FOCUS: VACCINES

Reducing Outbreaks: Using International Governmental Risk Pools to Fund Research and Development of Infectious Disease Medicines and Vaccines

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The deadliest Ebola outbreak the world has ever seen is currently ravaging West Africa, despite the concerted efforts of the World Health Organization and many national governments. The current picture is troubling, but not altogether unexpected. Ebola was initially identified in 1976, and since that time, few drugs have been developed to combat it. The same is true for myriad other dangerous infectious diseases to which the world is currently susceptible. One proposal that might prevent outbreaks of this scale and magnitude from recurring would be to have the World Health Organization (WHO†) and its technical partners assess which of its member states are at high risk for a disease, either directly or indirectly, and facilitate the creation of international governmental risk pools of those member states. Risk pools would offer open-indexed grant contracts to fund vaccine and drug development for a particular disease, and pharmaceutical companies could browse the index to apply for these grants. If the risk-pool states and a particular company sign a contract, a mutually agreed upon amount of the vaccine or drug would be produced at a below-market purchase price for those states. In return, the company would keep any patents or intellectual property rights for the developed vaccines or drugs. Risk-pool countries that did not use their vaccine or drug could resell that supply on secondary markets to other countries outside of the risk pool. This arrangement will increase the supply of tested drug and vaccine candidates available for combatting unexpected outbreaks of any previously discovered major infectious disease in the future.

†Abbreviations: CCM, Country Coordinating Mechanism; GAIN, Generating Antibiotics Incentives Now; H1N1, Influenza A virus subtype H1N1; H5N1, Influenza A virus subtype H5N1; HIV, Human Immunodeficiency Virus; INSEAD, Institut Européen d’Administration des Affaires; IP, Intellectual Property; MERS-CoV, Middle East Respiratory Syndrome-Coronavirus; MIT, Massachusetts Institute of Technology; NIH, National Institutes of Health; NGO, non-governmental organization; R&D, Research and Development; SARS, Severe Acute Respiratory Syndrome; UNICEF, United Nations Children’s Fund; WHO, World Health Organization.

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INTRODUCTION

The deadliest outbreak of Ebola fever, one of the world’s most lethal infectious diseases, is currently unfolding in Africa. This outbreak is the largest ever recorded for the Ebola virus, both in terms of the number of cases and the number of fatalities [1]. The degree and speed with which the virus has overrun the health infrastructure of Liberia, Sierra Leone, and Guinea, the care of several high-profile doctors who contracted the disease while treating patients, and the death in Dallas of a West African man afflicted with Ebola who traveled from Liberia in September has worried many Americans and prompted heightened airport security [2,3,4]. Panic-inducing pandemics now appear frequently: SARS in 2003, H5N1 influenza in 2005, H1N1 influenza in 2009, and MERS-CoV in 2012 [5]. Many dangerous infectious diseases or their precursors have been known for decades; Ebola, for example, was initially identified in 1976 [6].

What has changed between now and 1976? Why is the virus only creating an epidemic now? The world’s strategy for controlling Ebola, according to the Belgian researcher who first identified the virus, has been to develop strict containment protocols, but these have failed to curtail the spread of this current outbreak because decades of increasing African urbanization, lower barriers to international travel, rapid population growth, and various political factors and economic capital and labor supply constraints have created a “perfect storm” that has allowed this virus to spread further than any public health worker or physician previously imagined [7]. The lesson here is that no level of proper planning can safely ensure, with full certainty, that a deadly disease will be contained, and instead, cures or vaccines must be developed should the unfortunate contingency of an epidemic arise. Failing to find cures for infectious diseases before they strike enables the inevitable expansion of their geographic ranges over time and increased cumulative morbidity. Ebola is not the first virus for which the world has failed to develop a vaccine or cure in a timely manner. For example, since its isolation in 1937, West Nile Virus has spread from Uganda to several other continents [8]. The problem is not isolated to Ebola, but is rather characteristic of a systemic, international approach to vaccine and drug development against infectious diseases that does not adequately protect the world’s population.

