### 1AC: Innovation

#### Advantage 1 is Innovation:

#### Most recent evidence concludes Aff – 78% of New Drugs aren’t innovative but rather repurposed.

PFAD 21 Patients for Affordable Drugs 2-3-2021 “BIG PHARMA’S BIG LIE: THE TRUTH ABOUT INNOVATION & DRUG PRICES” <https://patientsforaffordabledrugs.org/2021/02/03/innovation-report/> (a patient advocacy and lobbying organisation based in Washington, D.C. founded by David Mitchell who suffers from multiple myeloma. Ben Wakana is the executive director. It focuses on policies to lower drug prices.)//Elmer

The drug industry talks a lot about how reforms to lower prices threaten cutting-edge breakthroughs, but in reality, **only a fraction of new medications are truly innovative**. **Since 1975**, **only 10** to 15 **percent** of drugs entering the market **represented** **therapeutic advances**; **instead**, **drug companies prioritized the development of existing drugs with minor variations that lack clinical significance**.21 Drug patents offer a stark illustration of this point. Between 2005 and 2015, **78 percent of drug patents were related to drugs already on the market.**22 **Instead of investing in R&D that could lead to new** breakthrough **therapies**, **drug companies spend resources obtaining patents on old drugs** — not to improve user experience — but **to extend patent protection**, prolong monopoly pricing periods, and keep generic competitors off the market. So if we understand that new drugs are not the same as new cures, a small reduction in new drugs doesn’t pose a threat to innovation. Harvard economist Richard Frank summed it up this way: “If drug companies claim lowering drug prices means somewhat fewer new drug launches, remember that there are **numerous new products sold every year whose elimination would have little to no impact on the health of Americans**.”23 If our current system of drug development does not result primarily in truly innovative drugs, we can’t let the pharmaceutical industry use the threat of R&D cuts as a scapegoat to thwart reforms. We can create a system that incentivizes valuable innovation that delivers meaningful clinical benefit to patients — instead of repurposing old drugs.

#### The only major study confirms our Internal Link – Evergreening decimates competition by resulting in functional monopolies

Arnold Ventures 20 9-24-2020 "'Evergreening' Stunts Competition, Costs Consumers and Taxpayers" <https://www.arnoldventures.org/stories/evergreening-stunts-competition-costs-consumers-and-taxpayers/> (Arnold Ventures is focused on evidence-based giving in a wide range of categories including: criminal justice, education, health care, and public finance)//Elmer

In 2011, Elsa Dixler was diagnosed with multiple myeloma. That August, she was prescribed Revlimid, a drug that had come on the market six years earlier. By January 2012, she went into full remission, where she has remained since. So long as Revlimid retains its effectiveness, she will take it for the rest of her life. “I was able to go back to work, see my daughter receive her Ph.D, and have a pretty normal life,” said Dixler, a Brooklyn resident who is now 74. “So, on the one hand, I feel enormously grateful.” But Dixler’s normal life has come at a steep financial cost to her family and to taxpayers. Revlimid typically costs nearly $800 per capsule, and Dixler takes one capsule per day for 21 days, then seven days off, and then resumes her daily dose, requiring 273 capsules a year. Since retiring from The New York Times at the end of 2017, she has been on Medicare. Dixler entered the Part D coverage gap (known as the donut hole) “within minutes,” she said. She estimates that adding her deductible, her copayment of $12,000, and what her Part D insurance provider pays totals approximately $197,500 a year. Revlimid should have **been subject to competition** from generic drug makers starting in 2009, bringing down its cost by many orders of magnitude. But by obtaining **27 additional patents**, eight orphan drug exclusivities and 91 total additional protections from the U.S. Food and Drug Administration (FDA) since Revlimid’s introduction in 2005, its manufacturer, Celgene, has extended the drug’s **monopoly** **period** **by 18 years** — through March 8, 2028. “I cannot fathom the immorality of a business that relies on **squeezing people with cancer**,” Dixler said, noting her astonishment that Revlimid has obtained orphan drug protections when it treats a disease that is not rare and does not serve a very limited population. She also observed that Revlimid’s underlying drug is thalidomide, which has been around for decades. “They didn’t invent a new drug, rather, they found a new use for it,” she said. “The cost of Revlimid has imposed constraints on our retirement,” Dixler said, “but when I hear other people’s stories, I feel very lucky. A lot of people have been devastated financially.” Revlimid is a case study in a process known as “evergreening” — artificially sustaining a monopoly for years and even decades by manipulating intellectual property laws and regulations. Evergreening is most commonly used with blockbuster drugs generating the highest prices and profits. **Of the roughly 100 best-selling drugs, more than 70 percent have extended their protection** from competition at least once. More than half have extended the protection cliff multiple times. The true scope and cost of evergreening has been brought into sharper focus by a groundbreaking, publicly available, comprehensive database released Thursday by the Center for Innovation at the University of California Hastings College of Law and supported by Arnold Ventures. **The Evergreen Drug Patent Search is the first database to exhaustively track the patent protections filed by pharmaceutical companies**. Using data from 2005 to 2018 on brand-name drugs listed in the FDA’s Orange Book — a listing of relevant patents for brand name, small molecule drugs — it demonstrates the full extent of how evergreening has been used by Big Pharma to prolong patents and delay the entry of generic, lower-cost competition. “Competition is the backbone of the U.S. economy,” said Professor Robin Feldman, Director of the UC Hastings Center for Innovation, who spearheaded the database’s creation. “But it’s not what we’re seeing in the drug industry. “With evergreening, pharmaceutical companies repeatedly make slight, often trivial, modifications to drugs, dosage levels, delivery systems or other aspects to obtain new protections,” she said. “They pile these protections on over and over again — so often that 78 percent of the drugs associated with new patents were not new drugs coming on the market, but existing drugs.” Competition is the backbone of the U.S. economy. But it’s not what we’re **seeing in the drug industry**. Professor Robin Feldman Director of the UC Hastings Center for Innovation In recent decades, evergreening has systematically undermined the Drug Price Competition and Patent Term Restoration Act of 1984, which created the generic drug industry. Commonly known as the Hatch-Waxman Act, it established a new patent and market exclusivity regime in which new drugs are protected from competition for a specified period of time sufficient to allow manufacturers to recoup their investments and earn a reasonable profit. When that protection expires, generic drug makers are incentivized to enter the market through a streamlined regulatory and judicial process. Drug prices typically drop by as much as 20 percent when the first generic enters the market**, and with more than one generic manufacturer, prices can plummet by 80 to 85 percent**. “Hatch-Waxman created an innovation/reward/competition cycle, but it’s been distorted into an innovation/reward/more reward cycle,” Feldman said. “To paraphrase something a former FDA commissioner once said, the greatest creativity in Big Pharma should come from the research and development departments, not from the legal and marketing departments.” Feldman led the development of the Evergreen Drug Patent Search in response to repeated requests from Congressional committees, members of Congress, state regulators and journalists for information about specific drugs and companies. “We want to make it so anyone can have the question about drug protections at their fingertips whenever they want,” Feldman said. “It’s designed to be easy and user-friendly, and to enhance public understanding about how competition may be limited rather than enhanced through the drug patent system.” The **database** was **created through** a painstaking process of **combing** through **160,000 data points** **to examine every instance where a pharmaceutical company added a new drug patent or exclusivity**. “Most of it was done by hand,” Feldman said, “with multiple people reviewing it at every stage. And along the way we repeatedly made conservative choices. **We erred on the side of underrepresenting the evergreen gain** to be sure we were as fair and reasonable as possible.” Among the 2,065 drugs covered in Evergreen Drug Patent Search, there are many examples of the evergreening strategy used by pharma to delay the entry of competition, especially generics, often for widely prescribed drugs, including those used to treat heartburn, chronic pain, and opioid addiction. Nexium Before Nexium, there was Prilosec, a popular drug to treat gastroesophageal reflux disease (GERD). But its patent exclusivity was due to expire in April 2001. In the late 1990s, with a precipitous drop in revenue looming, Prilosec’s manufacturer, AstraZeneca, decided to develop a replacement drug. Using “one-half of the Prilosec molecule — an isomer of it,” the result was Nexium, which received approval in February 2001. Essentially an evergreened version of Prilosec, Nexium’s exclusivity was then extended by more than 15 years, as AstraZeneca received 97 protections stemming from 16 patents. These included revised dosages, compounds, and formulations. Feldman said that tinkering changes such as Nexium’s do not involve the substantial research and development required for a new drug, nor do they constitute true innovations, yet for a decade and a half, patients and taxpayers were forced to pay far more than was warranted for GERD relief. In fact, in 2016 — one year after patent exclusivity expired — Nexium still topped all drugs in Medicare Part D spending, totaling $1.06 billion. Suboxone Use of this combination of buprenorphine and naloxone for treating opioid addiction has exploded in the wake of the opioid epidemic. Since its approval, Suboxone’s manufacturer, Reckitt Benckiser (now operating as Indivior), extended its protection cliff eight times, gaining nearly two extra decades of exclusivity through early 2030. The drug maker gained six patents for creating a film version of the drug — notably around the time protection was expiring for its tablet version. (The therapeutic benefits of the film and tablet are identical.) An earlier version of Suboxone also obtained an orphan drug designation, despite an opioid epidemic that has expanded Suboxone’s customer base to millions of potential customers. Suboxone generates more than $1 billion in annual revenue and ranks among the 40 top-selling drugs in the U.S. Truvada When Truvada, commonly referred to as PrEP, was approved in 2004, this HIV-prevention drug was a breakthrough. But 16 years later — and 14 years after its original exclusivity was to expire — it retains its monopoly status. Truvada’s manufacturer, Gilead, has received 15 patents and 120 protections since it came on the market, extending its exclusivity for more than 17 years, until July 3, 2024. In countries where generic Truvada is available, PrEP costs $100 or less per month, compared to $1,600 to $2,000 in the U.S. As a result, Truvada is unaffordable to many people **who need protection from HIV**. Barred from access, they are left vulnerable to infection. “We’re establishing a precedent that a pharmaceutical company can charge whatever it wants even as it allows an epidemic to continue, and the government refuses to intervene,” said James Krellenstein, co-founder of the group PrEP4All. “That should scare every American. If it’s HIV today, it will be another disease tomorrow.” EpiPen First approved in 1987, the EpiPen has saved the lives of countless numbers of people with deadly allergies. But it is protected from competition until 2025 — 38 years after its introduction — because its owner, Mylan, has filed five patents, four since 2010, all involving tweaks to the automatic injector. The actual medication used, epinephrine, has existed for more than a century — the innovation here is in the delivery device. Because these small changes to the injector have maintained its monopoly for so long, the cost of an EpiPen package (containing two injectors) has risen from $94 when Mylan purchased the device to between $650 and $700 today. For many people, especially parents of children with severe reactions to common allergens like peanuts, EpiPen’s increasing price tag imposes an onerous financial burden. What Can Be Done As the Evergreen Drug Patent Search makes clear, the positive impact of Hatch-Waxman has been steadily and severely eroded by a regulatory system vulnerable to increasingly sophisticated forms of manipulation. “You might say that the patent and regulatory system has been weaponized,” Feldman said. “When billions of dollars are at stake, there’s a lot of money available to look for ways to exploit the legal system. And companies have become adept at this, as our work has found.” There are several key steps that Congress could take to restore the balance between innovation and competition that is the key to a successful prescription drug regulatory process. These may include: Imposing restrictions on the number of patents that prescription drug manufacturers can defend in court to discourage the use of anticompetitive patent thickets. Limiting the patentability of so-called secondary patents — which don’t improve the safety or efficacy of a drug — through patent and exclusivity reform. Reforming the 180-day generic exclusivity, which can currently be abused to block other competitive therapies. “**The Evergreen Drug Patent Search provides the publicly available, evidence-based foundation that defines the extent of the problem**, and it can be used to develop policies that solve the problem of anti-competitive patent abuses,” said Kristi Martin, VP of Drug Pricing at Arnold Ventures. “Our incentives have gotten out of whack,” Martin said. “The luxury of monopoly protection should only be provided to innovations that provide meaningful benefits in saving lives, curing illnesses, or improving the quality of people’s lives. It should not be provided to those gaming the system. If we can change that, we can save consumers, employers, and taxpayers many billions of dollars while increasing the incentives for pharmaceutical companies to achieve breakthroughs."

#### Reject Negative Turns – they’re pharmaceutical lies – the Plan isn’t anti-Patent, just pro-innovation – breaking down secondary patents is key.

* AT Advantage CPs to solve Drug Prices

Radhakrishnan 16 Priti Radhakrishnan 6-14-2016 "Pharma’s secret weapon to keep drug prices high" <https://www.statnews.com/2016/06/14/secondary-patent-gilead-sovaldi-harvoni/> (Priti Radhakrishnan is cofounder and director of the Initiative for Medicines, Access & Knowledge (I-MAK), a US-based nonprofit group of scientists and lawyers working globally to get people lifesaving medicines. Before founding I-MAK, she worked as a health attorney in the US, Switzerland, and India.)//Elmer

Skyrocketing drug prices are forcing states to take **unprecedented measures** to rein in health care spending. Vermont just became the nation’s first state to require prescription drug pricing transparency. The New York and Massachusetts attorneys general have launched investigations into major pharmaceutical companies’ and insurers’ drug pricing policies and strategies. These **are important steps**. **But** they **ignore a key driver of the problem: secondary patents**. Familiar to only a few people inside the insular world of intellectual property law, secondary patents work like this: Companies file for additional, defensive patents to thicken the protection around their original base patents. These additional patents **rarely represent anything new in terms of science**. Instead, their **purpose is to** **prolong** **a** company’s **monopoly** and, along with that, its ability to charge high prices for its drugs. Some drugs have dozens of secondary patents. Abbott Labs, for example, has over 108 patents on its HIV drug Kaletra. Take the case of Sovaldi, a treatment for hepatitis C developed by Gilead Sciences. In the United States, Gilead prices Sovaldi at up to $1,000 a pill, or about $84,000 for a complete course of treatment. This pricing strategy helped Gilead clear $18 billion in profits last year, while taxpayer-funded Medicaid programs, state health programs, and patients have trouble affording this astronomically priced drug. Sovaldi is comprised of a base compound — sofosbuvir — for which the pharma giant has filed three patents. On top of that, Gilead has pursued an additional 24 patents, with more likely to come. My organization, the Initiative for Medicines, Access & Knowledge (I-MAK), aims to ensure that people with hepatitis C and HIV around the world get the medicines they need to survive and lead healthy lives. We have evaluated Gilead’s patent portfolio and found that, based on US and international patent law, Gilead does not deserve any of its 27 patents for Sovaldi. Both the base and secondary patents for the drug are based on old science and commonly known techniques. Yet because of its defensive patenting strategy, Gilead will maintain an iron lock on its market share and charge exorbitantly high prices to Americans with hepatitis C until well into the 2030s. Harvoni, another medication that treats hepatitis C, combines sofosbuvir and a drug called ledipasvir. Currently, Harvoni has 27 secondary patents. If these were removed, people in the US could access far cheaper versions of the same drug as soon as 10 years earlier. Based on I-MAK’s conservative estimates, this could open access to treatment for millions of people in the US, saving patients and payers like Medicare and Medicaid $5 billion over an eight-year period. In the US, Harvoni is priced at $94,000 for a course of treatment. In middle-income, high-population countries like Argentina, Brazil, and China, people are forced to pay thousands of dollars for sofosbuvir. Stripping away unmerited patents would reduce drug costs and increase access for millions of people in the US and around the world. **Pharmaceutical companies love to claim that winnowing** their armada of **patents would be a disincentive to innovation** and would limit research into new drugs. **Don’t believe it**. **The industry devotes shockingly little funding to research and development**. Companies **spend** roughly **one-third** of their revenues **on marketing** **and only half as much on research** and development, while spending big on armies of lawyers to devise and defend secondary patents and other so-called “life cycle management” strategies. Drug **research funding** has been **declining for more than a decade**, **while** strategies of **secondary patenting have steadily increased.** We support patents — just not those that are unmerited and that unjustly prolong companies’ market power and prevent legitimate competition.

