The Health Impact Fund

How Might It Work for Novel Anticoagulants in Atrial Fibrillation?

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ABSTRACT

Cardiovascular diseases represent the greatest burden of global disease. Spending on cardiovascular diseases is higher than for other diseases, with the majority being spent on drugs. Therefore, these drugs and these diseases are hugely important to health systems, society, and pharmaceutical companies. The Health Impact Fund represents a new mechanism by which pharmaceutical innovators would be rewarded on the basis of the health impact of their new drugs. This review illustrates the concept of the Health Impact Fund using the example of novel anticoagulants for prevention of stroke and thromboembolism in atrial fibrillation. By considering existing data and the current situation for novel anticoagulants, we suggest that epidemiologic data and modeling techniques can be used to predict future trends in disease and the health impact of new drugs. The Health Impact Fund may offer potential benefits to pharmaceutical companies, patients, and governments and warrants proper investigation.

Burden of disease due to cardiovascular disease (CVD) is greater than for any other disease globally [1—3]. CVD are firmly on the global health policy agenda [4—6]. Spending on CVD is greater than for any other disease globally; for example, hypertension represents over 10% of healthcare expenditure globally [7,8]. Intersectoral and interdisciplinary approaches are essential to reduce global CVD [4,9].

Most healthcare spending (as in CVD), particularly in low- and middle-income countries (LMIC) and particularly out-of-pocket expenditure, is on drugs [10—12]. Every stage of CVD (primary prevention, secondary prevention, and acute management) requires drugs. Efforts to reduce global healthcare costs must involve drugs used to prevent or treat CVD.

Drugs to treat CVD and its risk factors have topped blockbuster charts for over 30 years, whether anticlotting drugs (e.g., clopidogrel, Plavix), statins (e.g., simvastatin, Zocor), or antihypertensives (e.g., lisinopril, Carace) [13,14]. Some of the largest cases of misconduct in trials have occurred in CVD (e.g., rofecoxib, Vioxx) [15]. These drugs and diseases are important to health systems, society, and pharmaceutical companies, and improved drug access may produce the greatest gains.

In this review, implications of intellectual property rights on access to medicines and innovation are examined. Potential solutions are explored. We will define the Health Impact Fund (HIF), a novel proposal to incentivize development and distribution of drugs depending on global health impact. The potential role of the HIF will be considered with respect to novel anticoagulants (NOAC) for stroke prevention in atrial fibrillation (AF).

INTELLECTUAL PROPERTY RIGHTS

Until 1994, intellectual property rights were enforced strictly in wealthy countries, whereas LMIC had much weaker patent laws, if any. Since 1994, LMIC agreed to institute TRIPS (Trade-Related Aspects of Intellectual Property Rights)-compliant systems [16]. TRIPS has become more constraining as increased numbers of countries implement patent exclusivity, shaping all intellectual property rights, including those for drugs. Although TRIPS implementation and affordability are not the only factors contributing to access, TRIPS has probably widened global health inequalities [17—19] (Fig. 1).

New technologies, including drugs, have been "produced by companies from high-income countries for high-income markets" [20,21]. The industries and the incentives are not aligned with access, which acts as both determinant and consequence of inequalities in health, income, and development [17,19]. Access to drugs is among global health's greatest challenges. Even for cheap, generic drugs with proven efficacy, rates of use and access are suboptimal. A recent study of global secondary CVD prevention showed that few individuals took antiplatelet drugs (25.3%), beta-blockers (17.4%), angiotensin-converting enzyme inhibitors or angiotensin 2—receptor blockers (19.5%), or statins (14.6%) [22]. These data suggest that health system improvements are needed to affect drug access. New CVD drugs may not have a major effect when established drugs are so underused. However, in certain instances, new drugs have transformed disease management (e.g., statins in CVD prevention or angiotensin-converting enzyme inhibitors for hypertension). Intellectual property rights can directly influence affordability, sustainability, and rational selection by practitioners by highlighting new drugs with the greatest impact on health. Indirectly, pharmaceutical companies may be incentivized to improve infrastructure and proper use by health professionals and individuals (Fig. 1). Therefore, intellectual property rights and new drugs may have wide implications on global health impact.