In economics, society’s failure to find cures, medicines, or vaccines for fatal infectious diseases is an example of a “market failure.” The problem is that companies bear the cost of producing the drugs that would also benefit citizens and governments, which currently do not contribute enough to the cost of developing and bringing a drug to market. Fewer drug candidates in the pipeline means fewer effective drugs. One possible innovation is to encourage governments to share more directly in the costs and risks undertaken by companies during the drug development process. Governments may be convinced to help cover the upfront costs of drug research if they perceive the threat of pandemics to be akin to the hazards covered by actuarial insurance. Like an “act of God,” pandemics often unpredictably strike in the environmental range of a disease vector. Economic arrangements can solve this problem inasmuch as the societal cost of epidemics is much higher than the market entry and research and development (R&D) costs facing manufacturers. This is likely because the economic burden of an outbreak is often substantial — for example, SARS in 2003 is estimated to have caused losses of at least US $40 billion to the world economy [9].

SUPRANATIONAL RISK POOLS FOR INFECTIOUS DISEASES

One innovative proposal would be to use risk pools, comprised of government representatives from countries at risk for a particular disease, to provide grants to companies interested in developing new vaccines and medicines for that disease. Varying funding amounts would be awarded to companies that produce well-performing drugs.
In return, governments in a risk pool have the right to purchase drugs at a below-market price or to resell their drug allotment on a secondary market. Figure 1 summarizes the key elements of this proposal.

**Funding Sources**

For this proposal to succeed, countries that are within the natural geographic range for a disease should pool their resources and support drug discovery and development. However, it is true that if the risk pool for a disease were limited only to those countries that are at greatest direct risk for primary epidemics, then in many cases the funding generated would be insufficient to meaningfully mitigate the cost of drug development. One solution is that the sharing of risk should not be limited to countries that would be directly affected by a hypothetical outbreak — other countries that frequently trade goods or labor with at-risk countries should consider joining the risk pool themselves since infected products or people can easily cross borders. This would likely bring in much larger sums of money because workers from low- and middle-income countries tend to immigrate to higher-income countries [10] whose governments would have strong incentives to join risk pools to protect their citizens from diseases endemic to those low-income countries.

A second solution is that the sharing of risk should be encouraged regionally so that countries in close proximity to disease hotspots should be made parties to risk sharing even if they assess their own internal domestic risk to be quite low. For example, during the ongoing Ebola outbreak, a traveler from West Africa boarded a plane to Lagos, the largest city in Africa, in Nigeria, the richest country in Africa in terms of nominal GDP and the 24th largest economy in the world [11]. Fortunately, the passenger was already symptomatic and was safely quarantined before Nigerians contracted the disease. However, the lesson here is that while West African nations alone had limited capacity to support disease research prior to this outbreak, a regional economic giant like Nigeria could have devoted some of its GDP toward a risk-sharing arrangement and should have done so because it is clearly at risk of spillover effects from a West African epidemic. Other examples of rich countries in close proximity to poor countries with endemic infectious diseases can be found in Latin America, the Middle

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**Figure 1.** World Health Organization-managed risk pool grant system for stimulating research and development of infectious disease medicines and vaccines.
East, and Asia, and it is these wealthy nations that should form a cornerstone of the global risk-sharing funding strategy.

**World Health Organization (WHO) Management & Operation Protocols**

The World Health Organization (WHO) is best suited to facilitate the formation and transactions of supranational risk pools because the national governments of WHO member states already frequently communicate over joint funds. The WHO can serve an advisory role by using its technical expertise and disease surveillance data and its partnership with the World Bank to recommend country groupings for each risk pool.

The operation protocols for each risk pool should be carefully devised and managed (Figure 1). Within each pool, national representatives and technical advisors should formalize grants for which drug manufacturers can apply (Figure 1A). Grant monies should be allocated by countries in direct proportion to their projected risk, as calculated by the WHO, for an epidemic of the targeted infectious agent over the grant period. Risk pools should provide a flat sum to help cover a fraction of manufacturers’ up-front costs, and additional “earnable” awards may be paid based on the performance of drug candidates. For instance, risk pools might consider offering additional money to the producers of drugs that save more lives, have fewer side effects, or cost less to create (Figure 1B,G). Pharmaceutical companies would be free to browse an open listing of grants to which they could apply in order to help reduce their R&D costs (Figure 1C). Risk-pool member states would jointly review grant applications and enter a contractual agreement with the grant winner that specifies the baseline funding level and additional funds awardable according to drug performance (Figure 1D). Exclusivity clauses, regulatory fast-tracking, and patent lifetime extensions are contractual options that might also be explored on a case-by-case basis for certain drug candidates or producers with good track records (Figure 1E). Drug development, approval, and production would proceed in line with the appropriate industry standards (Figure 1F). Governments in a risk pool earn the right to purchase drugs at below-market prices for an agreed-upon timeframe and quantity (Figure 1H,I) or if their country was fortunate not to experience an epidemic during the contract period, to resell the purchased drugs in a secondary market to other countries (Figure 1J). Countries should be free to join several pools, one for each disease to which they are vulnerable, if they have the financial means to contribute to a grant fund.