#### Patents incentivize Negative Innovation.

Feldman 21, Robin C., et al. "Negative innovation: when patents are bad for patients." <https://www.nature.com/articles/s41587-021-00999-0.pdf> (Arthur J. Goldberg Distinguished Professor of Law, Albert Abramson ’54 Distinguished Professor of Law Chair, and Director of the Center for Innovation)//Elmer

Patent law in the United States is historically premised on advancing the interests of society. From the store of productive activity available to all, the government restricts some activities for a limited time in hopes this will redound to the benefit of all by incentivizing innovation1 . The law thereby restricts competition, forgoing the concomitant advantages of the free market, but only during the patent period. After that time, the law expects that competition will enter, driving down prices and spurring new innovation. From this perspective, US patent law centers on the benefit to the public, with the inventor’s reward providing the vehicle for accomplishing this jurisprudential goal. In the health care space, these incentives have resulted in extraordinary success stories, but the **same incentives** can also **result in** a range of undesirable consequences, including excessive development of **similar (but not better) products** (‘me-too drugs’), the focus on drugs for diseases that affect wealthy people and wealthy countries rather than diseases that disproportionately affect the poor and developing nations, and a lack of innovation for types of medicines that may return fewer profits, such as antibiotics2–4 . Similarly, drug companies will **not research the utility of a known** (**and hence unpatentable) chemical**, since the ability to obtain patent protection is central to their business model5 . Past literature has highlighted these problems but has largely overlooked the problem of ‘**negative innovation’**, in which **patent** law **drives innovation into spaces that are affirmatively harmful to patients**. By this, we mean **scenarios** **whereby** **patents create incentives to bring a product to market in a way that is** relatively **harmful to consumers**, and the existence of a patent (and the associated rents) discourages the patentee from taking steps to improve the product so as to prevent the adverse health outcomes. Of course, there are other patent-driven situations of problematic utility, including scenarios that result in purely financial harms, such as drugs that are no better than existing options but are more expensive; scenarios where a small, heightened risk of direct physical harm is offset by lower prices for the drug in question6 ; and scenarios where there is no existing product on the market and inadequate incentives to develop such a product, so any physical harm is the result of the underlying disease or illness7 . Finally, there is a general concern that inadequate new information about existing products is generated in the current system8 . All of these scenarios are different in kind from negative innovation, which results in a harmful (but profitable) product. We focus on this dangerous but overlooked space of the patent landscape, wherein patents themselves lead fairly directly to patient harm. What does negative innovation look like? We highlight a particularly pernicious example, the case of Imbruvica (ibrutinib); suggest the likelihood of broader problems; and outline various strategies for preventing such outcomes going forward. The case of ibrutinib Ibrutinib, a small molecule drug discovered by Pharmacyclics (now a subsidiary of AbbVie), is an irreversible inhibitor of Bruton’s tyrosine kinase (BTK), a key regulator of B cell signaling and growth. It is approved by the US Food and Drug Administration for multiple indications and is most commonly used to treat B cell cancers, such as chronic lymphocytic leukemia. While ibrutinib is effective, it, like all anticancer agents, is toxic. It is all the more puzzling, then, that ibrutinib’s recommended dosage appears to be substantially higher than necessary to achieve the necessary therapeutic effect—or at least, what evidence is available points to that conclusion9 . Problematic incentives created by the patent system make this result unfortunately unsurprising. The basic story is disheartening but simple. Early studies published by Pharmacyclics showed efficacy at low doses (partial response at 1.25 milligrams per kilogram body weight, approximately 40% response at 2.5 mg kg–1, and no relationship of response to dose between 2.5 and 12.5 mg kg–1)10. These reports were shared by Pharmacyclics in a conference abstract in 200911,12 and a press release in 201013. An early patent application by Pharmacyclics (US 2012/0087915 A1) accordingly claimed a full range of doses. Trials to support approval by the US Food and Drug Administration (FDA) continued. In July 2013, ibrutinib received accelerated approval for mantle cell lymphoma based on a 66% response rate in 111 patients treated at 560 mg daily. Notably, the 2013 FDA review included an analysis of the relationship of ibrutinib dose and trough plasma concentration to both response and toxicity. This analysis demonstrated no relationship with response: “Dose-response relationship for BTK occupancy and clinical response in the phase 1 dose escalation trial showed that maximum BTK occupancy and maximum response were achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for average weight of 70 kg)”14—far below the approved dosage of 560 mg. Meanwhile, the FDA also granted accelerated approval for previously treated chronic lymphocytic leukemia on 12 February 2014 on the basis of a 58% response rate in 48 patients treated at a dose of 420 mg daily. Thus, there were now two different doses approved for ibrutinib, with the labeled dose based solely on the dose that was used in the single-arm studies supporting the accelerated approvals. Furthermore, in the context of that approval, the FDA reiterated its assessment that the labeled dose was higher than necessary and included the explicit suggestion to study lower doses: “However, the proposed dose is 2.4-fold higher than the lowest dose that resulted in maximum BTK occupancy and maximum clinical response. Dose-response relationship for ORR and BTK occupancy from phase 1 study suggested that maximum ORR and maximum occupancy was achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for average weight of 70 kg) [see Pharmacometrics review in DARRTS dated 11/01/2013]. The sponsor should thus consider exploring lower doses in future development programs.”15 Those lower doses have not, to our knowledge, been rigorously explored in clinical trials—an unfortunate outcome for patients, since if a lower dose is just as effective with lower side effects, treatment would be safer and better. However, if the lower dose were found to provide better patient outcomes and resulted in a change in the labeled dose, it is likely that the labeled dose would not be covered by the patent. Thus, generic competitors might be able to enter the market sooner, once the primary compound patent lost exclusivity. In fact, the process at the US Patent and Trademark Office (USPTO) and the limits of the granted patents encourage the patent holder to avoid such information entirely. The patent examiner evaluating Pharmacyclics’ method of treatment patents found lower doses obvious on the basis of the 2009 and 2010 conference and press release disclosures, which occurred more than a year before the relevant patent was filed. **Only the highest doses**—420 mg and higher—**were granted** in the issued method of **treatment patent16**. **Patent law thus created incentives to pursue a higher, more toxic dose rather than the lower doses the FDA suggested be explored**. And, adding insult to injury, **once the patent was issued** with narrower claims covering the high doses only, **the drug sponsor** not only lacked incentives to explore the possibility of lower doses, it **had an active incentive not to explore** those **doses** **because evidence that lower doses were safe** and effective **would** sharply **reduce the economic significance of the method of treatment patent** it had narrowly managed to obtain. The patent holder already knew it could not get protection on a lower dose––the USPTO had rejected lower doses as obvious–– so any evidence of the importance of lower doses would have undermined the value of the company’s patent-protected, higher-dose product. Broader possibilities Although ibrutinib is only one example, we are concerned that it may be an indicator of a broader problem, one that either lies ahead or is already lurking. More generally, consider combination products with two drugs at fixed dosages. Many treatment method patents exist in which an independent claim specifies a dose, nominally designed to increase patient adherence but often at a much higher cost17,18. The result is that a prescriber cannot adjust the dosage for only one of the two drugs or discontinue only one component. It is possible, perhaps likely, that some of these combination regimens mirror the dosage issue with ibrutinib, in which the incentives of the patent system have encouraged the development of a drug in a form that is suboptimal for patient health in certain circumstances. This would not be the first time in history that combination medications have proven problematic. More than 50 years ago, a US Senate investigation found that certain combination antibiotics products— developed in an effort to bring something ‘new’ to the market—were useless or dangerous19. Nor is ibrutinib the only time in history that medications have been sold at higher dosages than appropriate for safety and efficacy. Millions of women received the birth control pill Enovid (mestranol/ noretynodrel), containing ten times the necessary dose, before studies pointed to a concerning risk of blood clots19. In another sign of negative innovation, **Gilead** Sciences is alleged to have **intentionally delayed a less-toxic version of its HIV medicine** **until just a few years before the original version’s patent expiration20**. Unfortunately, the pernicious impact of patent incentives described above means that not only are these situations possible, but it is hard to know how frequent or how serious these situations are. Pharmacyclics did not follow the recommendation from the FDA and others to study lower doses. Because its method of treatment patents were tied to the higher dose, they had no economic incentive to do such research— any information on safer dosing outside the scope of the issued claims would undermine the value of their existing patent, and they would be unable to get a new patent for the safer dose on grounds of obviousness. The safety data are starting to emerge anyway, albeit from sources other than the company9.

#### Extinction - generic defense doesn’t apply.

Srivatsa 17 Kadiyali Srivatsa 1-12-2017 “Superbug Pandemics and How to Prevent Them” <https://www.the-american-interest.com/2017/01/12/superbug-pandemics-and-how-to-prevent-them/> (doctor, inventor, and publisher. He worked in acute and intensive pediatric care in British hospitals)//Elmer

It is by now no secret that the human species is locked in a race of its own making with “**superbugs**.” Indeed, if popular science fiction is a measure of awareness, the theme has pervaded English-language literature from Michael Crichton’s 1969 Andromeda Strain all the way to Emily St. John Mandel’s 2014 Station Eleven and beyond. By a combination of massive inadvertence and what can only be called stupidity, we must now invent new and effective antibiotics faster than deadly bacteria evolve—and regrettably, they are rapidly doing so with our help. I do not exclude the possibility that bad actors might deliberately engineer deadly superbugs.1 But even if that does not happen, humanity faces an existential threat largely of its own making in the absence of malign intentions. As threats go, this one is entirely predictable. The concept of a “black swan,” Nassim Nicholas Taleb’s term for low-probability but high-impact events, has become widely known in recent years. Taleb did not invent the concept; he only gave it a catchy name to help mainly business executives who know little of statistics or probability. Many have embraced the “black swan” label the way children embrace holiday gifts, which are often bobbles of little value, except to them. But the threat of inadvertent pandemics is not a “black swan” because its probability is not low. If one likes catchy labels, it better fits the term “gray rhino,” which, explains Michele Wucker, is a high-probability, high-impact event that people manage to ignore anyway for a raft of social-psychological reasons.2 A pandemic is a quintessential gray rhino, for it is no longer a matter of if but of when it will challenge us—and of how prepared we are to deal with it when it happens. We have certainly been warned. The curse we have created was understood as a possibility from the very outset, when seventy years ago Sir Alexander Fleming, the discoverer of penicillin, predicted antibiotic resistance. When interviewed for a 2015 article, “The Most Predictable Disaster in the History of the Human Race, ” Bill Gates pointed out that one of the costliest disasters of the 20th century, worse even than World War I, was the Spanish Flu pandemic of 1918-19. As the author of the article, Ezra Klein, put it: “No one can say we weren’t warned. And warned. And warned. A pandemic disease is the most predictable catastrophe in the history of the human race, if only because it has happened to the human race so many, many times before.”3 Even with effective new medicines, if we can devise them, we must contain outbreaks of bacterial disease fast, lest they get out of control. In other words, we have a social-organizational challenge before us as well as a strictly medical one. That means getting sufficient amounts of medicine into the right hands and in the right places, but it also means educating people and enabling them to communicate with each other to prevent any outbreak from spreading widely. Responsible governments and cooperative organizations have options in that regard, but even individuals can contribute something. To that end, as a medical doctor I have created a computer app that promises to be useful in that regard—of which more in a moment. But first let us review the situation, for while it has become well known to many people, there is a general resistance to acknowledging the severity and imminence of the danger. What Are the Problems? Bacteria are among the oldest living things on the planet. They are masters of survival and can be found everywhere. Billions of them live on and in every one of us, many of them helping our bodies to run smoothly and stay healthy. Most bacteria that are not helpful to us are at least harmless, but some are not. They invade our cells, spread quickly, and cause havoc that we refer to generically as disease. Millions of people used to die every year as a result of bacterial infections, until we developed antibiotics. These wonder drugs revolutionized medicine, but one can have too much of a good thing. Doctors have used antibiotics recklessly, prescribing them for just about everything, and in the process helped to create strains of bacteria that are resistant to the medicines we have. We even give antibiotics to cattle that are not sick and use them to fatten chickens. Companies large and small still mindlessly market antimicrobial products for hands and home, claiming that they kill bacteria and viruses. They do more harm than good because the low concentrations of antimicrobials that these products contain tend to kill friendly bacteria (not viruses at all), and so clear the way for the mass multiplication of surviving unfriendly bacteria. Perhaps even worse, hospitals have deployed antimicrobial products on an industrial scale for a long time now, the result being a sharp rise in iatrogenic bacterial illnesses. Overuse of antibiotics and commercial products containing them has helped superbugs to evolve. We now increasingly face microorganisms that cannot be killed by antibiotics, antifungals, antivirals, or any other chemical weapon we throw at them. Pandemics are the major risk we run as a result, but it is not the only one. Overuse of antibiotics by doctors, homemakers, and hospital managers could mean that, in the not-too-distant future, something as simple as a minor cut could again become life-threatening if it becomes infected. Few non-medical professionals are aware that antibiotics are the foundation on which nearly all of modern medicine rests. Cancer therapy, organ transplants, surgeries minor and major, and even childbirth all rely on antibiotics to prevent infections. If infections become untreatable we stand to lose most of the medical advances we have made over the past fifty years. And the problem is already here. In the summer of 2011, a 43-year-old woman with complications from a lung transplant was transferred from a New York City hospital to the Clinical Center at the National Institutes of Health (NIH), in Bethesda, Maryland. She had a highly resistant superbug known as Klebsiella pneumoniae carbapenemase (KPC). The patient was treated and eventually discharged after doctors concluded that they had contained the infection. A few weeks later, a 34-year-old man with a tumor and no known link to the woman contracted KPC while at the hospital. During the course of the next few months, several more NIH patients presented with KPC. Doctors attacked the outbreak with combinations of antibiotics, including a supposedly powerful experimental drug. A separate intensive care unit for KPC patients was set up and robots disinfected empty rooms, but the infection still spread beyond the intensive care area. Several patients died and then suddenly all was silent on the KPC front, with doctors convinced they had seen the last of the dangerous bacterium. They couldn’t have been more mistaken. A year later, a young man with complications from a bone marrow transplant arrived at NIH. He became infected with KPC and died. This superbug is now present in hospitals in most, if not all U.S. states. This is not good. This past year an outbreak of CRE (carbapenem-resistant enterobacteriaceae) linked to contaminated medical equipment infected 11 patients and killed two in Los Angeles area hospitals. This family of bacteria has evolved resistance to all antibiotics, including the powerful carbapenem antibiotics that are often used as a last resort against serious infections. They are now so resilient that it is virtually impossible to remove them from medical tools such as catheters and breathing tubes placed into the body, even after cleaning. Then we have gonorrhea, chlamydia, and other sexually transmitted diseases that we cannot treat and that are spreading all over the world. Anyone who has sex can catch these infections, and because most people may not exhibit any symptoms they spread infections without anyone knowing about it. Sexually transmitted diseases used to be treatable with antibiotics, but in recent years we have witnessed the rise of multi-drug resistant STDs. Untreated gonorrhea can lead to infertility in men and women and blindness and other congenital defect in babies. As is well known, too, we have witnessed many cases of drug-resistant pneumonia. These problems have arisen in part because of simple mistakes healthcare professionals repeatedly make. Let me explain. Neither superbugs nor common bacterial infections produce any special symptoms indicative of their cause. Rashes, fevers, sneezing, runny noses, ear pain, diarrhea, vomiting, coughing, fatigue, and weakness are signs of common and minor illnesses as well as uncommonly deadly ones. Therefore, the major problem for clinicians is to identify a common symptom that may potentially be an early sign of a major infection that could result in an epidemic. We know that dangerous infections in any given geographical area do not start at the same time. They start with one victim and gradually spread. But that victim is only one among hundreds of patients a doctor will typically see, so many doctors will miss patients presenting with infections that are serious. They will probably identify diseases that kill fast, but slow-spreading infections such as skin infections that can lead to septicemia are rarely diagnosed early. In addition, I have seen doctors treating eczema with antibiotic cream, even though they know that bacteria are resistant to the majority of these drugs. This sort of action encourages simple infections to spread locally, because patients are therefore not instructed to take other, more useful precautions. On top of that, some people are frivolous about infections and assume doctors are exaggerating the threat. And some people are selfish. Once I was called to see a passenger during a flight who had symptoms consistent with infection. He boarded the plane with these symptoms, but began to feel much worse during the flight. I was scared, knowing how infections such as Ebola can spread. This made me think about a way to screen passengers before they board a flight. Airlines could refund a traveler’s ticket, or issue a replacement, in case of sickness—which is not the policy now. We currently have no method to block infectious travelers from boarding flights, and there are no changes in the incentive system to enable conscientious passengers to avoid losing their money if they responsibly miss a flight because of illness. Speaking of selfishness, I once saw a mother drop her daughter off at school with a serious bout of impetigo on her face. When I asked her why she had brought her daughter to school with a contagious infection, she said she could not spare the time to keep her at home or take her to the doctor. By allowing this child to contact other children, a simple infection can become a major threat. Fortunately, I could see the rash on the girl’s face, but other kids in schools may have rashes we cannot see. Incorrect diagnosis of skin problems and mistaken use of antibiotics to treat them is common all over the world, and so we are continually creating superbugs in our communities. Similarly, chest infections, sore throats, and illnesses diagnosed as colds that unnecessarily treated with antibiotics are also a major threat. By prescribing antibiotics for viral infections, we are not only helping bacteria develop resistance, but we are also polluting the environment when these drugs are passed in urine and feces. All of this helps resistant bacteria to spread in the community and become an epidemic. Ebola is very difficult to transmit because people who are contagious have visible and unusual symptoms. However, the emerging infections and pandemics of the future may not have visible symptoms, and they could break out in highly populous countries such as India and China that send thousands of travelers all over the world every day. When a person is infected with a contagious disease, he or she can expect to pass the illness on to an average of two people. This is called the “reproduction number.” Two is not that high a number as these things go; some diseases have far greater rates of infection. The SARS virus had a reproduction number of four. Measles has a reproduction number of 18. One person traveling as an airplane passenger and carrying an infection similar to Ebola can infect three to five people sitting nearby, ten if he or she walks to the toilet. The study that highlighted this was published in a medical journal a few years ago, but the airline industry has not implemented any changes or introduced screening to prevent the spread of infections by air travel passengers, a major vehicle for the rapid spread of disease. It is scary to think that nobody knows what will happen when the world faces a lethal disease we’re not used to, perhaps with a reproduction number of five or eight or even ten. What if it starts in a megacity? What if, unlike Ebola, it’s contagious before patients show obvious symptoms? Past experience isn’t comforting. In 2009, H1N1 flu spread around the world before we even knew it existed. The Questions Remains Why do seemingly intelligent people repeatedly do such collectively stupid things? How did we allow this to happen? The answer is disarmingly simple. It is because people are incentivized to prioritize short-term benefits over long-term considerations. It is what social scientists have called a “logic of collective action” problem. Everyone has his or her specialized niche interest: doctors their patients’ approval, business and airline executives their shareholders’ earnings, hospitals their reputations for best-practice hygienics, homemakers their obligation to keep their own families from illness. But no one owns the longer-term consequences for hundreds of millions of people who are irrelevant to satisfying these short-term concerns. Here is an example. At a recent Superbug Super Drug conference in London that I attended, scientists, health agencies, and pharmaceutical companies were vastly more concerned with investing millions of dollars in efforts to invent another antibiotic, claiming that this has to be the way forward. Money was the most pressing issue because, as everyone at the conference knew, for many years pharmaceutical companies have been pulling back from antibiotics research because they can’t see a profit in it. Development costs run into billions of dollars, yet there is no guarantee that any new drug will successfully fight infections. At the same conference Dr. Lloyd Czaplewski spoke about alternatives to antibiotics, in case we cannot come up with new ones fast enough to outrun superbug evolution. But he omitted mention of preventive strategies that use the internet or communication software to help reduce the spread of infections among families, communities, and countries. It is madness that we don’t have a concrete second-best alternative to new antibiotics, because we need them and we need them quickly. Of course, this is why we have governments, which have been known occasionally in the past as commonwealths. Governments are supposed to look out for the wider, common interests of society that niche-interested professionals take no responsibility for, and that includes public health. It is why nearly every nation’s government has an official who is analogous to the U.S. Surgeon General, and nearly every one has a public health service of some kind. Alas, national governments do not always function as they should. Several years ago physician and former Republican Senator Bill Frist submitted a proposal to the Senate for a U.S. Medical Expeditionary Corps. This would have been a specialized organization that could coordinate and execute rapid responses to global health emergencies such as Ebola. Nothing came of it, because Dr. Frist’s fellow politicians were either too shortsighted or too dimwitted to understand why it was a good idea. Or perhaps they simply realized that they could not benefit politically from supporting it. Plenty of mistakes continue to be made. In 2015, a particularly infectious form of bird flu ripped through 14 U.S. states, leading farmers to preventively slaughter nearly 40 million birds. The result of such callous and unnecessary acts is that, instead of exhausting themselves in the host population of birds, the viruses quickly find alternative hosts in which to survive, and could therefore easily mutate into a form that can infect humans. Earlier, during the 1980s, AIDS garnered more public attention because a handful of rich and famous people were infected, and because the campaign to eradicate it dovetailed with and boosted the political campaign on behalf of homosexual rights. Methicillin resistant Staphylococcus aureus (MRSA) in hospitals, by far the bigger threat at the time, was virtually ignored. Some doctors knew that MRSA would bring us to our knees and kill millions of people worldwide, but pharmaceutical companies and device and equipment manufacturers ignored these doctors and the thousands of patients dying in hospitals as a result of MRSA. They prioritized the wrong thing, and government did not correct the error. And that is partly how antibiotic-resistant infection went from an obscure hospital problem to an incipient global pandemic. Politics well outside the United States plays several other roles in the budding problem that we are confronting. Countries often will not admit they have a problem and request help because of the possible financial implications in terms of investment and travel. Guinea did not declare the Ebola epidemic early on and Chinese leaders, worried about trade and tourism, lied for months in 2002 about the presence of the SARS virus. In 2004, when avian influenza first surfaced in Thailand, officials there displayed a similar reluctance to release information. Hospitals in some countries, including India, are managed and often owned by doctors. They refuse to share information about existing infections and often categorically deny they have a problem. Reporting infections to public health authorities is not mandatory, and so hospitals that fail to say anything are not penalized. Even now, the WHO and the CDC do not have accurate and up-to-date information about the spread of E. coli or other infections, and part of the reason is that for-profit hospitals are reluctant to do anything to diminish their bottom line. Syria and Yemen are among those countries that are so weak and fragmented that they cannot effectively coordinate public healthcare. But their governments are also hostile to external organizations that offer relief. Part of the reason is xenophobia, but part is that this makes the government look bad. Relatedly, most poor-nation governments do not trust the efficacy of international institutions, and think that cooperating with them amounts to a re-importation of imperialism. They would rather their own people suffer and die than ask for needed help. That brings us to the level of international public health governance. Alas, sometimes poor-country governments estimate the efficacy of international institutions accurately. The WHO’s Ebola response in 2014-15 was a disaster. The organization was slow to declare a public health emergency even after public warnings from Médecins Sans Frontières, some of whose doctors had already died on the front line. The outbreak killed more than 28,000 people, far more than would have been the case had it been quickly identified. This isn’t just an issue of bureaucratic incompetence. The **WHO is under-resourced for the problems it is meant to solve. Funding comes from voluntary donations, and there is no mechanism by which it can quickly scale up its efforts during an emergency. The result is that its response to the next major disease outbreak is likely to be as inadequate as were its responses to Ebola, H1N1, and SARS**. Stakeholders admit that we need another mechanism, and most experts agree that the world needs some kind of emergency response team for dangerous diseases. But no one knows how to set one up amid the dysfunctional global governance structures that presently exist. Maybe they should turn to Bill Frist, whose basic concept was sound; if the U.S. government will not act, perhaps some other governments will, and use the UN system to do so. But as things stand, we lack a health equivalent of the military reserve. Neither government leaders nor doctors can mobilize a team of experts to contain infections. People who want to volunteer, whether for government or NGO efforts, are not paid and the rules, if any, are sketchy about what we do with them when they return from a mission. Are employers going to take them back? What are the quarantine rules? It is all completely ad hoc, meaning that humanity lacks the tools it needs to protect itself. And note, by the way, the contrast between how governments prepare for facing pandemics and how they prepare for making war. War is not more deadly to the human race than pandemics, but national defense against armed aggression is much better planned for than defense against threats to public health. There is a wealth of rules regarding it, too. Human beings study and plan for war, which kills people both deliberately and accidentally, but they do not invest comparable effort planning for pandemics, which are liable to kill orders of magnitude more people. To the mind of a medical doctor, this is strange. Creating Conditions for Infections to Spread Superbug infections spread for several interlocking reasons. Some are medical-epidemiological. Most of the infections of the past thirty years have started in one place and in one family. As already noted, they spread because many infectious diseases are highly contagious before the onset of symptoms, and because it is difficult to prevent patients who know they are sick from going to hospitals, work, and school, or from traveling further afield. But again, one reason for the problem is political, not medical. Many governments have no strategies in place to prevent pandemics because they are unwilling to tell their people how infections spread. They don’t want to worry people with such talk; it will make them, they fear, unpopular. So governments may have mountains of bureaucracy with great heaps of rules and regulations concerning public health, but they are generally unwilling to trust their own citizens to use common sense on their own behalf. This, too, seems very strange. Until now, no one has come forward to help us develop strategies to educate people how to identify and prevent the spread of infection to their families and communities. The majority of stakeholders have also been oblivious to the use of new technologies to help reduce the spread of these infections. There are some exceptions. In a fun blog post called Preparedness 101: Zombie Apocalypse, the CDC uses the threat of a zombie outbreak as a metaphor to encourage people to prepare for emergencies, including pandemics. It is well meaning and insightful, yet when my colleagues and I try to discuss ways of scaling up the CDC’s example with doctors and nurses, they shut down. Nobody plans for an actual crisis partly because it is too scary and hence paralyzing to think about. But it is also because it is not most health professionals’ job; it is not what they are trained and paid to do. It is always someone else’s job, except that it has turned out to be nobody’s job. Worse, the situation is not static. While we sit paralyzed, superbugs are evolving. Epidemiological models now predict how an algorithmic process of disease spread will move through the modern world. All urban centers around the entire globe can become infected within sixty days because we move around and cross borders much more than our ancestors did, thanks to air travel. A new pandemic could start crossing borders before we even know it exists. A flu-like disease could kill more than 33 million people in 250 days.3