Thomas Pogge conceived the original idea of the Health Impact Fund. Amitava Banerjee has been Medical Advisor to the Health Impact Fund since its inception. There has been no significant financial support for this work that could have influenced its outcome.
The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP/2007-2013)/ERC Grant Agreement no. 339239.
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GLOBAL HEART

VOL. 9, NO. 2, 2014
ISSN 2211-8160/$36.00.
http://dx.doi.org/10.1016/j.gheart.2014.01.005

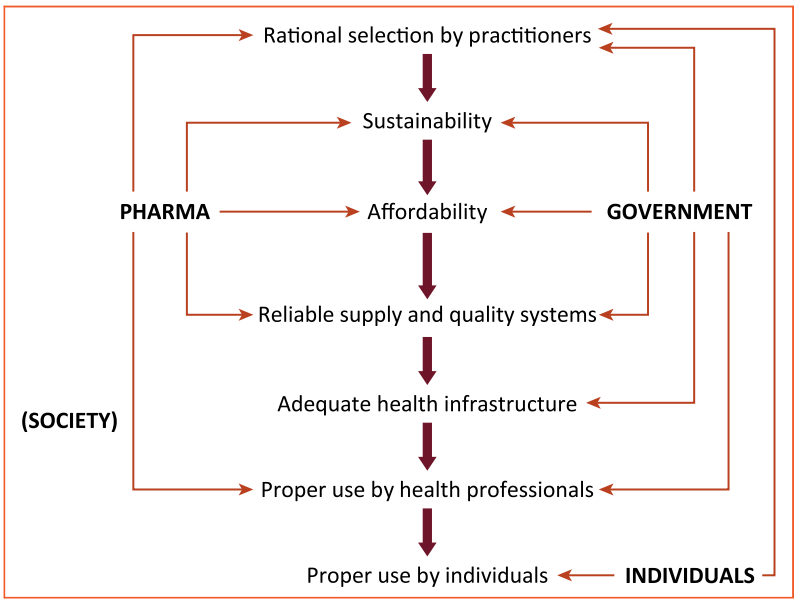

FIGURE 1. Access to medicines. Adapted, with permission, from: Banerjee A. Whose responsibility is access to essential drugs for chronic diseases? Ethics Econ 2006;4:2 [19].

Ethical and human rights arguments have been used for access to health care [4,23,24], which should guide governments and industries to produce accessible medicines. However, access is not simply based on cost and affordability. If other factors are neglected, benefits of available drugs will not be realized. Even if appropriate, essential medications are available, their correct use is not guaranteed [17,19]. Governments, pharmaceutical companies, society, and individuals all have a role to play. However, responsibility for providing access to drugs is in the hands of the stakeholders with greatest capability, namely pharmaceutical companies and governments [19]. Cost of drugs represents a unique opportunity to change the current paradigm (Fig. 1).

CURRENT SOLUTIONS

Where cost of medications restricts their provision, several potential solutions have been used. First, generic drugs are cheaper than branded versions. Indian companies supply low-cost generics (including CVD drugs), domestically, to other LMIC and increasingly to wealthier countries as well. If generics are substituted for branded drugs, especially in CVD, economic and public health benefits are likely [25]. Until 2005, India could avoid introducing product patents, although process patents were already available prior to TRIPS [26,27]. However, a recent analysis of new patents filed in India since 2005 suggests no relationship with disease burden or public health priorities [28].

Second, charitable donations from wealthy countries and pharmaceutical companies are possible. Because treatments for CVD are often long term, if not lifelong, a more sustainable supply is needed.

Proponents of TRIPS state that it contains provisions that allow prioritization of public health needs. Parallel imports are imports of a patented or trademarked product from a country where it is already marketed [29]. Compulsory licensing is when a government allows someone else to produce the patented product or process without the consent of the patent owner [30]. However, LMIC have not adequately used existing provisions with public health consequences [31]. In summary, CVD drugs are neither available nor affordable in many countries, particularly in the public sector [32].

THE HEALTH IMPACT FUND

There are no incentives for pharmaceutical companies to develop, market, or deliver drugs that will have a maximal impact on global health. Such mechanisms would make the greatest difference in CVD, which represent the largest disease burden, highest drug spending, and greatest number of new drugs in recent years.

