shock on governments and populations since World War II. It can, should, and will jolt leaders and citizens to view health as a basic human right. All inhabitants of the planet should enjoy the highest possible level of protection against exogenous and chronic threats.

The unprecedented, dramatic, and effective development of vaccines demonstrated human resilience and ingenuity. It showed that technology had taken us to new heights. It showed that the unimaginable is doable. The same spirit must infuse our approach to human health.

That leads us to devise and advocate the concept of preemptive medicine, and its two planks. The first, health security, will enhance protections from exogenous threats such as disease. The second will prevent or delay endogenous threats—those that the body can inflict on itself because of age, genetic makeup, or social patterns.

Preemptive medicine will bring with it a new operating system; a new approach to measurement that focuses on the stock of health in a population; an understanding that health is an asset that is basic to national productivity; a view of value that transcends the unit cost incurred; new regulations that suit preemptive medicine; and incentives and frameworks to keep the long view front and center.

The payoff would be significant. People would live longer, healthier lives, and they would contribute more productively to society. Families will be able to invest more in children and expand educational opportunities. To maximize these benefits, new national and international organizations should be established to ensure optimal international coordination and technology transfer. The opportunity is clear. We should not wait until the next pandemic takes its toll to find a better approach.

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