#### Disease is a non-linear, existential risk - encompasses AND outweighs other threats

Pamlin and Armstrong 15 Dennis Pamlin and Stuart Armstrong February 2015 “Global Challenges: 12 Risks that threaten human civilization: The case for a new risk category” https://web.archive.org/web/20171006070112/https://api.globalchallenges.org/static/wp-content/uploads/12-Risks-with-infinite-impact.pdf (Dennis Pamlin, Executive Project Manager Global Risks, Global Challenges Foundation, and Stuart Armstrong, James Martin Research Fellow, Future of Humanity Institute, Oxford Martin School, University of Oxford)//Re-cut by Elmer

3.1 Current risks Pandemic 3.1.4 Global **A pandemic** (from Greek πᾶν, pan, “all”, and δῆμος demos, “people”) is an epidemic of infectious disease that has spread through human populations across a large region; for instance several continents, or even **worldwide**. Here only worldwide events are included. A widespread endemic disease that is stable in terms of how many people become sick from it is not a pandemic. 260 84 Global Challenges – Twelve risks that threaten human civilisation – The case for a new category of risks 3.1 Current risks 3.1.4.1 Expected impact disaggregation 3.1.4.2 Probability Influenza subtypes266 Infectious diseases have been one of the **greatest causes of mortality in history**. Unlike many other global challenges pandemics have happened recently, as we can see where reasonably good data exist. **Plotting** historic epidemic **fatalities** on a log scale **reveals** that these tend to follow **a power law with a small exponent**: many plagues have been found to follow a power law with exponent 0.26.261 These kinds of power laws are **heavy-tailed**262 **to a significant degree**.263 In consequence most of the fatalities are accounted for by the top few events.264 If this law holds for future pandemics as well,265 then **the majority** of people who **will die** from epidemics will likely die **from the single largest pandemic**. Most epidemic fatalities follow a power law, with some extreme events – such as the Black Death and Spanish Flu – being even more deadly.267 There are other grounds for suspecting that such a highimpact epidemic will have a **greater probability than usually assumed**. **All the features** of an extremely devastating disease **already exist** in nature: essentially **incurable** (Ebola268), nearly **always fatal** (rabies269), **extremely infectious** (common cold270), and **long incubation periods** (HIV271). **If a pathogen** were to emerge that somehow **combined these** features (and **influenza** has **demonstrated antigenic shift**, the **ability to combine features from different viruses272**), **its death toll would be extreme**. Many relevant features of **the world have** **changed** considerably, **making past comparisons problematic**. The modern world has better sanitation and medical research, as well as national and supra-national institutions dedicated to combating diseases. Private insurers are also interested in modelling pandemic risks.273 Set against this is the fact that **modern transport** and **dense** human **population** allow infections to spread much more rapidly274, and there is the potential for urban slums to serve as breeding grounds for disease.275 Unlike events such as nuclear wars, pandemics would not damage the world’s infrastructure, and initial survivors would likely be resistant to the infection. And there would probably be survivors, if only in isolated locations. Hence the risk of a civilisation collapse would come from the **ripple effect** of the fatalities and the policy responses. These would include **political and agricultural disruption** as well as economic dislocation and damage to the world’s trade network (including the food trade). Extinction risk is only possible if the aftermath of the **epidemic fragments** and diminishes **human society to the extent that recovery becomes impossible277 before humanity succumbs to other risks (such as** **climate** change **or further pandemics**). Five important factors in estimating the probabilities and impacts of the challenge: 1. What the true probability distribution for pandemics is, especially at the tail. 2. The capacity of modern international health systems to deal with an extreme pandemic. 3. How fast medical research can proceed in an emergency. 4. How mobility of goods and people, as well as population density, will affect pandemic transmission. 5. Whether humans can develop novel and effective anti-pandemic solutions.

#### We’re on the Brink – new diseases are emerging.

Deccan Herald 21 1-4-2021 Deccan Herald "New deadly virus 'Disease X', much more fatal than COVID-19, could affect humans: Scientists" (Indian English language daily newspaper published from the Indian state of Karnataka by The Printers Mysore Private Limited, a privately held company owned by the Nettakallappa family. It has seven editions printed from Bengaluru, Hubballi, Davanagere, Hosapete, Mysuru, Mangaluru, and Kalaburagi)//Elmer

A **woman** in a remote town in the Democratic Republic of Congo has been **showing** symptoms of hemorrhagic fever, which scientists fear may be a **sign of a new deadly virus, termed ‘Disease X’,** which could be **as contagious as** **COVID**-19 virus **but have Ebola’s fatality** **rate of** 50-**90 per cent**. Disease X, where the ‘X’ standard for ‘unexpected’, has been termed by the World Health Organization (WHO) as hypothetical for now. But the woman in Ingende has been tested for many diseases, including Ebola, but they have all come out negative. Scientists now fear this could be **that deadly virus**, one of many that **could emerge from the** African tropical **rainforests**. “We are now **in a world where new pathogens will come out**. And that is what **constitutes** a **threat for humanity**,” Professor Jean-Jacques Muyembe Tamfum, the scientist who helped discover the Ebola virus in 1976 told CNN, adding that **these new viruses** could be **much deadlier than Covid-19**. The scientist has warned of **many** animal-based **viruses** or those viruses that **can jump the species barrier** and infect humans. He said that Covid-19 is among those diseases, along with rabies and yellow fever.

#### Expanding breadth of Pharma Innovation into neglected diseases results in global linkages that revitalizes global health diplomacy.

Hotez 16, Peter J. Blue marble health: an innovative plan to fight diseases of the poor amid wealth. JHU Press, 2016. (Sabin Vaccine Institute and Texas Children’s Hospital Center for Vaccine Development, Departments of Pediatrics and Molecular Virology and Microbiology)//Elmer