**Pharmaceutical Companies**

Why would pharmaceutical companies choose to participate in these schemes? Economic theory predicts that profit-seeking enterprises, such as pharmaceutical companies, are motivated to respond to favorable long-term financial incentives. Ultimately, as outlined in Figure 1, a company that enters into a contractual agreement with the members of a risk pool would be entitled to keep the intellectual property (IP) rights to any novel drugs or vaccines it produces. If a drug is able to offer significant advancements in the reduction of morbidity and mortality, then the economic gains from IP ownership could be an enormous boon for the company. This is because for a set number of years after drug discovery, the company’s ability to sell the drug at a protected price to any government in the world, not only those in the original risk pool, will provide it with substantial revenues.

It is true, though, that the risky prospect of investigating deadly infectious diseases, many of which are difficult to study due to the limited number of study subjects available at any given time, may be unappealing for many companies. However, it is also true that the nature of the global R&D funding environment is shifting in such a way that pharmaceutical companies may now consider options that were heretofore deemed too risky to pursue. For instance, the United States’ once-unassailable position as the global leader in drug and vaccine development has come under fire, thanks to repeated budget reduction legislation that has continually reduced National Institutes of Health
(NIH) biomedical research funding since 2003 [12]. An inflation-adjusted study of the compound annual growth rate of R&D expenditures by country from 2007 to 2012 shows that R&D funding has decreased in Europe, Canada, and the United States, while it has increased tremendously in several Asian countries, led by China, which saw growth of 32.8 percent [12]. Indeed, major Western pharmaceutical companies, including Pfizer, AstraZeneca, and Merck, have been scaling back R&D investment in the name of short-term profits, but this will eventually lead to shrinking pipelines [13]. Adding more money to the global pot available for drug and vaccine development would likely be welcomed by Western pharmaceutical companies thirsty for funds; on the other hand, Asian companies, with their more limited budgets, an eye toward innovation, and a desire to keep their positive growth track record of recent years, may attempt to research these infectious diseases despite the inherent business risks.

**Hard-to-Reach Areas and Conflict Zones**

An additional concern is how to provide drugs and vaccines to developing countries that have limited transportation infrastructure and/or dangerous conflict zones. If companies are successful in developing drugs that meet clinical benchmarks for safety and efficacy, then drug production should be coordinated with established international bodies and public-private partnerships equipped with the resources and expertise for supplying the hard-to-reach areas with medical supplies. For instance, the global vaccine alliance Gavi, UNICEF, the Red Cross, and countless other organizations and partnerships have played critical roles in distributing drugs and vaccines to developing nations with limited supply-chain resources or compromised rule-of-law. However, the risk pools should not rely solely on these partners; they should create mechanisms for ensuring the safe and efficient domestic distribution in target countries. The Global Fund to Fight AIDS, Tuberculosis and Malaria famously instituted Country Coordinating Mechanisms (CCMs), which were committees of in-country stakeholders required to include a range of supranational, governmental, non-governmental organizations (NGOs), private, and faith-based organizations to ensure proper implementation and drug disbursement [14]. The member nations of a risk pool should try something similar.