The HIF would reward pharmaceutical companies in proportion to the global health impact of their innovation [17]. As a global agency underwritten by governments, it would offer pharmaceutical companies the option to register new products. Registration would entitle innovators to receive, for a defined period (e.g., 10 years), a share of fixed remuneration from a reward pool. The fund would disburse at least US$6 billion annually, paying each registrant a share corresponding to the contribution to the global health impact of all registered drugs, as estimated with a global health impact assessment exercise (Online Appendix 1). In return, the registrant would sell the medicine wherever needed at no more than the lowest feasible cost of production and distribution. After the reward period, free licenses would enable generic manufacture and sales [17].

The HIF has gained momentum [33,34], but the next challenges are finding pharmaceutical companies willing to license their novel products and credible methodology for a health impact assessment to test the HIF.

NEW DRUGS AND NEW TRIALS

AF is the commonest arrhythmia and is a major cause of stroke and thromboembolism [35]. NOAC are an alternative to warfarin, the mainstay of anticoagulation for over 50 years [36,37]. In the last 3 years, following successful phase 3 clinical trials, 3 agents (dabigatran, apixaban, and rivaroxaban) have been incorporated into guidelines worldwide and more NOAC are in the pipeline [38–40]. As with statins, angiotensin-converting enzyme inhibitors, angiotensin 2–receptor blockers, and other CVD drug classes, "me-too" agents are anticipated and trials are already underway [41–44]. Me-too drugs are expensive and do not serve society well [41–43]. The HIF may combine profits with patient benefit in a mutually beneficial manner.

Imagine that the pharmaceutical companies producing NOAC registered with the HIF. On the basis of trials or predicted trial outcomes (for edoxaban [44]), the reward for each NOAC would be estimated. Most NOAC have been subject to trials in deep vein thrombosis prior to trials in AF. Potential impact of NOAC could be estimated on the basis of deep vein thrombosis trials if AF trials were not yet completed.

Subgroup analyses are often reported in trials to quantify drug effects in different subpopulations. Ideally, subgroups should be defined before trial initiation, but post-hoc analyses are often reported. Although post-hoc analyses have possible biases and limitations, they may be useful for modeling. Possible subgroups for NOAC include age, renal function, or other cardiovascular risk factors [38–40,45,46].

NOAC, like warfarin, and all drugs, have risks (excess bleeding) as well as benefits (prevention of stroke/thromboembolism). Trial data may be used to estimate risks as well as benefits and to compare different agents. The health impact assessment will aim to model incremental benefit of new drugs versus current gold-standard therapy or other new drugs. For anticoagulants, "net clinical benefit" balances risk of bleeding versus benefit of stroke prevention [47] and has been used to compare NOAC and warfarin [48,49]. Similar concepts could be used for a health impact assessment of other new drugs.

IDENTIFYING DATASETS

National and local datasets (e.g., the United Kingdom's Clinical Practice Research Datalink [50] and the Danish National Patient Registry [48]) offer invaluable resources from which the target population can be modeled. Regional variations occur in distribution of risk factors and disease [51]. The more accurately these variations can be incorporated into models, the better the estimation of drug effects. The GBD (Global Burden of Disease) study has revolutionized knowledge of prevalence, time trends, and predictions for disease and risk factors [52,53]. GBD data could be used to model patient populations and drug effects at the country level. However, there is variation in missing data and methodologies of data collection across countries; for example, there is incomplete death registration in many LMIC, with some having no death registration data at all [54,55].

Registries can be local, regional, national, or multinational [56]. AF registries have highlighted risk associations [57] and have been used to model effects of population-wide implementation of NOAC [58] and differences between real-world and clinical trial effects [59]. Global registries can be powerful in learning about current risk factor and disease trends and clinical practices [60,61]. However, registries also have limitations, including variable data selection and data quality due to varying methodologies [62].