We also need to better understand how these NTDs are actually transmitted within US borders, and I think it is extremely important to learn more about the links between these diseases and poverty. As I noted earlier, a drive through Houston’s Fifth Ward provides some insights, as one can quickly identify predisposing risk factors, including stray animals, dilapidated houses without window screens, standing water and discarded tires, and other evi- dence of environmental degradation, but we need to conduct careful epidemiological studies to really understand the links between poverty and NTDs, as well as animal reservoirs for illnesses such as Chagas disease and others. All of this presents an important research and development agenda for the **NTDs** in the United States. There are no point-of-care diagnostic tests available for most of the NTDs endemic to the nation, so blood from pa- tients must be sent to the CD С or other specialty research laboratories in order to establish a diagnosis for these conditions. As I sometimes point out to general audiences, when you go to your physician and get blood work done, there is no box to check off for toxocariasis or Chagas disease as there is for blood chemistries or other routine tests. We need diagnostic tests that are easily accessible to physicians and nurses. We also need new and improved treatments and vaccines. Because the NTDs are poverty-related diseases, they often fly below the radar screen of the major pharmaceutical companies and are not prioritized. Thus, the drugs used to treat these illnesses are not widely available, so typically the CDC has to be contacted in order to access them. In addition, many of these medicines were developed decades ago and produce a lot of side effects. For instance, the two medicines for Chagas disease—benznidazole and nifurtimox—cause skin rashes, diarrhea, and other unpleasant or even dangerous symptoms and illnesses. Patients using these medications have to interrupt their treatments up to 20% of the time. Moreover, these drugs cannot be used by pregnant women. Currently, new innovations for NTDs like Chagas dis- multinational ease still rely on nonprofit PDPs. The Geneva-based Drugs pharmaceutical for Neglected Diseases Initiative is leading efforts to de- companies have velop new and safer Chagas disease medicines [60], while shown little or modest at our National School of Tropical Medicine the Sab in interest in American Vaccine Institute and Texas Childrens Hospital Center for NTDs. As a result, new Vaccine Development (Sabin PDP) is working to develop products are being a therapeutic vaccine that could be used alongside exist- developed in the ing treatments [61]. These efforts rely on major philan- nonprofit sector. thropic donors. In our case at the Sabin PDP, they include the Kleberg Foundation, the Carlos Slim Foundation, the Southwest Electronic Energy Medical Research Institute, and Texas Childrens Hospital. Summary Points 1. In the United States, 45.3 million people live below the poverty line, roughly the same number of impoverished Americans alive during the early 1960s when Michael Harrington wrote The Other America. Approximately 20 million Americans now live in extreme poverty at one-half the US poverty level, and approximately 5 million are living on less than $2 per day 2. American poverty concentrates in specific areas, especially in southern states, with Texas having the largest numbers who live in poverty Important areas in the South include the Gulf Coast, border areas with Mexico, the Mississippi Delta, and Appalachia. 3. Approximately 12 million Americans are infected with NTDs, led by toxocariasis and trichomoniasis—which disproportionately affect African Americans—and Chagas disease (American trypanosomiasis) and cysticercosis—which disproportionately affect people of Hispanic origin. Toxoplasmosis is another important NTD. Toxocariasis, cysticercosis, and toxocariasis exert important mental health effects on impoverished Americans. Many of these NTDs are transmitted within US borders (autochthonous infections). 4. Arboviral infections are also important NTDs, led by dengue fever in Gulf Coastal areas and West Nile virus infection. WNV can cause chronic, persistent viral infections linked to chronic neurologic and renal disease. 5. There is an urgent need to promote awareness about the NTDs, especially for physicians and other health-care providers. 6. New policies are needed to expand surveillance for the NTDs affecting the United States. New legislation has been adopted in Texas, while additional bills are being introduced in the US Congress. Epidemiological studies are also needed to better understand how these diseases are transmitted and how they are linked to extreme poverty in the American South and elsewhere. 7. There is an urgent need for new “control tools” for American NTDs, including point-of-care diagnostics, antiparasitic and antiviral drugs, and vaccines. Many of these products are being developed by nonprofit PDPs rather than pharmaceutical companies. he G20 "A Theory of Justice" In his landmark 1971 book A Theory of Justice, the Harvard political philosopher John Rawls articulates two overriding principles of a just and fair society, namely, (1) “equality in the assignment of basic rights and duties” and (2) allowance of some social and economic inequalities, but only if they ultimately benefit “the least advantaged members of society” [1]. In terms of Rawls’s worldview, I believe that finding widespread NTDs among the extreme poor (and least-advantaged) who live amidst wealth—the central tenet of blue marble health—might represent one of the most jarring affronts to what he terms “justice as fairness” Because NTDs are now widespread among the leastadvantaged members of the worlds wealthiest economies, and they represent a major basis for thwarting their future growth, it is urgent for these nations, especially the G20 countries, to adopt strong internal policies to combat these diseases. I envision a three-pronged strategy to best address the G20 s (and Nigeria’s) poorest citizens afflicted by NTDs: 1. Each of the G20 nations and Nigeria has the capacity to fully understand the extent of these diseases within their own borders and then provide their own impoverished populations access to essential medicines used in mass drug administration to target helminth infections, in addition to trachoma, leprosy, yaws and scabies, and to provide treatments for other high-disease burden NTDs, including leishmaniasis and Chagas disease. The G20 countries and Nigeria Three major steps are required to effectively address blue marble health. 141 142 Blue Marble Health need to allocate resources and implement programs to achieve universal coverage for these diseases. 2. Each of the G20 nations and Nigeria has the capacity to conduct research and development for new NTD biotechnologies; they need to allocate resources toward this goal. 3. Both activities should be conducted within an overall framework of health system strengthening. Mass Drug Administration in the G20 A good place to revisit MDA among the G20 countries is to more closely examine the six G20 countries with positive worm indices—Brazil, China, India, Indonesia, Mexico, and South Africa—in addition to Nigeria. Together these countries account for one-half of the worlds helminth infections [2]. An analysis of WHO s PCT database reveals that most of these nations are severely underachieving when it comes to providing MDA for people who require regular and periodic treatment for their intestinal helminth infections, schistosomiasis, and LF. Shown in table 11.1 is WHO’s estimate of the percentage that received treatment in 2013 [3-5]. Overall, the G20 nations affected by helminth infections and Nigeria perform poorly when it comes to treating their affected populations through MDA. In terms of specific countries in Latin America, Brazil is reaching only approximately one-third of its children and population at risk. And although Mexico provides complete coverage for intestinal worms, it—as previously mentioned—neither diagnoses nor treats hundreds of thousands (and possibly millions) of people with Chagas disease. In Africa, Nigeria’s MDA reaches less than 25% of its children at risk for helminth infections, and there is no information about schistosomiasis coverage in South Africa forthcoming from WHO. However, as Dr. Eyrun Kjetland (who works extensively in South Africa) has pointed out, female genital schistosomiasis remains widespread there, in part because praziquantel has been mostly unavailable in the country, owing to its drug importation laws. Schistosomiasis and other NTDs are still found among the poor in the Kingdom of Saudi Arabia. The entire MENA region severely underdiagnoses most of its NTDs, including leishmaniasis. In Asia, Indonesia largely does not promote widespread deworming for its children, and only a small percentage of its population receives treatment for LF, while India does only marginally better. Indonesia also suffers from high rates of yaws, which can also be targeted by MDA using the antibiotic azithromycin. Similarly in India, the vast majority of its children do not have access to regular and periodic deworming, and only about one-half of the population receives MDA for LF. India also has the worlds largest numbers of leprosy cases. This disease can also be attacked through MDA using a multidrug therapy regimen. WHO does not present information on China, either because it has not been determined or is unavailable. However, China has made great strides in reducing its schistosomiasis prevalence since 1949, and it has eliminated LF. Similarly, Japan and South Korea have achieved significant success both in economic development and in reducing or eliminating its NTDs. 144 Blue Marble Health Key common factors for poor performance in meeting MDA targets are vast geographies, decentralization of health care, inadequate resource allocation, and lack of political will. Overall, the six G20 countries with positive worm indices, together with Nigeria, have the means and capacity to eliminate LF within their own borders, while greatly reducing the disease burdens of their intestinal helminth infections and schistosomiasis through MDA. Some of the key common factors for poor performance in meeting MDA targets are vast geographies, decentralization of health care that results in fragmentation of drug delivery, inadequate resource allocation, and lack of political will and commitment. What about G20 countries affected by NTDs but without a positive worm index? In the United States, the 12 million Americans infected and living with NTDs are largely unrecognized, undiagnosed, and untreated. The United States also does very little in terms of conducting active surveillance for Chagas disease (and other major NTDs), and only a tiny percentage of its population receives access to diagnosis and treatment—the same is true for Argentina. In both North America and Europe, toxocariasis and other parasitic zoonotic infections are seldom diagnosed and treated. Minimal information is available on eastern ------------------- Europeans, Turks, and Russians with intestinal worms or zoonotic NTDs or their access to diagnosis and treatment. NTDs remain widespread among Aboriginal Australians, including intestinal helminth infections and scabies—both of which can be targeted through MDA. Thus, the current status of access to essential medicines for people living in poverty and with NTDs among the G20 countries and Nigeria can be summarized as abysmal. The fact that so few are being treated through MDA programs is especially sad, given its low costs. As previ- ------------------- ously mentioned, there are approximately 1.07 billion treatments required among the populations at greatest risk in the G20 countries and Nigeria. At a cost of 50 cents per person per year, approximately $500 million would be required—that is, a dollar amount representing a tiny percentage (<0.001%) of the $65 trillion combined economy of these countries. The bottom line is that each of these nations has the internal capacity to provide these low-cost treatments to its impoverished populations. WHO has now launched a Universal Health Coverage (UHC) initiative that builds on its 1978 “Health for All” Alma-Ata declaration and the MillenThe current status of access to essential medicines for people living in poverty and with NTDs among the G20 countries and Nigeria can be summarized as abysmal. The G20 145 nium Development Goals, with a focus on protecting the health of the worlds most economically vulnerable populations. The activities highlighted here clearly fall within WHO s UHC mandate. Research and Development for New Control Tools and Biotechnologies For many of the leading NTDs—including vector-borne diseases such as dengue, leishmaniasis, Chagas disease, African sleeping sickness, and malaria, and also some helminth infections such as hookworm, schistosomiasis, onchocerciasis, and foodborne trematodiases—there are equally urgent needs to develop new drugs, diagnostics, and vaccines. Each year, the Australian policy group known as Policy Cures publishes an annual G-FINDER Report that measures the global investment in new technologies for neglected diseases, defining them broadly to include both the NTDs and the “big three” diseases: HIV/ AIDS, ТВ, and malaria [6]. For the year 2014, G-FINDER determined that approximately $3.37 billion was invested globally in neglected disease R&D technology, with most of that support going toward the big three diseases [6]. A look at total government support for neglected disease R&D, almost all of it from G20 countries, is also interesting. The public sector provided 64% of the total funding, and the United States provided two-thirds of that funding, mostly from the US National Institutes of Health [6]. In all, 71% of the total government funding for neglected diseases comes from the United States, European Commission, and United Kingdom. However, as the G-FINDER Report points out, these absolute numbers do not consider the GDPs of these nations. In terms of public funding relative to GDP ratios, countries such as Ireland, Denmark, Norway, and Argentina do particularly well in this regard [6]. Shown in table 11.2 are selected estimates from G-FINDER of the percentage of their GDP that various governments have devoted to R&D on Of government funding for neglected diseases R&D, a whopping 71% comes from the United States, European Commission, and United Kingdom. We need greater involvement and support from the remainder of the G20 countries, including positive worm index G20 countries— Brazil, China, India, Indonesia, Mexico, and South Africa, in addition to Nigeria. 146 Blue Marble Health Although NTDs and other poverty-related diseases account for almost 14% of the global disease burden, they receive only a bit more than 1% of the global health-related R&D funds. neglected diseases. Using data from the G-FINDER Report combined with GDP information, I calculate that the world spends approximately 0.0028% of its GDP on neglected diseases R&D. Only three G20 countries—United States, United Kingdom, and Australia—match or exceed that percentage, ------------------- although India and France come close to it. The worstperforming countries were China and Japan. However, in 2013 the Japanese government, together with Japans major pharmaceutical companies and the Bill & Melinda Gates Foundation, formed a partnership known as the Global Health Innovative Technology (GHIT) Fund for supporting PDPs and other entities to develop and shape new biotechnologies for neglected diseases, with an emphasis on NTDs [7, 8]. China is a different matter. The New York Times has reported that China paid out $86.3 billion in foreign investments in the year 2013 [9], with much of that spent in fragile nations where health systems are broken and NTDs are widespread. Clearly, China needs to allocate some of those funds to neglected diseases, either for MDA or new technologies. In addition, the nation of Brazil could easily increase its global contribution to NTD technologies by ю -fold in order to match higher-performing nations in this regard. Germany is now looking at supporting NTD technologies as part of an overarching G7 initiative on NTDs. In 2011, the German government launched a policy roadmap for neglected and poverty-related diseases [10]. Indeed, a recent analysis conducted by German investigators has found although NTDs ------------------- and other poverty-related diseases account for almost 14% of the global disease burden, they receive only a bit more than 1% of the global health-related R&D funds [11]. As shown in figure 11.1, by presenting R&D expenditures for a particular disease divided by the disability adjusted life years (DALYs) it is possible to get a sense of ------------------- diseases that are especially underfunded—even compared with other NTDS—such as the intestinal helminth infections and other neglected enteric diseases, as well as rheumatic fever [11]. Such data argue for the great urgency needed in addressing these health disparities by increasing R&D funding and support. Recently, the Dutch and German governments and the European Union (EU) have established important initiatives to support NTD R&D. The Dutch Ministry of Foreign Affairs, for instance, has been a major partner in our human hookworm vaccine initiative, while the EU has an important Frameworks Program 7 (FP7) for supporting new technologies [12], including a HOOKVAC Consortium of partners organized through the Amster dam Institute of Global Health and Development [13]. Most recently, the EU has established an ambitious Horizon 2020 program for expanding R&D in Europe, including NTD R&D activities [14], on top of a European and Developing Countries Clinical Trials Partnership (EDCTP) for clinically evaluating new NTD technologies [15]. New German government funding for NTD R&D funding was just announced. These Dutch, German, and EU initiatives represent an important advance for shaping the next generation of products to treat and prevent NTDs. Yet another aspect of blue marble health is the rise in comorbid conditions between the NTDs, the big three diseases, and the noncommunicable diseases. Impoverished and neglected populations in the G20 countries and Nigeria are facing a double hit resulting from the convergence of NTDs and NCDs. For instance, in Texas, Mexico, and India (but presumably elsewhere) they include both ТВ and diabetes interactions and, lately, dengue and diabetes interactions. In South Africa, HIV/AIDS now flourishes amidst the high prevalence of female genital schistosomiasis. Studying the pathogenesis and epidemiology of these comorbid interactions will also be an important theme in the coming years. Shaping a Policy for the G20 The G20 began meeting in 2008 in response to that years global recession and have since convened in a summit each year to discuss the major policy issues of the day [16]. At the 2015 G20 Summit held in Turkey, the major areas of broad emphasis included strengthening the global recovery and enhancing resilience, while ensuring sustainability [17]. Clearly, lifting the bottom segments of their populations out of poverty through NTD control and elimination could fall within the G20 remit. It is imperative that the six member nations with positive worm indices commit to providing total MDA coverage for their populations affected by the major helminth infections, and also that the four Western Hemispheric countries step up surveillance, diagnosis, and treatment for Chagas disease. Leishmaniasis, both kala-azar and the cutaneous form, also represent major NTDs affecting the G20, and these diseases need to be targeted for control and elimination. The US, Dutch, German, and Japanese governments, along with the EU, stand out for their contributions toward supporting product development to counter NTDs, 150 Blue Marble Health Equally important is the R&D agenda. There are some obvious underachievers among the G20 countries that must step up and contribute to R&D for new drug, diagnostic, and vaccine products to fight the neglected diseases [18]. Toward that aim, several investigators have proposed the establishment of R&D funds to support neglected disease research. They include a global vaccine development fund [19] and a general biomedical R&D fund focused on antimicrobial resistance, emerging infectious diseases, and neglected diseases [20]. Both proposals are thoughtful, have a lot of merit, and need to be considered, but I offer an alternative or complementary solution. In 2013, the World Health Assembly passed a resolution (66.22) that proposes a “strategic work plan” to achieve sustainable funding for health R&D that could emphasize NTDs. The plan commits the director-general of the World Health Organization to establish a global “observatory” in order to identify gaps and opportunities for health R&D related to neglected diseases [21]. Through a pooled fund managed by WHO-TDR (a special program on tropical disease research and training), several pilot projects are now being supported [22]. Given that todays neglected disease R&D support comes mostly from the United States—and indeed mostly from a single agency, the National Institutes of Health—it is difficult to envision how such a fund would be created without calling on the NIH yet again. Realistically, it is unlikely the NIH leadership or the well-established community of US scientists would be willing to cede control of NIH budgets to an international body. Instead, I think it is worth considering the possibility of having each of the G20 countries establish its own version of the Japanese GHIT Fund, which builds on indigenous scientists and academic institutions and their own pharmaceutical industries. A Chinese or South Korean version of GHIT for example could become a vital and important institution. Creating twenty separate innovation funds could achieve the same goals as a global fund, while simultaneously ensuring national ownership and capacity building for indigenous academic and industrial institutions. Many of them could develop and shape new biotechnologies in collaboration with the 16 international PDPs. This approach would be especially useful for the less developed G20 countries, including Brazil, Global funds for R&D are an option. An attractive alternative is to create national funds for product development R&D in each of the G20 countries and Nigeria—ones that resemble those put forward by the Dutch and Japanese governments. The G20 151 India, Indonesia, and Mexico. These nations have indigenous vaccine manufacturers, which are represented by the Developing Country Vaccine Manufacturers Network, and therefore have a level of sophistication for producing next-generation NTD vaccines. Still another option is for smaller groups of G20 countries to come together to support R&D investments. The EU’s programs for new NTD technologies highlighted above represent important examples. In addition, if institutions from China and India (both rivals and neighbors) collaborated in the area of neglected diseases [23], some important NTD problems affecting Asia could be solved in the coming years. The United States has potential to extend its outreach on NTDs by collaborating with other G20 nations in the Americas or other countries [24]. As a UN agency, WHO could certainly partner with one or more of these G20 NTD R&D investment funds, especially through its global health R&D observatory mechanism. Another key United Nations agency might include WIPO—the World Intellectual Property Organization. Through the Patent Cooperation Treaty mechanism, the Geneva-based WIPO represents one of the few revenue-generating UN agencies. In 2011, in collaboration with BIO Ventures for Global Health, it established WIPO Re:Search to facilitate the development of products to combat NTDs by bringing together major pharmaceutical companies and academic investigators working on these diseases [25]. As a revenue-generating UN agency under the charismatic leadership of Francis Gurry, WIPO has the potential to expand this remit to support NTD product R&D. Looking beyond the G20 The major NTDs linked to wealthy countries and blue marble health could also be addressed by nongovernmental organizations, including faith-based groups. For example, in 2011 the Pew Research Centers Forum on Religion and Public Life reported that the center of the worlds Christian-majority countries has shifted from Europe and North America to the Global South, meaning Africa, Asia, and Central and South America [26]. Thus, countries such as Brazil, Philippines, Angola, Democratic Republic of Congo, and Papua New Guinea now have some of the highest percentages of Christian populations. As shown in table 11.3, from an analysis published in PLOS NTDs I found that almost all of the world s Chagas disease cases and African trypanosomiasis (sleeping sickness) can be found in Christian-majority countries, in addition to almost one-half of the schistosomiasis cases [26]. These findings suggest the possibility of bringing in new actors to combat NTDs. They could include the Vatican and Pope Francis, especially given the new popes renewed commitment to impoverished populations [19]. The Orthodox Christian Church also has opportunities to highlight NTDs in countries such as Ethiopia or those in the Middle East, as do many Christian faith-based organizations and universities. The G20 153 Summary Points 1. The six G20 countries with positive worm indices—Brazil, China, India, Indonesia, Mexico, and South Africa, together with Nigeria, have the means and capacity to eliminate LF within their own borders, while greatly reducing the disease burdens of their intestinal helminth infections and schistosomiasis through MDA. 2. G20 countries without classical worm indices, including the United States, also need to find mechanisms for promoting surveillance and access to essential medicine options for the poor living with NTDs within their own borders. 3. The G20 countries also have important biotechnology capabilities, which have yet to be adequately tapped for producing new NTD diagnostics, drugs, and vaccines. Beyond the United States, European nations, Australia, and Japan, they also include Brazil, China, India, Indonesia, Mexico, Russian Federation, Saudi Arabia, South Africa, and South Korea. 4. Yet another aspect of blue marble health is the rise in comorbid conditions between the NTDs, the big three diseases, and the NCDs. 5. The EU and the Dutch and German governments have launched important NTD technology initiatives, as has the Japanese government and its partners through a new GHIT Fund. These activities support PDPs committed to NTDs as well as indigenous academic institutions and industrial organizations. 6. Large G20 economies such as Brazil and China must increase their global commitment to support new NTD technologies and R&D. 7. There are opportunities to link these new investments with parallel activities ongoing at two UN agencies, namely, WHO and WIPO. 8. These topics should be highlighted at future G20 summits. 9. Faith-based organizations could have a future role. For instance, the Vatican and related entities have opportunities to expand commitments to control those NTDs that are found to be prevalent among Christian-majority countries. Central to the blue marble health concept is that each of the G20 nations and Nigeria need to take greater responsibility for their own neglected diseases and neglected populations. Doing so could result in the control or elimination of one-half or more of the planets NTDs, with substantial gains made against HIV/AIDS, ТВ, and malaria. Thus, while programs of overseas development assistance devoted to health, such as PEPFAR, GFATM, PMI, and USAID’s NTD Program, in which the worlds richest countries provide support to the poorest nations for their neglected diseases, must continue and should even expand, we need increasingly to recognize the hidden burden of neglected diseases among the poor living in wealthy countries. As a first step, we must expand initiatives that raise awareness about the problem of NTDs within each of the G20 countries and Nigeria. The Global Network for NTDs linked to the Sabin Vaccine Institute has been working closely with the governments of India and Nigeria, respectively, in order to explain the opportunity for mass drug administration and its potential impact on health and economic development. MDA coverage rates are disappointingly low in these nations, especially for intestinal helminth infections and LF, as well as for schistosomiasis in the case of Nigeria. An extraordinary finding is that at least three nations with positive worm indices—India, Pakistan, and China—also maintain nuclear stockpiles [1]. Could the scientific horsepower of these nuclear states be partly redirected toward reducing endemic NTDs at home? 154 A Framework for Science and Vaccine Diplomacy 155 Outside of India and Nigeria, there is a need to promote NTD awareness in each of the G20 countries. For example, in the United States, our National School of Tropical Medicine has been highlighting the plight of some 12 million Americans living with NTDs. We have now worked with the Texas Legislature to enact a bill for NTD surveillance in suspected high-prevalence areas. However, similar initiatives need to be enacted across the G20 nations, including the European Union. In addition, international cooperation between the different G20 nations and Nigeria could be critical in achieving higher population coverage for MDA. For instance, China, despite its billions of dollars of business investments in sub-Saharan Africa, has not yet promoted NTD control efforts there. Yet China has tre- mendous expertise in MDA for NTDs and could provide Africa with valuable advice in this area. China was the first country to eliminate LF and has achieved successes in re- ducing its burden of schistosomiasis more than ю -fold since the 1949 revolution. China could also share its best practices with neighboring India, where NTDs remain practically ubiquitous [ 2]. Similarly, Japan and South Korea have made great gains toward eliminating intestinal helminth infections, while the former has also successfully eliminated LF and schistosomiasis. International cooperation between these three East Asian nations and Nigeria, or with the G20 countries with positive worm indices, especially India, Indonesia, and Brazil (where they are the highest), could result in important, positive health and economic gains. Each of these activities represents examples of what some refer to as global health diplomacy. Global Health Diplomacy My former colleague at Yale University, Ilona Kickbusch, currently the director of the Global Health Programme at the Graduate Institute of International and Development Studies in Geneva, has provided several working definitions of global health diplomacy, including efforts to “position health in foreign policy negotiations,” together with the establishment of global health governance initiatives [3]. Indeed, the creation of the GAVI Alliance, GFATM, UN AIDS, and other Geneva-based organizations might be considered vital examples of organizations created under the auspices of global health diplomacy, with the first two created following the 2000 Millennial Development Goals. The MDGs themselves represent an important framework for global health diplomacy, and arguably the most successful. Since 2005, several global health diplomacy initiatives have been enacted that could facilitate NTD activities among the G20 and Nigeria, although most of these actions are more focused on emerging viral infections of pandemic potential rather than the widespread chronic and debilitating NTDs. The International Health Regulations (IHR) were enacted in 2005 as a binding legal mechanism for all member states of WHO and focused on responses to acute public health emergencies [4]. IHR demands that countries report outbreaks and other public health events, while WHO responds with measures to uphold and enforce global health security [4]. IHR also establishes an emergency committee that advises the WHO director-general on whether an unexpected event should be considered a public health emergency. It also provides recommendations on initial steps for travel restrictions, surveillance, and infection control. With the possible exception of dengue fever, it is not clear how IHR will substantively address the NTDs or other blue marble health conditions. Moreover, even with IHR in place, the global response to the 2014 emergence of Ebola in West Africa was slow and inadequate and led to a catastrophic outbreak in the fall of that year [5]. This failure may require future revisions in the IHR, as recently recommended in a 2015 Lancet article by Lawrence Gostin and his colleagues at Georgetown University [6]. The Global Health Security Agenda (GHSA) is an interagency initiative of the US government conducted in partnership with other nations and international organizations, including WHO [7]. GHSA is also focused on preventing or reducing the impact of epidemics and outbreaks of pandemic potential, such as H7N9 influenza virus or MERS coronavirus, as well as detecting emerging threats and implementing rapid and effective responses. In some respects, GHSA represents the US component or response to IHR. It also covers intentional or accidental releases of dangerous infectious disease pathogens. Global Health 203s and The Lancet Commission were launched in 2013, coinciding with the twentieth anniversary of a landmark 1993 World Development Report that helped to ignite international efforts to link investments in health with economic development [8]. The Lancet Commission identifies four key messages and actions: (1) the substantial economic return on investing in health, which can be as much as 24% in low- and middle-income countries; (2) implementation of a “grand convergence” in global health through scale-up of health technologies and strengthening health systems by the year 2035; (3) fiscal policies such as taxation of tobacco and reduction of subsidies for fossil fuels, which represent powerful forces or “levers” for elected leaders; and (4) universal health coverage as an efficient mechanism to improve health as well as to provide “financial protection” [8]. The Addis Ababa Action Agenda (AAAA) is the product of the first of three international meetings for implementing the UN s 2015 Sustainable Development Goals. However, health is at present only a minor component of the AAAA. Indeed, the SDGs have been criticized because health is now only 1 of the 17 goals, whereas it was front and center among the 2000 MDGs. So far, the AAAAs recommendations have included the promotion of the health systems strengthening component of the GFATM and GAVI Alliance and the establishment of a Global Financing Facility (GFF) for womens and childrens health that would go hand-inhand with the UN secretary generals new Global Strategy for Every Woman Every Child [9]. The emphasis of these initiatives is to reduce preventable maternal, child, and adolescent deaths by 2030. Despite the evidence that hookworm infection and Chagas disease rank among the leading complications of pregnancy among women living in poverty in low- and middle-income countries, while female genital schistosomiasis is among sub-Saharan Africa’s most common gynecologic condition, there is not yet a specific mention of NTDs in the AAAA or GFF. Ultimately, the G20 nations can identify ways to address blue marble health disparities under the auspices of the SDGs or the global health diplomacy initiatives highlighted above. However, at present there is no specific mandate for them to do so. Vaccine Science Diplomacy Concurrently, the G20 nations have opportunities to collaborate in scientific activities leading to the development of new drugs, diagnostics, and vaccines. I have used the term “vaccine science diplomacy” to refer to inter- national scientific codevelopment of lifesaving vaccines between scientists of different nations, but particularly from nations with strained or evenly openly contentious international relations. The best historical example of vaccine science diplomacy is the codevelopment of the oral polio vaccine, led on the American side by Dr. Albert B. Sabin, and his Soviet virologist counterparts, including Dr. Mikhail Petrovich Chumakov [3]. In modern times there is potential interest in explor ing vaccine science diplomacy opportunities between the United States and some of the worlds Muslim-majority nations belonging to the Organisation of Islamic Cooperation [10,11]. OIC countries include most of the Middle East and North Africa, as well as some highly populated Southeast Asian nations, including Bangladesh, Indonesia, and Malaysia, as well as most of central Asia. New estimates that we published in PLOS NTDs in 2015 indicate that the 30 most-populated OIC countries account for 35% of the worlds helminth infections comprising the global Worm Index, including 50% of the worlds children who require MDA for schistosomiasis [11]. Given that approximately 1.5 billion people live in OIC countries, or about 20% of the global population, helminth infections appear to disproportionately affect the health and economic development of Muslim-majority countries, as does leishmaniasis, trachoma, and possibly other NTDs [11]. As shown in figure 12.1, there is also tight inverse association between the worm index and human development index in the Muslim world [11]. OIC nations with strong infrastructures in science and biotechnology are potentially attractive candidates to pursue joint vaccine science diplomacy initiatives with the United States. Here the idea would be to promote scientific collaborations between US scientists and scientists from selected OIC countries in order to create new NTD technologies for some of the worst-off Muslim-majority countries. The “worst-off” might include OIC countries at the high end of the worm index, including Mali, Cote d’Ivoire, Mozambique, Cameroon, Burkina Faso, and Niger, as well as Nigeria [11].

