Debating the scope of a health research and development convention

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Despite recent advances in global health, appropriate tools to prevent, diagnose and treat diseases are often in short supply in the developing world. As a result, poverty-related and neglected diseases cause an average annual loss of 13.7 million lives and 377 million years of healthy and productive life.[1]

Over the past decade, the World Health Organization (WHO) has hosted a series of consultations on the financing of health research and development (R&D) to address two key needs of developing countries: filling R&D gaps when suitable products do not exist because of insufficient investment, and improving access to products that do exist but that are unaffordable or unavailable.

Multiple World Health Assembly resolutions have defined the scope of these WHO consultations as "R&D related to the Type II and III diseases, and the specific R&D needs of developing countries related to Type I diseases", based on a typology proposed in 2001 by the Commission on Macroeconomics and Health (CMH).[2] In this paper, all subsequent references to Type I, II and III diseases therefore refer to the CMH categories (Box 1). The most recent of the WHO consultations took place in 2012, through the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG). In its 2012 report, the CEWG proposed a binding convention that would mandate every signatory country to invest a minimum of 0.01% of its gross domestic product (GDP) in R&D falling within the established scope.

Throughout this article we use CMH and CEWG terminology (e.g. "developing" and "developed" countries, "rich" and "poor" countries), although we acknowledge that debate exists around these terms.

Definitional difficulties

The CMH report distinguished three classes of diseases based on the relationship between the geographical burden of a given disease and the existence of R&D incentives. The report highlighted that as the prevalence of a disease in rich countries decreases, so too does the incentive for R&D to develop new drugs, vaccines or diagnostics. On this basis, Type I designates diseases for which sufficient R&D incentives exist, but without the resulting products being necessarily accessible to developing countries. This situation creates an access gap. By contrast, Type II and Type III designate diseases in which R&D incentives are too weak to generate enough suitable products, a situation that results in an R&D gap rather than an access gap. These were ground-breaking statements that helped the global health community to think differently about access and R&D gaps and the broad causes of these.

The broad correlation just described, however, cannot be the basis for defining R&D gaps, priorities or investment needs because R&D cannot be discussed at the disease level, but only at the product level. For example, the CMH classifies HIV infection as a Type II disease occurring globally but mainly in developing countries, but from an R&D perspective, HIV infection can be viewed as a Type I, Type II or Type III disease. For adult HIV drugs there is a large commercial market in high-income countries that drives substantial R&D investment. As a result, drugs exist but access to them in developing countries is poor. Hence, in this sense HIV infection can be viewed as a Type I disease. It can also be viewed as a Type II disease if we consider HIV vaccines, for which a modest commercial market exists in high-income countries but with little overlap with developing country HIV subtypes. The result is underinvestment in vaccines that are suitable for developing countries. Finally, HIV infection can be seen as a Type III disease from the perspective of paediatric HIV drugs. Since paediatric HIV patients are virtually non-existent in high-income countries, R&D investment in paediatric HIV drugs is limited

and few drugs exist. In other words, the CMH's categorization system works very poorly at the disease level but very well at the product level.

During the WHO consultations discussants were aware that some Type I diseases had a high shared global burden but no products suitable for the developing world (e.g. heat-stable insulin). From a product-based perspective, these gaps would result in a Type II categorization, but because a disease-based approach was adopted during WHO discussions, R&D gaps in this area were instead identified by the somewhat awkward phrase, "specific R&D needs of developing countries related to Type I diseases". This apparently innocuous wording has triggered confusion, since it inadvertently conflates access gaps (Type I products) with R&D gaps (Type II and III products). It has also triggered controversy since, for some, it refers only to gaps in the R&D of Type I products (e.g. heat-stable insulin), whereas for others it also encompasses R&D intended to overcome gaps in access to such products in developing countries (e.g. a more affordable cancer drug).

In subsequent sections we explore the implications of using narrower and broader scopes of disease coverage in the proposed binding convention on global health R&D. Despite the foregoing provisos, this exploration will be based on *disease*-level Type I, II and III categories, since this categorization forms the framework of WHO negotiations and the CEWG report. The scope implications of the convention can therefore be reasonably discussed only within this framework.

A convention addressing R&D gaps only

In its narrowest interpretation, the proposed convention would only address R&D gaps in areas where no suitable products exist. This would involve funding a publicly-driven pharmaceutical ef-

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Box 1. **Disease typology used by the Consultative Expert Working Group (CEWG)[a]**

- **Type I diseases** (e.g. diabetes and cardiovascular diseases): These occur in both rich and poor countries, with a large vulnerable population in each. As a result, R&D incentives exist in rich country markets.
- **Type II diseases** (e.g. HIV/AIDS and tuberculosis): These diseases occur in both rich and poor countries, but a substantial proportion of the cases occur in poor countries. R&D incentives exist in rich country markets but the level of R&D spending on a global basis is not commensurate with disease burden.
- **Type III diseases** (e.g. sleeping sickness [trypanosomiasis] and African river blindness [onchocerciasis]): These occur primarily or exclusively in developing countries. They receive extremely little R&D overall and essentially no commercially based R&D in rich countries.