Tools are increasingly used to predict risk of disease outcomes in different populations. In AF, several risk prediction tools for stroke/thromboembolism and bleeding are validated, widely used [63–66], and have been used to define subgroups within studies [49]. In individuals, these tools allow trial results to be personalized. For example, stroke/thromboembolism risk associated with each level of the CHA_2DS_2-VASc score (which evaluates congestive heart failure, hypertension, age, diabetes mellitus, previous stroke, prior vascular disease, and sex) has been investigated in multiple studies. If the CHA_2DS_2-VASc distribution can be estimated in a population, the drug effects at each level of CHA_2DS_2-VASc may be modeled for the health impact assessment.

Optimal data sources will be identified for a particular context (preferably at multiple levels—local, regional, national) [67]. Growing transparency and public availability of data from trials will benefit the HIF [68,69].

MODELING

Analyses of population impact, potential cost, and comparative analysis of NOAC would be required. The population-attributable risk is the proportion of a given disease that can be attributed to a specific risk factor (e.g., AF), whether clinical [70] or subclinical [71] and may be useful for estimating burden of AF and stroke/thromboembolism. The "potentially modifiable burden" of disease (e.g., stroke) may be useful in describing potential benefits of drugs [72].

The IMPACT model shows how evidence can inform public health policy [73,74]. The "policy effectiveness-feasibility loop" involves: 1) epidemiological modeling; 2) situation analysis; and 3) option appraisal [74]. The first stage can be adapted to include modeling of effects of new drugs so that this same framework can be applied to the health impact assessment. The IMPACT model has been used to estimate proportion of change in rates of disease that can be attributed to changes in a particular risk factor [75,76]. The IMPACT model has largely been restricted to congenital heart disease, but it could be used in other diseases.

Projections of AF burden and representativeness of trial populations for NOAC have been studied [50,76]. Trial data can be used to model different levels of prescription, adherence, cost, and other environmental factors. Cost-effectiveness analyses are another data source [77,78] that is subject to quality of cost and efficacy data. Incremental cost-effectiveness data are of greatest relevance and value to the HIF, but they are often ignored in favor of "cost-effectiveness thresholds" [79,80]. As with all modeling, limitations and ranges of data must be acknowledged transparently. Different scenarios may be constructed within models to simulate the impact of several competing drugs: 1) competing drugs have sustained and equal sales; 2) one of the drugs overtakes its competitors; and 3) none of the drugs is taken up to an appreciable extent. Health impact assessment of drugs will take into account many factors, including adherence, side effects of new drugs, indications stipulated in the drug license, and ongoing post-marketing data collection. "Scenario planning" begins by identifying focal issues or decisions (e.g., effect

TABLE 1. Potential benefits of the Health Impact Fund

Pharmaceutical companies
More predictable financial returns over the lifespan of a drug
Greater sustainability of research and development
Opportunity to make increased profits by development of new high-effect drugs that would be unprofitable in the absence of the HIF
Greater integration of data
Patients
Benefit from lowered drug prices mostly canceling out government and taxpayer costs of financing rewards
Greater equity of access to drugs
Research will be more focused on the diseases causing greatest burden, rather than those that are most profitable
Greater adherence to drugs because pharmaceutical companies and other stakeholders will be incentivized to ensure that drugs have the desired effect
Governments
More predictable spending on new drugs
Health system improvements due to the incentives for drug companies to ensure that their drugs have real-world effects close to those in clinical trials
Greater knowledge regarding present and future burdens of disease and future effects of novel drugs
Integration of health systems and data around drugs and their usage

HIF, Health Impact Fund.

of introduction of a NOAC on use of warfarin, use of NOAC, access to drugs, and rates of stroke/thromboembolism) and predicts the future environment [81–84]. Four factors shape future scenarios [83]:

Social

Social factors include the following: the increasing burden of AF and stroke due to aging populations and demographic transition values systems (e.g., more demand for equity and corporate social responsibility); lifestyle (e.g., adherence); demand (increasing demand for NOAC from providers and patients); and political energy (to enforce uptake of new drugs).

Economic

Macroeconomic (e.g., How will international trade flow and exchange rates affect the price of drugs? How will global pharmaceutical companies respond to pharmaceutical companies from LMIC?) and microeconomic factors (e.g., How much appetite is there in the system for increased spending on new drugs? What financial protections protect patients from catastrophic out-of-pocket expenditures on drugs? How might the structure of pharmaceutical companies change? How much partnership will exist between different producers of NOAC?) influence the uptake and effect of new drugs.