#### Public Health Diplomacy solves Existential Threats.

James 17 Wilmot James 4-2-2017 “In an Age of Zika and a Threat of Biochemical Terror, Health Security Must Be Everybody’s Concern” https://archive.is/tUlRX#selection-927.0-930.0 (Honorary Professor in the Division of Human Genetics at the University of Cape Town's Medical School and Non-residential Senior Fellow at Bard College’s Hannah Arendt Centre, Ph.D. from University of Wisconsin at Madison)//re-cut by Elmer

With Zika there too was political failure to act quickly, give honest advice and confront the abortion conundrum head-on, the result being that 3,000 and likely more children with microcephaly will test the emotional resilience and financial resources of their families to breaking point. We should never cease to invest in the public health and medical science of disease, but it seems to me that our fundamental problem is not the quality of the health sciences but the grim mediocrity of our politics. Party-political bickering for short-term gain paralyses and drains the national effort in South Africa as much as it does in the United States, undermining our ability to see with compelling clarity the solutions the issues of the day deserve. **Health** security **is humanity’s shared concern**. Promoting health and preventing death define us at our most altruistic and advanced. The Hippocratic Ideal, the concept of the physician as the guardian of human health, encapsulates a fundamental human quality common to all the world’s great religions. **Medicine** is one of the earliest and greatest human achievements because it is a **co-operative enterprise** involving highly skilled individuals; and it is **as a result** of cooperation – and our unusual ability for complex language – that cumulative **civilisation is possible**. In the age of globalisation, it is **health security**, a recent Lancet editorial stated, that “is now the **most important foreign policy issue** of our time”. The rapid emergence and re-emergence of pathogenic infectious **disease**, of which Zika is the most recent, the slow but steady cumulative acts of nature associated with **climate change**, high-risk **forced migration** caused by desperation and war, the creeping reality of **biochemical terror and** the threat of **nuclear war, propel human survival** and well-being **to the frontline** of what today must be everybody’s concern. The field of **health diplomacy provides** an **unprecedented opportunity to build** human **solidarity**. It is an area of human endeavour that **cuts through** inherited **antagonisms**. Governments that offer **health improvements** as part of aid to nations with whom they wish to **develop** stronger **diplomatic links** succeed in cultivating deeper cultural relationships precisely because of their direct benefit to citizens. To advance health diplomacy requires health leaders with an inclusive global vision...

#### Evergreening restricts Generic Patents by artificially extending Patent Cliffs.

Moir and Gleeson 14 Hazel Moir and Deborah Gleeson 11-5-2014 "Explainer: evergreening and how big pharma keeps drug prices high" <https://theconversation.com/explainer-evergreening-and-how-big-pharma-keeps-drug-prices-high-33623> (Adjunct Associate Professor; economics of patents, copyright and other "IP", Australian National University AND Lecturer in Public Health, La Trobe University)//Elmer

Efforts by pharmaceutical companies to extend their patents cost taxpayers millions of dollars each year. In some cases they also mean people are subjected to unnecessary clinical trials. **Big pharma** makes big profits. Their useful new **drugs are patented**, **protecting them from competition** and allowing them to charge high prices. When the patent ends, other companies are allowed to supply the previously patented drug. These are **known as generics**. The prices of generic drugs are much lower than the prices of in-patent drugs – it has been suggested that for widely used drugs price falls can be as much as 95%. Pharmaceutical companies want to get their new products listed on the Pharmaceutical Benefits Scheme (PBS), because they will sell in much higher volumes. Taxpayers have an interest in ensuring that these drugs move from the high in-patent price to the much lower off-patent price as early as possible. On average, a patent provides effective protection from competition for about 14 years. But, of course, **companies** like monopolies and would like to **extend the patent period**. Over the past few decades they have **used** a process known as evergreening to keep generic companies out of the market for longer. How evergreening works **Evergreening** is achieved by seeking extra patents on variations of the original drug – new forms of release, new dosages, new combinations or variations, or new forms. Big pharma refers to this as “lifecycle management”. Even if the patent is dubious, the company can earn more from the higher prices than it pays in legal fees to keep the dubious patent alive. Evergreening is possible because in Australia the standard required to get a patent is very low. Different methods of delivering drugs (such as extended release, for example) have been known for decades. But when one of these known delivery methods is combined with a known drug, the patent office considers this sufficiently inventive to grant a new 20-year patent. Another favourite evergreening strategy is to patent a slight variation of the drug. Brand pharmaceutical companies argue that these “lifecycle management” patents provide improved health outcomes to the community. They meet the (very low) patentability thresholds of novelty and inventiveness. Critics argue that the claimed improved health outcomes are small or non-existent. An evergreening story: from Efexor to Efexor-XR to Pristiq An example is useful. In the case of the depression drug **venlafaxine** (marketed as Efexor), the original version had major side-effects. However, when provided in extended release form these side-effects were substantially reduced. Naturally the extended release form (Efexor-XR) became preferred. Although it might seem obvious to combine venlafaxine with an extended release form to overcome the side-effect problem, the patent office **granted two new patents** for extended release versions of venlafaxine. One of these was written in such a broad form that it **delayed generic entry by two and a half years**, while legal wrangling took place. Eventually the evergreening patent was declared invalid. But the cost to taxpayers of this delay is estimated at $209 million. Pfizer has a second evergreening strategy for venlafaxine. When venlafaxine is taken, the human body converts it to desvenlafaxine. In other words desvenlafaxine is a variant of the original active pharmaceutical ingredient venlafaxine. Clearly the two compounds are closely related. So it is astonishing that desvenlafaxine passed the tests for getting a patent. Desvenlafaxine is marketed as Pristiq. Pristiq entered the market early in the two-and-a-half-year period of legal wrangling over the extended release venlafaxine (Efexor-XR) patent. Pfizer’s marketing of Pristiq in February 2009 was so lavish that it attracted the attention of investigative journalists. Pristiq has no additional benefits for patients. Despite this, during the first six months of 2014 half of prescriptions were written for Pristiq rather than for the clinically identical Efexor-XR. But Pristiq costs between $A22.32 and $A26.50 more than Efexor-XR, depending on the dose. Based on reported prescription volumes in 2013-14, the cost to the taxpayer of doctors prescribing Pristiq rather than Efexor-XR exceeds $21 million a year. Unless generic companies challenge the desvenlafaxine patent, there will be **no generic versions of Pristiq until after August 2023**, when the patent expires.