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; R&D, research and development.
[a] These categories were created by the Commission on Macroeconomics and Health of the World Health Organization and were accepted by the CEWG in its 2012 report.

fort since, by definition, no commercial incentive exists in these areas. But even this approach leaves room for interpretation. If narrowly interpreted, coverage would be limited to R&D gaps for Type II and III diseases; if more broadly interpreted, coverage would also extend to R&D gaps in Type I products suitable for developing countries.

Including Type II and III diseases only

Under this approach, R&D financing under the convention would be restricted to Type II and III "neglected diseases", such as helminthiasis, diarrhoeal diseases and Chagas' disease. A limited convention such as this could readily build on the existing foundation of R&D efforts, structures and funding for neglected diseases. As of 2012, over 360 product candidates for Type II and III diseases were in development and over 40 products for neglected diseases had been registered since the year 2000, with support from public and charitable funds amounting to more than US$ 3000 million annually.[3]

This parallel system already includes many of the features of the proposed convention: R&D is funded by public or philanthropic groups rather than from sales, with final prices usually set at close to manufacturing cost (e.g. US$ 0.50 per dose in the case of the meningitis A vaccine). Certain products are erroneously classified as "high-priced Type II and III products". These are invariably expensive commercial technologies that have subsequently been applied to developing country uses. Because intellectual property (IP) rights have an extremely low market value in these disease areas that entail no profit, IP also tends to be shared more freely

through collaborative public–private R&D, patent pools, compound libraries, open source drug discovery and other means.

Despite the above, restricting the convention's scope to neglected diseases – which will soon represent less than one third of the disease burden in developing countries – would limit health benefits and ignore the long-standing inclusion of Type I diseases in WHO deliberations.

Including Type I diseases also

Under this proposal, the convention would cover not just R&D in the area of neglected diseases, but also in connection with Type I diseases that affect developing countries, such as hypertension, diabetes and cancer. For most Type I diseases, existing commercial products are sufficient and suited to developing country needs but are not sufficiently affordable or available. This represents an access gap. However, for a relatively small number of Type I diseases, existing products are unsuitable or insufficient for developing country needs. This represents an R&D gap. For example, the same disease (e.g. pneumonia) may be caused by different viral strains in developing and developed countries or developing countries may require different formulations for better treatment compliance (e.g. inhaled rather than injectable oxytocin for postnatal haemorrhage).

Expanding the convention's scope to address R&D gaps for Type I diseases has important advantages. It is the only solution that addresses all product gaps affecting developing countries, including those linked to high-burden Type I diseases whose prevalence is on the rise. Furthermore, a publicly-driven R&D ef-

fort to fill these commercial R&D gaps is likely to find acceptance among most groups. However, this expanded scope also raises some practical hurdles, such as how to secure global agreement on those diseases for which therapeutic options do exist for developing country use but are sometimes unsuitable or partially suitable, or how to treat public investments in "R&D suitable for developing countries" in upper-middle-income countries such as Brazil, China and South Africa. These countries have a domestic market for "products suitable for developing countries", but they also have domestic industries that are eager to sell products to those countries. Would these public investments result in benefit to public health or act as a commercial subsidy for these countries' emerging industries?

Development of product extensions, adaptations or reformulations suitable for developing countries will also require access to the baseline IP or products to be adapted. Some approaches to gaining access to the baseline IP are controversial, an example being compulsory licensing of the industry IP needed for product adaptation.[4] Although less controversial, voluntary industry provision of commercial IP is also less reliable, and companies may be particularly reluctant to provide commercial IP for further development by or for those upper-middle-income countries where local industry is a direct competitor.

A final option would be to bypass the need to access commercial IP by creating new public products for developing countries "from scratch". However, this would be substantially more expensive and inefficient.

An R&D convention addressing access

Under a broader interpretation, the proposed binding convention would also include R&D to improve developing-country patients' access to products that are created and owned by the pharmaceutical industry but priced out of their reach. Access to essential medicines for Type I diseases is becoming increasingly important in developing countries as the incidence of non-communicable Type I diseases (e.g. cancer and heart disease) rises and Type II and III infectious diseases become less predominant. By 2004,

Type I diseases comprised more than half the burden of disease in developing countries; by 2020, they are projected to comprise more than two thirds of this burden.[5]

The producers of Type I medicines are also changing. Emerging industries in Brazil, China, India, the Russian Federation and South Africa now focus heavily on R&D for Type I diseases for both domestic use and export. Eight middle-income countries are now among the top 20 pharmaceutical markets in the world.[6–8]

These changing trends heighten the urgency of the debate surround-ing access, but they also make it rather complicated to expand the convention to include R&D intended to improve developing country access to commercial Type I medicines. This is because much of the R&D conducted in the developed world in the area of Type I diseases is now equally applicable to developing countries. As a result, the convention's funding cut-off of 0.01% of a country's GDP becomes somewhat ir-relevant, since most developed countries already invest considerably more than that in R&D of relevance for develop-ing countries by virtue of their very substantial funding for basic research on Type I diseases, which applies equally to developing-country patients with those diseases.

In conclusion, despite advances in global health, developing countries continue to have a shortage of appropri-ate tools to prevent, diagnose and treat many diseases. The proposed convention is intended to address this problem, but lack of clarity in the convention's remit has left its scope open to interpretation. This uncertainty must be resolved for discussions to move forward. ■

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