Political

Local (e.g., interpretation of practice guidelines and evidence), regional (e.g., competition between practice in other centers, competition between existing anticoagulation services, and new infrastructure for NOAC), national (e.g., implementation of NICE [National Institute for Health and Care Excellence] guidelines), and international (e.g., implementation of TRIPS) environments can affect the uptake and effectiveness of new drugs. Across all spheres, the level of funding within the health sector, and for drugs specifically, must be considered [85,86].

Technological

Direct evidence for effectiveness obviously influences how new drugs are incorporated into clinical practice and health systems. Evidence can change over time, relating to real-world effects, side effects, and new clinical indications: for instance, NOAC have proven effectiveness in treatment of deep vein thrombosis [87]. Indirect evidence includes data regarding other competing drugs, new and old. As me-too NOAC emerge, their effectiveness and cost-effectiveness may affect and limit uptake and impact of first-generation NOAC. Online Appendix 2 highlights an example of scenario modeling.

REWARD MECHANISM

The health impact assessment should be based on as much high-quality evidence as is possible and available. Although models have imperfections and assumptions, any measure of population-based impact will improve the current paradigm. At present, pharmaceutical companies' marketing strategies focus on trial data. The health impact assessment requires a longer-term view from both pharmaceutical companies and policymakers. It would be expensive because of the need to assess multiple medicines globally. However, there would also be economies of scale from assessing many medicines at the same time and efficiencies from assessing the same medicine year after year.

In consultation with stakeholders (including pharmaceutical companies), a reward for a specific health impact

threshold will be agreed on. If this target is met, then pharmaceutical companies will receive this agreed-on reward. A health impact assessment by independent assessors would occur annually to estimate the actual impact of new drugs and to determine rewards due to pharmaceutical companies. The HIF would reward any company that produces an effective new drug in proportion to how well the drug works, provided that the innovator agrees to sell it at cost price. After the 10-year reward period, the company would also offer free licenses to enable generic manufacture and sales. Pharmaceutical companies may be rewarded on the basis of early results, and longer-term results may later emerge, showing less benefit or potential harm associated with the drug. The HIF reward allocated to a drug will be evaluated annually on available evidence and can be changed. Therefore, if a drug actually causes harm, it will not be rewarded. A pharmaceutical company will only receive the full reward if the agreed target of impact is met. A consequence of using life-years or disability- or quality-adjusted life years as the primary health impact assessment modeling outcome may be that highly effective treatments for rare diseases occurring early in life will have a health impact reward similar to a moderately effective treatment for a common disease occurring in adulthood.

Table 1 summarizes potential benefits of the HIF for pharmaceutical companies, patients, and governments.

SUMMARY

The current intellectual property rights regime and the way in which novel drugs are evaluated after proof-of-efficacy trials are inadequate. The HIF offers an alternative mechanism by which pharmaceutical companies could be rewarded on the basis of the global health impact of their novel drugs. Using the example of NOAC for stroke prevention in AF, feasible methods of health impact assessment have been suggested. The same principles apply to other current examples, including antiplatelet agents' post–ST-segment elevation myocardial infarction [88,89]. Trials, registries, and other datasets offer the potential for modeling future trends in disease burden as well as impact of novel drugs.

Judicious use of available data and scenario modeling represent a significant improvement compared with the status quo where rewards have no association with the real-world impact of drugs. Feasibility of the prospective health impact assessment of novel drugs must now be properly tested using different drugs in different disease areas in order to take forward the concept of the HIF. There is a growing movement to increase the transparency of pharmaceutical companies and to improve access to their drugs [90]. The HIF may be the most sustainable and feasible solution.