#### That inhibits India’s Pharma Industry – exports of Generics is key to revitalize India Pharma Leadership.

Neelakantan 14 Murali Neelakantan 11-11-2014 “Indian Pharmaceutical Industry: Affordable Access to Healthcare for all” https://web.archive.org/web/20150315092713/https://abcmundial.com/en/news/brics/technology/3838-indian-pharmaceutical-industry-affordable-access-healthcare-all/ (consejero general global de Cipla Limited)//Elmer

The story of the Indian pharma sector could well have been like the IT sector if only enough attention was paid to its achievements and the huge impact it has had on healthcare around the world. Unlike other manufacturing or heavy industries in **India**, the **pharma** sector is innovative, widely **acknowledged as making a global impact in** the **treatment** of diseases like HIV AIDS[1] and also able to support the healthcare needs of the world[2]. The fact that Indian factories are licensed to produce 3,685 drugs compared with 3,815 made within the UK suggests that Indian factories meet global quality standards and are able to produce complex drugs.[3] While news of regulators visiting Indian manufacturing facilities and finding fault with processes is widely reported, very little is said about how routine this is. Gerald Heddell, director of inspections, enforcement and standards at the MHRA, stressed that the number of problems identified by regulators in India was in proportion to the volume of medicines they produced. “When we look back over 110 inspections we conducted over the last two years in India, we had significant concerns with 9 or 10 companies,” he said. “That does not represent a statistically higher proportion than in other parts of the world. India stands out because it is just such a big supplier.”[4] The **Indian pharma Industry** **produces** about **20%** [5] **of** the **global generic drugs** **with the US accounting for** nearly **28 per cent of Indian pharmaceutical exports**[6], followed by the European Union at 18 per cent and Africa at over 17 per cent.[7] This should be a clear acknowledgement of the **global leadership that Indian pharma industry has** achieved which would have been impossible without following global quality standards. Another popular criticism of Indian pharma has been that there is insufficient investment in innovation and R&D. Despite over 500 new drugs being discovered by Indian pharma companies during 1985 – 2005, there seems a perception that India thrives on copying foreign products[8]. A recent study by Evaluate[9], a leading independent specialist pharma consultancy, reports that there is little difference in the investment by “innovators” and “generics” and it is just a myth that “innovators” invest heavily in research while “generics” don’t. Despite well publicised claims of the Western world, there seems to be a marked decrease in R&D investments[10] and this trend is expected to continue.[11] When one realises that almost 50% of the European pharma patents are either lying dormant or filed in order to block competitors[12] one wonders how innovation is being defined and encouraged. Is it innovation if the effect is stifling further innovation and competition and creating barriers for improvements? **Indian pharma** industry has clearly demonstrated that it **has** the **potential to be** a part of **the solution** for universal access to healthcare. India’s strength is **innovating** **to improve global access to medicines** as opposed to developing more and more “me too” drugs which have been traditionally defined by the West as innovation. There is now a growing acknowledgment that the existing IPR regime that is being touted by the West doesn’t foster innovation. As such, the current patent system is itself reeling from the ill effects of patent assertion entities (trolls) that do not produce anything of value but merely hold patents with a view to threatening businesses with infringement actions to obtain licensing revenue. Patents have other flaws that relate to monopoly power, both because it harms consumers who have to pay high prices and because it can hinder improvements and subsequent innovations.[13] Static distortions, too little incentive for original research, and wasteful duplication of research are some of the most serious problems of the patent system.[14]In addition to TRIPs - compliant patent regimes which ostensibly promote innovation and discourage copying, the next generation of barriers to competition seems to be set up as global standards. Just as IPR was addressed by the WTO in TRIPs, the more recent barriers are likely to be in the form of harmonised regulations. Patent linkage[15] (in Canada and the US for example) denies access to markets on a mere allegation of patent infringement. Despite the US Supreme Court[16] indicating that patent linkage needs to be reconsidered and access to medicines should not be denied on allegation of patent infringement and recent attempts by Italy to introduce a system of patent linkage resulted in a notice from the European Commission asking for the removal of these provisions from Italian law,[17] patent linkage is a real barrier to competition in healthcare which is beset with unaffordable drugs. Data exclusivity extends the term of monopoly enjoyed by patent holders and keeps out competition and innovation without any benefits to society. This concept does not exist in sectors other than pharma and there seems to be no real rationale for pharma to get special treatment. In fact, data exclusivity raises several ethical and moral issues. Countries have always been allowed to customise their IP policy and regulation based on their unique local conditions. Some countries are more technologically proficient than others, and this distinction may warrant separate norms in areas of technology that they are strong in.[18] Even where harmonisation has been accepted as a concept, like the EU for example, it has been implemented in a manner that is sympathetic to the local conditions of individual countries. India’s strength and expertise lies in developing drugs which are accessible for patients across the globe. India’s stand on IPR regime acknowledges that diverse countries cannot be forced to one uniform regulatory system. This principled stand was recently demonstrated during the Bali round of talks on the Trade Facilitation Agreement.[19] In the background of the Trans Pacific and Trans Atlantic Partnerships being negotiated, India has the opportunity to demonstrate leadership in the global market place by pioneering the opposition to using harmonisation as a proxy for barriers to competition. While the US and its allies may officially oppose India’s view of the IPR regime they have realised that the key to their sustainable development is the ability of government to ensure that healthcare is accessible to everyone, not just the rich. Cost of healthcare has increased significantly causing an alarming number of patients to go off treatment, risk importing counterfeits[20] or in many cases, declare bankruptcy[21]. The issue of access to healthcare in the developing world has, despite some efforts by the UN, The Global Fund, PEPFAR and other aid institutions, not had the impact that it should have. There is a realisation, albeit unarticulated, that Indian Pharma companies have the potential to be, like Indian technology companies averted the y2K crisis, a key element of the solution to world's healthcare crisis. **Now is** a great **opportunity for India to demonstrate leadership** in IPR regimes as more and more countries like South Africa and Brazil are following India’s example.

#### Indian pharma strength is key to their soft power

Jha 16 Prem Shankar Jha 11-5-2016 “Let India unleash its soft power” <https://www.thehindu.com/opinion/lead/Let-India-unleash-its-soft-power/article13292272.ece> (Writer at the Hindu)//Elmer

And why stop at food grains? In drought-struck regions, contaminated water kills much faster than hunger and takes the very young and the very old first. The **Indian pharmaceuticals** industry **is the envy of the world**, **because it produces and sells** **medicines at a tenth to a thirtieth** of the **retail prices abroad**. **Can Delhi not buttress its** **food aid with medicines** and vitamins? This will give **an entirely new meaning to** the concept of **Soft Power for**, **unlike the West** in its present incarnation, **it would be seeking to build influence by protecting** and preserving, **not destroying**; by expanding peoples' futures instead of ending them in darkness. We have been relatively **slow to realise** our **full potential** for the exercise of soft power. This could be because of our too-ready acceptance of a concept that was created by an American to address American foreign policy concerns. In Joseph Nye's original definition, soft power originated in the capacity to attract others to your country's culture, values and institutions. Indian policymakers have taken this to heart and relied mainly upon India's open society, democratic institutions, lack of aggressive intent and willingness to share the burden of U.N. peacekeeping and policing the global commons, to garner respect and support in the international community. It is only in the last half-decade, as the Westphalian international order crumbled and India's neighbourhood became increasingly unstable, that New Delhi has begun to explore the economic dimensions of ‘soft power' seriously. Afghanistan has been the focus of its initial efforts, and its success is attested to by the threat (irrational though it is) that Pakistan feels from it.

#### Successful India Soft Power solves Extinction

Kamdar 7, Mira. Planet India: How the fastest growing democracy is transforming America and the world. Simon and Schuster, 2007. (Bernard Schwartz Fellow at the Asia Society in 2008)//Elmer

**No other country matters more to the future of our planet than India**. There is no challenge we face, no opportunity we covet where India does not have critical relevance. **From combating global terror to finding cures for dangerous pandemics, from dealing with the energy crisis to averting the worst scenarios of global warming**, from rebalancing stark global inequalities to spurring the vital innovation needed to create jobs and improve lives—**India is now a pivotal player**. The world is undergoing a process of profound recalibration in which the rise of Asia is the most important factor. India holds the key to this new world. India is at once an ancient Asian civilization, a modern nation grounded in Enlightenment values and democratic institutions, and a rising twenty-first-century power. With a population of 1.2 billion, India is the world’s largest democracy. It is an open, vibrant society. India’s diverse population includes Hindus, Muslims, Sikhs, Christians, Buddhists, Jains, Zoroastrians, Jews, and animists. There are twenty-two official languages in India. Three hundred fifty million Indians speak English. India is the world in microcosm. Its geography encompasses every climate, from snowcapped Himalayas to palm-fringed beaches to deserts where nomads and camels roam. A developing country, India is divided among a tiny affluent minority, a rising middle class, and 800 million people who live on less than $2 per day. India faces all the critical problems of our time—extreme social inequality, employment insecurity, a growing energy crisis, severe water shortages, a degraded environment, global warming, a galloping HIV/AIDS epidemic, terrorist attacks—on a scale that defies the imagination. India’s goal is breathtaking in scope: transform a developing country of more than 1 billion people into a developed nation and global leader by 2020, and do this as a democracy in an era of resource scarcity and environmental degradation. The world has to cheer India on. If India fails, there is a real risk that **our world will become hostage to political chaos, war over dwindling resources, a poisoned environment, and galloping disease**. Wealthy enclaves will employ private companies to supply their needs and private militias to protect them from the poor massing at their gates. But, if India succeeds, it will demonstrate that it is possible to lift hundreds of millions of people out of poverty. It will prove that multiethnic, multireligious democracy is not a luxury for rich societies. It will **show us how to save our environment, and how to manage in a fractious, multipolar world**. India’s gambit is truly the venture of the century.

### 1AC: Drug Prices

#### Advantage 2 is Drug Prices:

#### Evergreening is the root cause of high drug prices by delaying generics – that’s a critical internal link to healthcare costs.

Vanni 21 Amaka Vanni 3-23-2021 “On Intellectual Property Rights, Access to Medicines and Vaccine Imperialism” <https://twailr.com/on-intellectual-property-rights-access-to-medicines-and-vaccine-imperialism/> (PhD and LLM degrees in International Economic Law from the University of Warwick)//re-cut by Elmer

Third, **patent practices** in recent decades have **seen** **pharmaceutical companies engaging in trivial** and cosmetic **tweaking of a drug** **whilst** still **reaping the benefit of 20 years of patent protection**. This tweaking sometimes involves making minor changes to patented drugs, such as changes in mode of administration, new dosages, extended release, or change in color of the drug. These changes normally **do not offer** **any** significant **therapeutic advantage** even though pharmaceutical companies argue they provide improved health outcomes to patients. These additional patents on small changes to existing drugs, known as **evergreening** or patent thickets, **block** the early **entry of** competitive, **generic medicines** **that drive medicine prices down**. For example, while not mandated by TRIPS, many US led TRIPS-plus free trade agreements have expanded the scope for evergreening. These include the US-Jordan FTA (2000), US-Australia FTA (2004) as well as the US-Korea FTA (2007), which allow for the patenting of new forms, uses, or methods of using existing products. The cancer drug Gleevec®, owned by Novartis, is another example of how pharmaceutical companies often secure patents on new, more convenient versions with marginal therapeutic benefit to patients whilst blocking the entry of generic medicines. In 2013, Novartis’ patent application for Gleevec®– the β crystalline form of the salt imatinib mesylate – was rejected by the Indian Supreme Court because it lacked novelty. However, the company has secured patents for this product in other jurisdictions such as the US and has maintained a high price of Gleevec there. But in India the price of Gleevec® was reduced from approximately USD 2,200 to USD 88 for one month’s treatment in the generic drugs market as a result of the 2013 Indian Supreme Court judgement. Novartis is not the only culprit. The depression drug Effexor® by Pfizer was granted an evergreen patent when the company introduced an extended-release version, Efexor-XR®, even though there was no additional benefit to patients. Eventually, the patent was declared invalid, but by then it had already cost an estimated USD 209 million to Australian taxpayers and kept generic competition off the market for two and a half years. In another instance, Pfizer went on to secure an additional patent for the Pristiq®, which contained identical chemical compound as Efexor-XR®,and again with no added therapeutic benefit. These evergreening practices, of course, have material effects. Apart from delaying the entry of generic versions, they give brand-name pharmaceutical companies **free reign in the market**, which allows them to set the market price. Recent years have seen **monopoly prices rise** exorbitantly **causing** significant **financial strain to patients**, domestic **healthcare services and** even **insurance companies** in developed countries. A notorious example is Martin Shkreli, who in 2015 bought the rights to an anti-malarial drug, then raised the price by 5,000 per cent from a cost of USD 13.50 to USD 750. Similarly, a white paper by I-MAK shows how excessive patenting and related strategies are driving families to overspend on lifesaving medicines. Celgene, the makers of Revlimid® raised the price of the drug by more than 50 per cent since 2012 to over USD 125,000 per year of treatment. Using the example of Solvadi® by Gilead, which costs USD 84,000 per treatment, Feldman notes the drug would cost the US Department of Defense more than USD 12 billion to treat all hepatitis-infected patients in US Veterans Affairs. But the US is not alone. In Europe, expensive drugs have prompted a growing backlash against pharmaceutical corporations. Reacting to these price hikes, Dutch pharmacies are bypassing these exorbitant prices by preparing medicines in-house for individual patients. The broken IP system ranging from an extraordinarily low standard for granting patents to permissions of patent thickets around a single molecule has not only severely distorted the system of innovation, but they have also skewed access to life-saving drugs. As a result, prices for new and existing medicines are constantly rising, making essential medicines inaccessible for millions of people around the world.

#### Pharma’s the largest drive of healthcare costs.

Brennan 16, Hannah, et al. "A prescription for excessive drug pricing: leveraging government patent use for health." Yale JL & Tech. 18 (2016): 275. (Law Clerk to the Honorable Theodore McKee, Chief Judge, Third Circuit)//re-cut by Elmer

The **soaring cost of pharmaceuticals is one of the most pressing domestic policy issues** in the United States today. Nearly **one-fifth of** the U.S. Gross Domestic Product (**GDP) is spent on healthcare**, and **pharmaceuticals are a key expenditure**.1 In 2014, the **U**nited **S**tates **spent a record $297.7 billion** on pharmaceuticals, over 12% more than the previous 2 year. The 2014 increase in prescription drug spending can be attributed almost entirely to recently approved drugs that treat the Hepatitis C virus (HCV). 3 With list prices that approach $100,000 for a twelve-week regimen, 4 these new medicines have brought the issue of drug pricing roaring to the fore in policy debates. **High drug prices are of enormous concern** to voters, 5 policymakers, and politicians across the political 6 spectrum. High drug prices also have a significant impact on health. The new HCV drugs offer an excellent example. Potentially deadly if untreated, HCV is one of the most pressing health problems facing the United States. 7 The new drugs are far superior to previous treatments and could potentially enable elimination of the disease.8 But treating all of the approximately 5.2 million people who currently have HCV in the United States at the best reported prices offered by Gilead, the sole supplier of the most important new drugs, would cost at least $234 billion.9 Given the budget impact of these new medicines, most payors have sharply restricted their availability-covering them only for the very sickest, or refusing to cover them at all 0-instead of rapidly rolling them out. Medicaid, for example, treated only 2.4% of enrollees estimated to have HCV in 2014, despite spending more than a billion dollars on the new medicines1.1 Even with the small number treated, Gilead's earnings have been stratospheric: the company earned $36 billion from its new HCV medicines in their first twenty-seven months on the market. 12

#### That hurts the Economy

Sood et Al 7, Neeraj, Arkadipta Ghosh, and J. Escarse. "The effect of health care cost growth on the US economy." Office of the Assistant Secretary for Planning and Evaluation, US Department of Health and Human Services (September). Available at (http://aspe. hhs. gov/health/reports/08/healthcarecost/report. html (HHS) (2007). (PhD, is professor and vice dean for research at the USC Price School of Public Policy and a founding member the USC Schaeffer Center)//Elmer

2. CONCEPTUAL OVERVEIW OF POTENTIAL MECHNISMS THROUGH WHICH HEALTH CARE INFLATION COULD AFFECT THE US ECONOMY Not surprisingly, the dramatic increases in health care spending and the share of GDP devoted to health care have raised concerns about the **negative impact of health care cost inflation on the U.S. economy**. In an era of global economic markets, these concerns are reinforced by the status of the U.S. as a spending outlier among competing nations. The major concern is that **rapid increases in health care spending** **can affect** **major economic indicators such** per capita **GDP, employment and inflation**. The effects are likely to occur **across all sectors** of the economy – governments, businesses and households – as all these interrelated sectors play an important role in the provision, financing and consumption of health care in the US. For example, Federal, state and local governments collect taxes from businesses and households to finance public health insurance programs and to directly provide health care to households. Businesses provide employment to US households and also provide health insurance to their employees. Households are the final consumers of health care and also bear some incidence of health care costs. In this report we separately identify the effects of health care costs on the aggregate economy and on each one of these interrelated sectors. However, it is important to note that the **effects** of health care costs **on one sector** are **likely to affect** outcomes in **other sectors**. For example, **faced with rising health care costs** **governments** might **attempt to reduce health spending by reducing eligibility for public health insurance**, consequently **increasing** **uninsurance rates** among households. The increase in health care costs might also prompt governments **to raise taxes**, increase borrowing or **reduce investments in** other **critical sectors such as education and infrastructure,** **suppressing economic growth** and affecting both businesses and households. Similarly, **US companies** faced with rapidly growing health care costs **might reduce employment** and investments in the US economy. Rising health care costs could also **fuel inflation** in the U.S. and make U.S. goods and services less competitive in international markets over time, because increasing health care costs might eventually be reflected in higher product prices. Since most other nations do not have employer-sponsored health insurance, companies in thosenations may be better able to keep prices low.2 Finally, high health care costs could reduce access to health care, bankrupt consumers and deplete retirement savings.

#### Economic decline results in multilateral breakdown that causes state collapse, conflict, climate change, and Arctic and Space War.