**DISCUSSION**

This system of governmental risk pools utilizes pricing and production incentives (e.g., advance market commitments, price-volume agreements, and performance-based standards) similar to those that have succeeded elsewhere in public health. However, this proposal is innovative for three reasons. First, it formalizes an international funding system that aligns the incentives of several countries at risk for a disease. Without risk sharing among national governments, the world’s response to pandemics is sub-optimal. For example, the “securitization” of H5N1 vaccines caused supply chains to degenerate as countries began stockpiling and using vaccines as bargaining chips to advance national self-interests [15]. A lack of coordinated risk-sharing arrangements allows political gamesmanship to eclipse the needs of vulnerable populations in the midst of an epidemic. Second, the proposal enables manufacturers to share their initial costs with governments, thereby increasing drug supplies. Massachusetts Institute of Technology (MIT) and Institut Européen d’Administration des Affaires (INSEAD) researchers have demonstrated using non-linear mathematical modelling of an influenza vaccine supply chain that only when potential buyers of a vaccine support its upfront development costs can the socially optimal supply level be generated [16]. In other words, advance market commitments, price-volume agreements, and other cooperative arrangements meant for increasing the supply of new drugs are insufficient if they do not incorporate mechanisms for sharing initial R&D costs. Third, the proposal appropriates for the international setting the
governmental risk-pool model that has succeeded domestically in the United States. Having begun in the United States only 30 years ago, public sector risk pools now account for 80 percent of risk management and risk financing for U.S. public entities [17].

CONCLUSIONS AND OUTLOOK

In the battle against infectious diseases, economic innovations have previously solved formidable market failures. For example, the U.S. Generating Antibiotics Incentives Now (GAIN) Act of 2012 addressed the dwindling supply of potent antibiotics for drug-resistant bacteria through 5-year exclusivity guarantees [18]. Furthermore, the Clinton Foundation brokered pricing agreements with anti-retroviral drug suppliers to increase affordability and expand quantities of HIV drugs in Africa [19]. But these types of economic arrangements are insufficient for incentivizing R&D for drugs or vaccines against several extremely rare but fatal diseases affecting large swathes of the globe. A broader economic arrangement is needed, akin to the work of the Global Fund or Gavi. A WHO-administered grant system funded by at-risk countries that is meant to incentivize pharmaceutical research in return for favorable future drug prices for funders might be one possible answer.

Despite the innovative approach offered by this proposal, some critics might contend that the efficacy of the program would be limited since many risk pools would fail to find suitable drug or vaccine candidates. Certainly, the proposed system is complex, and there is no guarantee that every risk pool would partner with a company whose efforts will inevitably culminate in a worthy product. However, for the program as a whole to be successful, only a small fraction of the total risk-pool grants offered needs to be successful. An analogy can be made here. In the drug discovery process, typically tens of thousands of potential molecules are screened and the composite field is whittled away to hundreds of leading drug candidates. After successive iterations of biochemical modification and animal testing, clinical studies and, eventually, field trials are conducted. After many years, the original field of tens of thousands of possible molecules yields only a few actual drugs. Yet the failures of these many molecules do not constitute failure of the drug discovery process altogether; rather, the success of even just a handful of drugs can redeem the total financial and time costs of the entire program. Indeed, because there are myriad factors and systems — spanning from market economics to epidemiologic variation to rational drug design principles — that determine the commercial success of a drug over a 20-year period, the development of even one effective drug from a field of thousands of candidates can be deemed an overall success.

The same principle can be illustrated for risk pools with a numerical example. If the WHO identifies 1,000 infectious diseases, it may recommend, after careful technical inquiry and discussion with its partner organizations such as the World Bank, that because of market constraints, epidemiologic and environmental trends, and the financial resources of the relevant WHO member states, that a risk pool of member states can be assembled for only for 300 of those diseases. Of those 300 risk pools, it may be that only 150 of those pools’ member states can agree on the terms of a contractual grant that would be offered on an open index for which pharmaceutical companies can browse and choose to apply. Perhaps companies apply for only 100 of the 150 grants, and of those, only 50 result in actual grant contracts for companies. If, of the 50 contracts, only two or three result in marketable and effective drugs that substantially improve the quality or length of life for disease sufferers, then by some measures the program could be deemed a success.

The goal is simply to produce additional vaccines and if not vaccines then treatment drugs that would reduce overall morbidity and mortality for a few infectious diseases that would never have received substantial R&D funding in today’s economic climate. If one of those diseases had been
Ebola, for instance, then the current events spiraling out of control in West Africa may not have occurred. Only time will tell if our society continues to repeat these mistakes.

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