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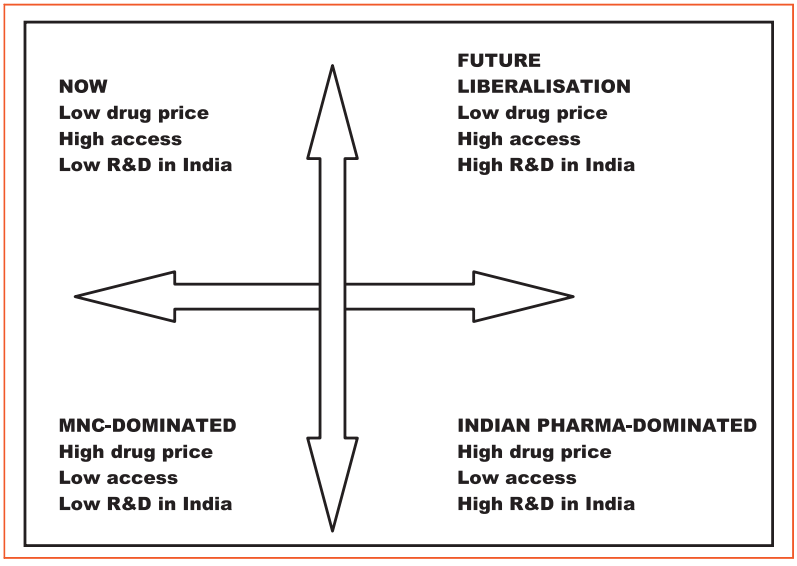
ONLINE APPENDIX 1

With an annual budget of $6 billion, the Health Impact Fund (HIF) could spend US$600 million on administration and assessment, with the majority on the latter, making it the largest global health assessment agency. In comparison, the United Kingdom's National Institute for Health and Clinical Excellence has a US$50 million budget, publishing 25 technology appraisals, 12 clinical guidelines, and 60 interventional procedures guidance annually [1]. Assuming 20 registered medicines at any time, the HIF would evaluate the impact of those medicines internationally; a considerably more difficult process than that undertaken by the National Institute for Health and Clinical Excellence. A US$600 million budget, spent on 20 medicines at a given time, creates an average budget per year per drug of US$30 million, allocated to: 1) evaluating clinical evidence; 2) auditing to ensure products are being distributed and used in ways consistent with evidence; and 3) administration shared across products [1].

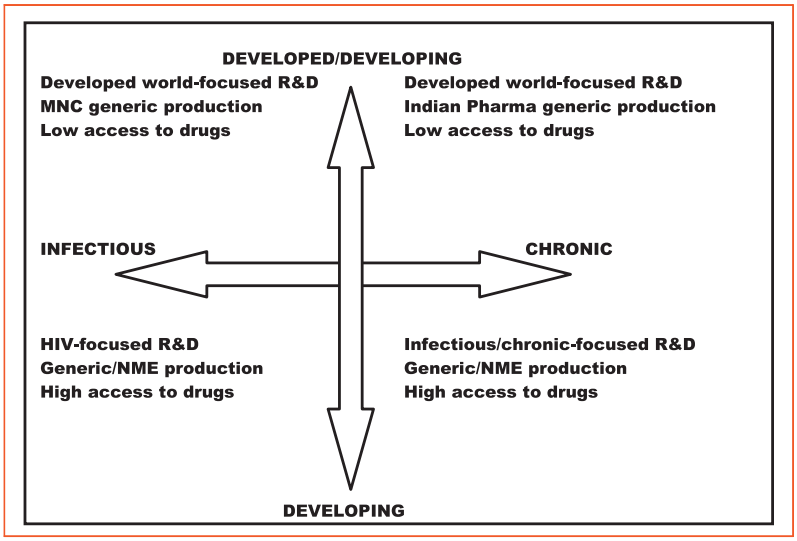
A fund of US$6 billion is affordable in global terms, representing 0.01% of global income. By comparison, the annual budget of the President's Emergency Plan for AIDS Relief is US$10 billion and is funded only by the United States. Assuming that countries representing one-third of the global product agree to underwrite the HIF, each country would need to contribute 0.03% of its gross national income to reach the minimum US$6 billion fund size [1].

Errors may be of the following types: 1) random (unlikely to significantly affect expected payments for a given product); 2) systematic (biases between diseases and countries, which may influence pharmaceutical companies' (PC) willingness to innovate or register their products with the HIF); and 3) systematic misrepresentation of health impact of drugs by registrants [1,2]. Careful auditing of data reported by registrants would minimize the extent to which such errors and misrepresentation influence payment allocation.