McLennan 21 – Strategic Partners Marsh McLennan SK Group Zurich Insurance Group, Academic Advisers National University of Singapore Oxford Martin School, University of Oxford Wharton Risk Management and Decision Processes Center, University of Pennsylvania, “The Global Risks Report 2021 16th Edition” “http://www3.weforum.org/docs/WEF\_The\_Global\_Risks\_Report\_2021.pdf //Re-cut by Elmer

Forced to choose sides, governments may face **economic** or diplomatic **consequences**, as proxy disputes play out in control over economic or geographic resources. The deepening of geopolitical fault lines and the lack of viable middle power alternatives make it harder for countries to cultivate connective tissue with a diverse set of partner countries based on mutual values and maximizing efficiencies. Instead, networks will become thick in some directions and non-existent in others. The COVID-19 crisis has amplified this dynamic, as digital interactions represent a “huge loss in efficiency for diplomacy” compared with face-to-face discussions.23 With some **alliances weakening**, diplomatic relationships will become more unstable at points where superpower tectonic plates meet or withdraw. At the same time, without superpower referees or middle power enforcement, global **norms** may **no longer govern** state **behaviour**. Some governments will thus see the solidification of rival blocs as an opportunity to engage in regional posturing, which will have destabilizing effects.24 Across societies, domestic discord and **economic crises will** **increase** the risk of **autocracy**, **with corresponding** **censorship, surveillance**, restriction of movement and abrogation of rights.25 Economic crises will also amplify the **challenges for middle power**s as they navigate geopolitical competition. **ASEAN countries, for example, had offered a potential new manufacturing base as the United States and China decouple, but the pandemic has left these countries strapped for cash to invest in the necessary infrastructure and productive capacity.26** Economic fallout is pushing many countries to debt distress (see Chapter 1, Global Risks 2021). While G20 countries are supporting debt restructure for poorer nations,27 larger economies too may be at **risk of default** in the longer term;28 this would **leave them further stranded**—**and unable to exercise leadership—on the global stage**. Multilateral meltdown **Middle power weaknesses** will be **reinforced** in weakened institutions, which may translate to **more uncertainty and lagging progress on shared global challenges such as climate change**, **health, poverty reduction and technology governance**. In the absence of strong regulating institutions, **the Arctic and space represent new realms for** potential **conflict** as the superpowers and middle powers alike compete to extract resources and secure strategic advantage.29 If the global superpowers continue to accumulate economic, military and technological power in a zero-sum playing field, some middle powers could increasingly fall behind. Without cooperation nor access to important innovations, middle powers will struggle to define solutions to the world’s problems. In the long term, GRPS **respondents forecasted “w**eapons of **m**ass **d**estruction” **and “state collapse**” as the two top critical threats: in the absence of strong institutions or clear rules, clashes— such as those in **Nagorno-Karabakh or the Galwan Valley**—**may more frequently flare into** full-fledged **interstate conflicts**,30 which is particularly worrisome where unresolved tensions among nuclear powers are concerned. These conflicts may lead to state collapse, with weakened middle powers less willing or less able to step in to find a peaceful solution.

#### COVID creates an economic brink---recovery is strong now because of effective monetary policy, but we’ve hit the zero-lower bound.

Christopher Rugaber 21. Associated Press. “Federal Reserve keeps key interest rate near zero, signals COVID-19 economic risks receding.” https://www.chicagotribune.com/business/ct-biz-fed-interest-rates-economy-20210428-bumyc3ynpza6ri4ygsntmdsmya-story.html.

WASHINGTON — The Federal Reserve is keeping its ultra-low interest rate policies in place, a sign that it wants to see more evidence of a strengthening economic recovery before it would consider easing its support.

In a statement Wednesday, the Fed expressed a brighter outlook, saying the economy has improved along with the job market. And while the policymakers noted that inflation has risen, they ascribed the increase to temporary factors.

The Fed also signaled its belief that the pandemic’s threat to the economy has diminished, a significant point given Chair Jerome Powell’s long-stated view that the recovery depends on the virus being brought under control. Last month, the Fed had cautioned that the virus posed “considerable risks to the economic outlook.” On Wednesday, it said only that “risks to the economic outlook remain” because of the pandemic.

The central bank left its benchmark short-term rate near zero, where it’s been since the pandemic erupted nearly a year ago, to help keep loan rates down to encourage borrowing and spending. It also said in a statement after its latest policy meeting that it would keep buying $120 billion in bonds each month to try to keep longer-term borrowing rates low.

The U.S. economy has been posting unexpectedly strong gains in recent weeks, with barometers of hiring, spending and manufacturing all surging. Most economists say they detect the early stages of what could be a robust and sustained recovery, with coronavirus case counts declining, vaccinations rising and Americans spending their stimulus-boosted savings.

#### The Alternative to the Aff isn’t no medicine but exploitive medicine – the Plan’s orientation is a sequencing strategy to resistance.

Ahmed 20 A Kavum Ahmed 6-24-2020 "Decolonizing the vaccine" <https://africasacountry.com/2020/06/decolonizing-the-vaccine> (A. Kayum Ahmed is Division Director for Access and Accountability at the Open Society Public Health Program in New York and teaches at Columbia University Law School.)//Duong+Elmer

Reflecting on a potential COVID-19 vaccine trial during a television interview in April, a French doctor stated, “If I can be provocative, shouldn’t we be doing this study in Africa, where there are no masks, no treatments, no resuscitation?” These remarks reflect a colonial view of Africa, reinforcing the idea that Africans are non-humans whose black bodies can be experimented on. This colonial perspective is also clearly articulated in the alliance between France, The Netherlands, Germany and Italy to negotiate priority access to the COVID-19 vaccine for themselves and the rest of Europe. In the Dutch government’s announcement of the European vaccine coalition, they indicate that, “… the alliance is also working to make a portion of vaccines available to low-income countries, including in Africa.” In the collective imagination of these European nations, Africa is portrayed as a site of redemption—a place where you can absolve yourself from the sins of “vaccine sovereignty,” by offering a “portion of the vaccines” to the continent. Vaccine sovereignty reflects how European and American governments use public funding, supported by the pharmaceutical industry and research universities, to obtain priority access to potential COVID-19 vaccines. The concept symbolizes the COVID-19 **vaccine** (when it eventually becomes available) as **an instrument of power deployed to exercise control** **over who will live and who must die**. In order to counter vaccine sovereignty, we must decolonize the vaccine. Africans have a particular role to play in leading this decolonization process as subjects of colonialism and as objects of domination through coloniality. Colonialism, as an expansion of territorial dominance, and coloniality, as the continued expression of Western imperialism after colonization, play out in the vaccine development space, most notably on the African continent. So what does decolonizing the vaccine look like? And how do we decolonize something that does not yet exist? For Frantz Fanon, “**Decolonization**, which sets out to change the order of the world, **is**, obviously, a program of **complete disorder**.” **Acknowledging** **that the** COVID-19 **vaccine has been weaponized** **as an instrument of power** by wealthy nations, **decolonization** **requires** a Fanonian program of **radical re-ordering.** In the context of vaccine sovereignty, this re-ordering **necessitates** the **dismantling** of the **profit-driven biomedical system**. This program starts with **de-linking from** **Euro-American constructions of knowledge and power** that reinforce vaccine sovereignty through the profit-driven biomedical system. Advocacy campaigns such as the “People’s Vaccine”, which calls for guaranteed free access to COVID-19 vaccines, diagnostics and treatments to everyone, everywhere, are a good start. Other mechanisms, such as the World Health Organization’s COVID-19 Technology Access Pool, similarly supports universal access to COVID-19 health technologies as global public goods. Since less than 1% of vaccines consumed in Africa are manufactured on the continent, regional efforts to develop vaccine manufacturing capacity such as those led by the Africa Center for Disease Control and Prevention, as well as the Alliance of African Research Universities, must be supported. These efforts collectively advance delinking and move us closer toward the re-ordering of systems of power. The opportunity for disorder is paradoxically enabled by the COVID-19 pandemic, which has permitted moments of existential reflection in the midst of the crisis. A few months ago, a press release announcing the distribution of “a portion of the vaccines” to Africans, may have been lauded as European benevolence. But in the context of a pandemic that is more likely to kill black people, Africa’s reliance on Europe for vaccine handouts is untenable, necessitating a re-examination of the systems of power that hold this colonial relationship in place. The Black African body appears to be good enough to be experimented on, but not worthy of receiving simultaneous access to the COVID-19 vaccine as Europeans. Consequently, Africans continue to feel the effects of colonialism and white supremacy, and understand the pernicious nature of European altruism. By reinforcing the current system of vaccine research, development and manufacturing, it has become apparent that European governments want to retain their colonial power over life and death in Africa through the COVID-19 vaccine. Resistance to this colonial power requires the decolonization of the vaccine.

#### This is a form of pharmaceutical capitalism – exploiting marginalized groups in the third world.

Lift Mode 17 3-10-2017 "Pharmaceutical Colonialism” <https://medium.com/@liftmode/pharmaceutical-colonialism-3-ways-that-western-medicine-takes-from-indigenous-communities-3a9339b4f24f> (We at Liftmode.com are a team of professionals from a variety of backgrounds, dedicated to the mission of providing the highest quality and highest purity nutritional health supplements on the market. We look specifically for the latest and most promising research in the fields of cognition enhancement, neuroscience and alternative health supplements, and develop commercial strategies to bring these technologies to the marketplace.)//Elmer

3. **Cost of medicine as a form of debt** **One of the biggest methods of extracting money from rural and indigenous communities is through increased costs of medication**. Pharmaceutical colonialism often uses the premise of providing cheap medication for the world’s neediest to acquire local knowledge and natural resources. This premise is pushed into society through advertising campaigns and processes like lobbying. However, those who benefit most are often the shareholders, and not the people who need help. An example was the 2009 Reuters report which found that nearly **a million people** were **dying from malaria** dying every year **due to overly expensive medication**. According to the report, Artemisinin combination therapies (ACTs) can cost up to 65 times the daily minimum wage in countries that are most affected by malaria. These high prices **come after the government subsidies** which push them down as low as possible.[19] Another famous and recent example was the businessman Martin Shkreli, who pushed the cost of an AIDS drug up from $13.50 to over $700 per pill. This created an outrage on social media and it highlighted the underlying mindset behind most pharmaceutical companies — profit above all. An interesting and disturbing source of information about this is the film Fire in the Blood, which documents how **western pharmaceutical companies** **blocked the sale of cheap antiretroviral drugs to AIDS patients** **in Sub-Saharan Africa**.[20] “There is indeed a sense in which all modern **medicine** is **engaged in a colonizing process**… It can be seen in **the** increasing **professionalization of medicine and the exclusion of ‘folk’ practitioners**, in the close and often symbiotic relationship between medicine and the modern state, in the far-reaching claims made by medical science for its ability to prevent, control, and even eradicate human diseases.”[21] — D Arnold, Colonizing the Body, 1993 Pharmaceutical companies have been responsible for saving millions of lives due to their advances in medicine. However, the number of lives that have been lost due to the lack of affordability of medicine and the lack of equity and sharing of profits is estimated to be extremely high. **Western capitalism** has the **potential to act as a new form of colonialism**, and the modern medical method is one great way to extend the branches of capitalism into developing countries. The slums in Brazil highlight the blatant inequality between nations and people.

### 1AC: Plan

#### Plan – The member nations of the World Trade Organization ought to reduce intellectual property protections for medicines by implementing a one-and-done approach for patent and exclusivity protection for patent originators.

#### The Plan solves Evergreening.

Feldman 3 Robin Feldman 2-11-2019 "‘One-and-done’ for new drugs could cut patent thickets and boost generic competition" <https://www.statnews.com/2019/02/11/drug-patent-protection-one-done/> (Arthur J. Goldberg Distinguished Professor of Law, Albert Abramson ’54 Distinguished Professor of Law Chair, and Director of the Center for Innovation)//SidK + Elmer

I believe that one period of protection **should be enough**. We should make the legal changes necessary to prevent companies **from building patent walls** and piling up mountains of rights. This could be accomplished **by a “one-and-done” approach** for patent protection. Under it, a drug would receive just one period of exclusivity, and no more. The choice of which “one” could be left entirely in the hands of the pharmaceutical company, with the election made when the FDA approves the drug. Perhaps development of the drug went swiftly and smoothly, so the remaining life of one of the drug’s patents is of greatest value. Perhaps development languished, so designation as an orphan drug or some other benefit would bring greater reward. The choice would be up to the company itself, based on its own calculation of the maximum benefit. The result, however, is that a pharmaceutical company chooses whether its period of exclusivity would be a patent, an orphan drug designation, a period of data exclusivity (in which no generic is allowed to use the original drug’s safety and effectiveness data), or something else — but **not all of the above** and more. Consider Suboxone, a combination of buprenorphine and naloxone for treating opioid addiction. The drug’s maker has extended its protection cliff eight times, including obtaining an orphan drug designation, which is intended for drugs that serve only a small number of patients. The drug’s first period of exclusivity ended in 2005, but with the additions its protection now lasts until 2024. That makes almost two additional decades in which the public has borne the burden of monopoly pricing, and access to the medicine may have been constrained. Implementing a one-and-done approach in conjunction with FDA approval underscores the fact that these problems and solutions are designed for pharmaceuticals, not for all types of technologies. That way, one-and-done could be implemented through **legislative changes to the FDA’s drug approval system**, and would apply to patents granted going forward. One-and-done would apply to both patents and exclusivities. A more limited approach, a baby step if you will, would be to invigorate the existing patent obviousness doctrine as a way to cut back on patent tinkering. Obviousness, one of the five standards for patent eligibility, says that inventions that are obvious to an expert or the general public can’t be patented. Either by congressional clarification or judicial interpretation, many pile-on patents could be eliminated with a ruling that the core concept of the additional patent is nothing more than the original formulation. Anything else is merely an obvious adaptation of the core invention, modified with existing technology. As such, the patent would fail for being perfectly obvious. Even without congressional action, a more vigorous and robust application of the existing obviousness doctrine could significantly improve the problem of piled-up patents and patent walls. Pharmaceutical companies have become adept at maneuvering through the system of patent and non-patent rights to create mountains of rights that can be applied, one after another. This behavior lets drug companies keep competitors out of the market and beat them back when they get there. We shouldn’t be surprised at this. Pharmaceutical companies are profit-making entities, after all, that face pressure from their shareholders to produce ever-better results. If we want to change the system, we must change the incentives driving the system. And right now, the incentives for creating patent walls are just too great.

#### Reforming the Patent Process would lower Drug Prices and incentivize Pharma Innovation by revitalizing the Market.

Stanbrook 13, Matthew B. "Limiting “evergreening” for a better balance of drug innovation incentives." (2013): 939-939. (MD (University of Toronto) PhD (University of Toronto))//Elmer

At issue in the Indian case was “evergreening,” a now widespread practice by the pharmaceutical industry designed to extend the monopoly on an existing drug by modifying it and seeking new patents.2 Currently, half of all drugs patented in Canada have multiple subsequent patents, extending the lifetime of the original patent by about 8 years.3 Manufacturers, in defence of these practices, predictably tout the advantages of new versions of their products, which often represent more potent isomers or salts of the original drugs, longer-lasting formulations or improved delivery systems that make adherence easier or more convenient. But the new versions are by definition “**me too” drugs**, and demonstration that the resulting **incremental benefits** in efficacy and safety are clinically meaningful **is often lacking**. Moreover, the original drugs have often been “blockbusters” used for years to improve the health of millions of patients. It seems hard to argue convincingly why such beneficial drugs require an upgrade, often just before their patents expire. Rather than the marginal benefits accrued from tinkering with already effective agents, patients worldwide are in desperate need of new classes of pharmaceuticals for the great many health conditions for which treatments are presently inadequate or entirely lacking. But developing truly innovative drugs is undeniably a high-risk venture. It is important and necessary that pharmaceutical companies continue to take these risks, because they are usually the only entities with sufficient resources to do so. Therefore, companies must continue to perceive **sufficient incentives** to continue investing in innovation. Indeed, there is evidence that the prospect of future evergreening has become part of the incentive calculation for innovative drug development.4 But surely it is perverse to extend unpredictably a period of patent protection that the government intended to be clearly defined and predictable, and to maintain incentives that drive companies to divert their **drug-development resources away from innovation**. **Current patent legislation may not be optimal** for striking the right balance between encouraging innovation and facilitating profiteering. Given the broad societal importance of patent legislation, ongoing research to enable active governance of this issue should be a national priority. In the last decade, Canada’s laws have been among the friendliest toward evergreening in the world.5 We should now reflect on whether this is really in our national interest. Governments, including Canada’s, would do well to take inspiration from India’s example and tighten regulations that currently facilitate evergreening. This might involve **denying future patents for modifications** that currently would receive one. An overall reduction in the duration of all secondary patents on a therapy might also be considered. Globally, a more flexible and individualized approach to the length of drug patents might be a more effective strategy to align corporate incentives with population health needs. Limits on evergreening would likely reduce the **extensive patent litigation** that contributes to the **high prices of generic drugs** in Canada.3 Reducing economic pressure on generic drug companies may facilitate current provincial initiatives to lower generic drug prices. As opportunities to generate revenue from evergreening are eliminated, research-based pharmaceutical companies would be left with no choice but to invest more in innovative drug development to maintain their profits.