Disagreements are expected between health impact assessments of different companies, with the HIF acting as arbitrator. No single methodology can be ideal in every circumstance, but the HIF will need to establish a transparent and unbiased methodology developed in conjunction with PC and governments, before beginning an actual health impact assessment, so that rules are in place.



ONLINE FIGURE 1. The drug pricing model of access to drugs. Pharma, pharmaceuticals; RD, research and development.



ONLINE FIGURE 2. The diseases model of access to medicines. HIV, human immunodeficiency virus; MNC, multinational companies; NME, new molecular entity; other abbreviations as in Online Figure 1.

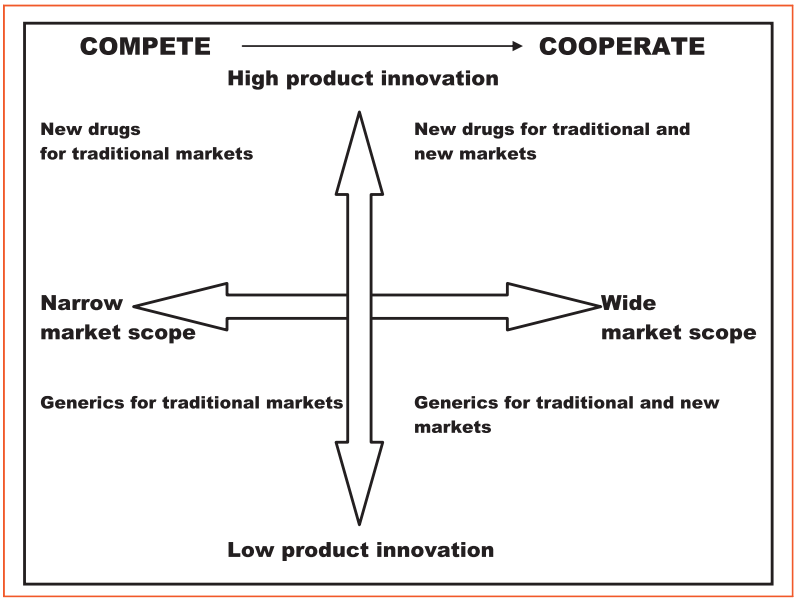
ONLINE APPENDIX 2

In Online Figures 1, 2, and 3, we illustrate how social, economic, political, and technological issues can be tackled by scenario modeling using the example of how the Indian PC may interact with multinational companies (MNC). In Online Figure 1, we consider a particular drug's price and access in scenarios with differing levels of market dominance by Big Pharma versus the Indian pharmaceutical industry. Access could be reduced if Indian companies move away from serving traditional low-priced/high-volume markets as they increasingly focus on more lucrative markets (e.g., novel anticoagulants), imitating the product/market focus of the research-based MNC (bottom half of Online Fig. 1).

Online Figure 2 attempts to model global access to drugs based on diseases. Although the epidemiological transition is already occurring, research into infectious diseases other than human immunodeficiency virus/acquired immunodeficiency syndrome and into chronic diseases (e.g., atrial fibrillation) in low-resource settings has been relatively minimal. Most new drugs for these diseases

(e.g., novel anticoagulants) are therefore patented by the MNC. As the disease burden changes and the demand for these drugs increases, the MNC can procure more profits from India and other similar low- and medium-income countries (LMIC) [3]. If Indian PC retain control of the Indian drug market (even if it enters into partnerships with MNC), then the situation in the bottom right of Online Figure 2 is postulated. The Indian industry will continue to focus on the low-priced/high-volume, developing world segment. Even if future research and development focuses on chronic diseases, it will be in the Indian context and perhaps more applicable to LMIC.

Online Figure 3 models global access based on the nature of the inevitable, ensuing partnerships between Indian PC and the MNC. In different countries and markets, the Indian firms will concentrate on generic or new drugs [4]. Due to drug pricing effects, new drugs will be relatively more expensive than the generics, and where they are the main product, access will be reduced.



ONLINE FIGURE 3. MNC/Indian pharmaceutical partnership model. Scenario planning would mean creating different future scenarios to address these factors and estimating predicted effects in each of these scenarios. Adapted, with permission, from Grace [4]. MNC, multinational companies.

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