### 1AC: Framing

#### The standard is maximizing expected wellbeing or act hedonistic util.

#### Prefer:

#### 1] Pleasure and pain *are* intrinsic value and disvalue – everything else *regresses* – robust neuroscience.

Blum et al. 18

Kenneth Blum, 1Department of Psychiatry, Boonshoft School of Medicine, Dayton VA Medical Center, Wright State University, Dayton, OH, USA 2Department of Psychiatry, McKnight Brain Institute, University of Florida College of Medicine, Gainesville, FL, USA 3Department of Psychiatry and Behavioral Sciences, Keck Medicine University of Southern California, Los Angeles, CA, USA 4Division of Applied Clinical Research & Education, Dominion Diagnostics, LLC, North Kingstown, RI, USA 5Department of Precision Medicine, Geneus Health LLC, San Antonio, TX, USA 6Department of Addiction Research & Therapy, Nupathways Inc., Innsbrook, MO, USA 7Department of Clinical Neurology, Path Foundation, New York, NY, USA 8Division of Neuroscience-Based Addiction Therapy, The Shores Treatment & Recovery Center, Port Saint Lucie, FL, USA 9Institute of Psychology, Eötvös Loránd University, Budapest, Hungary 10Division of Addiction Research, Dominion Diagnostics, LLC. North Kingston, RI, USA 11Victory Nutrition International, Lederach, PA., USA 12National Human Genome Center at Howard University, Washington, DC., USA, Marjorie Gondré-Lewis, 12National Human Genome Center at Howard University, Washington, DC., USA 13Departments of Anatomy and Psychiatry, Howard University College of Medicine, Washington, DC US, Bruce Steinberg, 4Division of Applied Clinical Research & Education, Dominion Diagnostics, LLC, North Kingstown, RI, USA, Igor Elman, 15Department Psychiatry, Cooper University School of Medicine, Camden, NJ, USA, David Baron, 3Department of Psychiatry and Behavioral Sciences, Keck Medicine University of Southern California, Los Angeles, CA, USA, Edward J Modestino, 14Department of Psychology, Curry College, Milton, MA, USA, Rajendra D Badgaiyan, 15Department Psychiatry, Cooper University School of Medicine, Camden, NJ, USA, Mark S Gold 16Department of Psychiatry, Washington University, St. Louis, MO, USA, “Our evolved unique pleasure circuit makes humans different from apes: Reconsideration of data derived from animal studies”, U.S. Department of Veterans Affairs, 28 February 2018, accessed: 19 August 2020, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6446569/>, R.S.

**Pleasure** is not only one of the three primary reward functions but it also **defines reward.** As homeostasis explains the functions of only a limited number of rewards, the principal reason why particular stimuli, objects, events, situations, and activities are rewarding may be due to pleasure. This applies first of all to sex and to the primary homeostatic rewards of food and liquid and extends to money, taste, beauty, social encounters and nonmaterial, internally set, and intrinsic rewards. Pleasure, as the primary effect of rewards, drives the prime reward functions of learning, approach behavior, and decision making and provides the **basis for hedonic theories** of reward function. We are attracted by most rewards and exert intense efforts to obtain them, just because they are enjoyable [10].

Pleasure is a passive reaction that derives from the experience or prediction of reward and may lead to a long-lasting state of happiness. The word happiness is difficult to define. In fact, just obtaining physical pleasure may not be enough. One key to happiness involves a network of good friends. However, it is not obvious how the higher forms of satisfaction and pleasure are related to an ice cream cone, or to your team winning a sporting event. Recent multidisciplinary research, using both humans and detailed invasive brain analysis of animals has discovered some critical ways that the brain processes pleasure [14].

Pleasure as a hallmark of reward is sufficient for defining a reward, but it may not be necessary. A reward may generate positive learning and approach behavior simply because it contains substances that are essential for body function. When we are hungry, we may eat bad and unpleasant meals. A monkey who receives hundreds of small drops of water every morning in the laboratory is unlikely to feel a rush of pleasure every time it gets the 0.1 ml. Nevertheless, with these precautions in mind, we may define any stimulus, object, event, activity, or situation that has the potential to produce pleasure as a reward. In the context of reward deficiency or for disorders of addiction, homeostasis pursues pharmacological treatments: drugs to treat drug addiction, obesity, and other compulsive behaviors. The theory of allostasis suggests broader approaches - such as re-expanding the range of possible pleasures and providing opportunities to expend effort in their pursuit. [15]. It is noteworthy, the first animal studies eliciting approach behavior by electrical brain stimulation interpreted their findings as a discovery of the brain’s pleasure centers [16] which were later partly associated with midbrain dopamine neurons [17–19] despite the notorious difficulties of identifying emotions in animals.

Evolutionary theories of pleasure: The love connection BO:D

Charles Darwin and other biological scientists that have examined the biological evolution and its basic principles found various mechanisms that steer behavior and biological development. Besides their theory on natural selection, it was particularly the sexual selection process that gained significance in the latter context over the last century, especially when it comes to the question of what makes us “what we are,” i.e., human. However, the capacity to sexually select and evolve is not at all a human accomplishment alone or a sign of our uniqueness; yet, we humans, as it seems, are ingenious in fooling ourselves and others–when we are in love or desperately search for it.

It is well established that modern biological theory conjectures that **organisms are** the **result of evolutionary competition.** In fact, Richard Dawkins stresses gene survival and propagation as the basic mechanism of life [20]. Only genes that lead to the fittest phenotype will make it. It is noteworthy that the phenotype is selected based on behavior that maximizes gene propagation. To do so, the phenotype must survive and generate offspring, and be better at it than its competitors. Thus, the ultimate, distal function of rewards is to increase evolutionary fitness by ensuring the survival of the organism and reproduction. It is agreed that learning, approach, economic decisions, and positive emotions are the proximal functions through which phenotypes obtain other necessary nutrients for survival, mating, and care for offspring.

Behavioral reward functions have evolved to help individuals to survive and propagate their genes. Apparently, people need to live well and long enough to reproduce. Most would agree that homo-sapiens do so by ingesting the substances that make their bodies function properly. For this reason, foods and drinks are rewards. Additional rewards, including those used for economic exchanges, ensure sufficient palatable food and drink supply. Mating and gene propagation is supported by powerful sexual attraction. Additional properties, like body form, augment the chance to mate and nourish and defend offspring and are therefore also rewards. Care for offspring until they can reproduce themselves helps gene propagation and is rewarding; otherwise, many believe mating is useless. According to David E Comings, as any small edge will ultimately result in evolutionary advantage [21], additional reward mechanisms like novelty seeking and exploration widen the spectrum of available rewards and thus enhance the chance for survival, reproduction, and ultimate gene propagation. These functions may help us to obtain the benefits of distant rewards that are determined by our own interests and not immediately available in the environment. Thus the distal reward function in gene propagation and evolutionary fitness defines the proximal reward functions that we see in everyday behavior. That is why foods, drinks, mates, and offspring are rewarding.

There have been theories linking pleasure as a required component of health benefits salutogenesis, (salugenesis). In essence, under these terms, pleasure is described as a state or feeling of happiness and satisfaction resulting from an experience that one enjoys. Regarding pleasure, it is a double-edged sword, on the one hand, it promotes positive feelings (like mindfulness) and even better cognition, possibly through the release of dopamine [22]. But on the other hand, pleasure simultaneously encourages addiction and other negative behaviors, i.e., motivational toxicity. It is a complex neurobiological phenomenon, relying on reward circuitry or limbic activity. It is important to realize that through the “Brain Reward Cascade” (BRC) endorphin and endogenous morphinergic mechanisms may play a role [23]. While natural rewards are essential for survival and appetitive motivation leading to beneficial biological behaviors like eating, sex, and reproduction, crucial social interactions seem to further facilitate the positive effects exerted by pleasurable experiences. Indeed, experimentation with addictive drugs is capable of directly acting on reward pathways and causing deterioration of these systems promoting hypodopaminergia [24]. Most would agree that pleasurable activities can stimulate personal growth and may help to induce healthy behavioral changes, including stress management [25]. The work of Esch and Stefano [26] concerning the link between compassion and love implicate the brain reward system, and pleasure induction suggests that social contact in general, i.e., love, attachment, and compassion, can be highly effective in stress reduction, survival, and overall health.

Understanding the role of neurotransmission and pleasurable states both positive and negative have been adequately studied over many decades [26–37], but comparative anatomical and neurobiological function between animals and homo sapiens appear to be required and seem to be in an infancy stage.

Finding happiness is different between apes and humans

As stated earlier in this expert opinion one key to happiness involves a network of good friends [38]. However, it is not entirely clear exactly how the higher forms of satisfaction and pleasure are related to a sugar rush, winning a sports event or even sky diving, all of which augment dopamine release at the reward brain site. Recent multidisciplinary research, using both humans and detailed invasive brain analysis of animals has discovered some critical ways that the brain processes pleasure.

Remarkably, there are pathways for ordinary liking and pleasure, which are limited in scope as described above in this commentary. However, there are **many brain regions**, often termed hot and cold spots, that significantly **modulate** (increase or decrease) our **pleasure or** even produce **the opposite** of pleasure— that is disgust and fear [39]. One specific region of the nucleus accumbens is organized like a computer keyboard, with particular stimulus triggers in rows— producing an increase and decrease of pleasure and disgust. Moreover, the cortex has unique roles in the cognitive evaluation of our feelings of pleasure [40]. Importantly, the interplay of these multiple triggers and the higher brain centers in the prefrontal cortex are very intricate and are just being uncovered.

Desire and reward centers

It is surprising that many different sources of pleasure activate the same circuits between the mesocorticolimbic regions (Figure 1). Reward and desire are two aspects pleasure induction and have a very widespread, large circuit. Some part of this circuit distinguishes between desire and dread. The so-called pleasure circuitry called “REWARD” involves a well-known dopamine pathway in the mesolimbic system that can influence both pleasure and motivation.

In simplest terms, the well-established mesolimbic system is a dopamine circuit for reward. It starts in the ventral tegmental area (VTA) of the midbrain and travels to the nucleus accumbens (Figure 2). It is the cornerstone target to all addictions. The VTA is encompassed with neurons using glutamate, GABA, and dopamine. The nucleus accumbens (NAc) is located within the ventral striatum and is divided into two sub-regions—the motor and limbic regions associated with its core and shell, respectively. The NAc has spiny neurons that receive dopamine from the VTA and glutamate (a dopamine driver) from the hippocampus, amygdala and medial prefrontal cortex. Subsequently, the NAc projects GABA signals to an area termed the ventral pallidum (VP). The region is a relay station in the limbic loop of the basal ganglia, critical for motivation, behavior, emotions and the “Feel Good” response. This defined system of the brain is involved in all addictions –substance, and non –substance related. In 1995, our laboratory coined the term “Reward Deficiency Syndrome” (RDS) to describe genetic and epigenetic induced hypodopaminergia in the “Brain Reward Cascade” that contribute to addiction and compulsive behaviors [3,6,41].

Furthermore, ordinary “liking” of something, or pure pleasure, is represented by small regions mainly in the limbic system (old reptilian part of the brain). These may be part of larger neural circuits. In Latin, hedus is the term for “sweet”; and in Greek, hodone is the term for “pleasure.” Thus, the word Hedonic is now referring to various subcomponents of pleasure: some associated with purely sensory and others with more complex emotions involving morals, aesthetics, and social interactions. The capacity to have pleasure is part of being healthy and may even extend life, especially if linked to optimism as a dopaminergic response [42].

Psychiatric illness often includes symptoms of an abnormal inability to experience pleasure, referred to as anhedonia. A negative feeling state is called dysphoria, which can consist of many emotions such as pain, depression, anxiety, fear, and disgust. Previously many scientists used animal research to uncover the complex mechanisms of pleasure, liking, motivation and even emotions like panic and fear, as discussed above [43]. However, as a significant amount of related research about the specific brain regions of pleasure/reward circuitry has been derived from invasive studies of animals, these cannot be directly compared with subjective states experienced by humans.

In an attempt to resolve the controversy regarding the causal contributions of mesolimbic dopamine systems to reward, we have previously evaluated the three-main competing explanatory categories: “liking,” “learning,” and “wanting” [3]. That is, dopamine may mediate (a) liking: the hedonic impact of reward, (b) learning: learned predictions about rewarding effects, or (c) wanting: the pursuit of rewards by attributing incentive salience to reward-related stimuli [44]. We have evaluated these hypotheses, especially as they relate to the RDS, and we find that the incentive salience or “wanting” hypothesis of dopaminergic functioning is supported by a majority of the scientific evidence. Various neuroimaging studies have shown that anticipated behaviors such as sex and gaming, delicious foods and drugs of abuse all affect brain regions associated with reward networks, and may not be unidirectional. Drugs of abuse enhance dopamine signaling which sensitizes mesolimbic brain mechanisms that apparently evolved explicitly to attribute incentive salience to various rewards [45].

Addictive substances are voluntarily self-administered, and they enhance (directly or indirectly) dopaminergic synaptic function in the NAc. This activation of the brain reward networks (producing the ecstatic “high” that users seek). Although these circuits were initially thought to encode a set point of hedonic tone, it is now being considered to be far more complicated in function, also encoding attention, reward expectancy, disconfirmation of reward expectancy, and incentive motivation [46]. The argument about addiction as a disease may be confused with a predisposition to substance and nonsubstance rewards relative to the extreme effect of drugs of abuse on brain neurochemistry. The former sets up an individual to be at high risk through both genetic polymorphisms in reward genes as well as harmful epigenetic insult. Some Psychologists, even with all the data, still infer that addiction is not a disease [47]. Elevated stress levels, together with polymorphisms (genetic variations) of various dopaminergic genes and the genes related to other neurotransmitters (and their genetic variants), and may have an additive effect on vulnerability to various addictions [48]. In this regard, Vanyukov, et al. [48] suggested based on review that whereas the gateway hypothesis does not specify mechanistic connections between “stages,” and does not extend to the risks for addictions the concept of common liability to addictions may be more parsimonious. The latter theory is grounded in genetic theory and supported by data identifying common sources of variation in the risk for specific addictions (e.g., RDS). This commonality has identifiable neurobiological substrate and plausible evolutionary explanations.

Over many years the controversy of dopamine involvement in especially “pleasure” has led to confusion concerning separating motivation from actual pleasure (wanting versus liking) [49]. We take the position that animal studies cannot provide real clinical information as described by self-reports in humans. As mentioned earlier and in the abstract, on November 23rd, 2017, evidence for our concerns was discovered [50]

In essence, although nonhuman primate brains are similar to our own, the disparity between other primates and those of human cognitive abilities tells us that surface similarity is not the whole story. Sousa et al. [50] small case found various differentially expressed genes, to associate with pleasure related systems. Furthermore, the dopaminergic interneurons located in the human neocortex were absent from the neocortex of nonhuman African apes. Such differences in neuronal transcriptional programs may underlie a variety of neurodevelopmental disorders.

In simpler terms, the system controls the production of dopamine, a chemical messenger that plays a significant role in pleasure and rewards. The senior author, Dr. Nenad Sestan from Yale, stated: “Humans have evolved a dopamine system that is different than the one in chimpanzees.” This may explain why the behavior of humans is so unique from that of non-human primates, even though our brains are so surprisingly similar, Sestan said: “It might also shed light on why people are vulnerable to mental disorders such as autism (possibly even addiction).” Remarkably, this research finding emerged from an extensive, multicenter collaboration to compare the brains across several species. These researchers examined 247 specimens of neural tissue from six humans, five chimpanzees, and five macaque monkeys. Moreover, these investigators analyzed which genes were turned on or off in 16 regions of the brain. While the differences among species were subtle, **there was** a **remarkable contrast in** the **neocortices**, specifically in an area of the brain that is much more developed in humans than in chimpanzees. In fact, these researchers found that a gene called tyrosine hydroxylase (TH) for the enzyme, responsible for the production of dopamine, was expressed in the neocortex of humans, but not chimpanzees. As discussed earlier, dopamine is best known for its essential role within the brain’s reward system; the very system that responds to everything from sex, to gambling, to food, and to addictive drugs. However, dopamine also assists in regulating emotional responses, memory, and movement. Notably, abnormal dopamine levels have been linked to disorders including Parkinson’s, schizophrenia and spectrum disorders such as autism and addiction or RDS.

Nora Volkow, the director of NIDA, pointed out that one alluring possibility is that the neurotransmitter dopamine plays a substantial role in humans’ ability to pursue various rewards that are perhaps months or even years away in the future. This same idea has been suggested by Dr. Robert Sapolsky, a professor of biology and neurology at Stanford University. Dr. Sapolsky cited evidence that dopamine levels rise dramatically in humans when we anticipate potential rewards that are uncertain and even far off in our futures, such as retirement or even the possible alterlife. This may explain what often motivates people to work for things that have no apparent short-term benefit [51]. In similar work, Volkow and Bale [52] proposed a model in which dopamine can favor NOW processes through phasic signaling in reward circuits or LATER processes through tonic signaling in control circuits. Specifically, they suggest that through its modulation of the orbitofrontal cortex, which processes salience attribution, dopamine also enables shilting from NOW to LATER, while its modulation of the insula, which processes interoceptive information, influences the probability of selecting NOW versus LATER actions based on an individual’s physiological state. This hypothesis further supports the concept that disruptions along these circuits contribute to diverse pathologies, including obesity and addiction or RDS.

#### 2] Death is bad and outweighs – a) agents can’t act if they fear for their bodily security which constrains every ethical theory, b) it destroys the subject itself – kills any ability to achieve value in ethics since life is a prerequisite which means it’s a side constraint since we can’t reach the end goal of ethics without life

#### 3] Actor spec—governments must use util because they don’t have intentions and are constantly dealing with tradeoffs—outweighs since different agents have different obligations—takes out calc indicts since they are empirically denied.