Rethinking the development of Ebola treatments

In response to the current outbreak, the international community has endorsed the clinical use of unregistered treatments for Ebola.[1] Even with this accelerated pathway to in-human testing and use, radically novel approaches to drug development will be needed to improve the likelihood that a treatment is realised. Bypassing steps in development does not alter the probability of success, and historical patterns in drug development suggest that there is a slim probability of success with the current portfolio of potential Ebola treatments (all of which are were in preclinical development prior to the outbreak).

First, preclinical research in drug development can suffer from a lack of replicability, which contributes to high development failure rates.[2] Second, if preclinical development is successful, the likelihood of successful regulatory approval of all investigational drugs reaching phase 1 is only 10·4%.[3] Third, these patterns and low rates are based on therapeutic areas with: (a) robust preclinical and clinical data collected (often) over decades from hundreds to thousands of research and development activities spanning the globe, and (b) socially and politically acceptable clinical development programmes spanning large populations, mainly in resource-wealthy settings with strong clinical trial infrastructure. Ebola stands in stark contrast to such therapeutic areas; thus, one could expect that the likelihood of successful regulatory approval for an Ebola treatment would be lower than these estimates.

Repurposing (use of approved drugs for new indications) or repositioning (use of drugs whose development was not continued for new indications) of existing drugs has been put forward as a method to overcome some of these issues.[4] Indeed, drug repositioning and repurposing could lead to higher rates of success, with lower costs of development, in a faster timeframe than de novo discovery approaches.[5] However, these potential advantages are far from certain. Furthermore, drug repurposing/repositioning in and of itself does not remove the need for certain preclinical studies and clinical trials. Drugs still need to be validated and studied in the indications for which they are proposed.

In silico approaches might hold a key to overcoming some of these obstacles. Use of bioinformatics-based high-end computing to simulate drug–disease biological processes provides the ability to bypass time-consuming and costly in vitro and in vivo studies and increase the probability of success of clinical trials.[6] For Ebola treatments, in silico approaches might offer two specific means to improve the current process and help address some of the critical preclinical and clinical concerns raised at the WHO meeting of international experts to discuss Ebola therapeutics on Sept 5.[7] First, the number of preclinical compounds already containing clinical data for other therapeutic indications could be considerably increased. Although traditional repositioning methods using in vitro screening have led to initial discoveries for Ebola,[8] computational screening could provide the needed efficiency to identify candidates more rapidly and accurately than de novo discovery methods. Second, virtual clinical trials could alleviate some of the logistical and ethical issues surrounding the clinical use of unregistered Ebola treatments, including the balance between generating safety data and the need to introduce treatments as soon as possible.[9] This method would permit non-interventional assessments of pharmacokinetic-pharmacodynamic parameters and allow precise and efficient clinical trial design[10] (the latter being particularly important because the epidemiology and infrequent emergence of Ebola often provides a narrow window of opportunity and limited population size to assess an intervention). There is at least one caveat, though. In silico approaches are dependent on drug and disease process data. Therapeutic Ebola research is heavily funded by the US government under the auspices of threats to national security,[11] and international activities are limited to a few research groups. To allow for greater participation of researchers globally, real-time accessibility of crucial data is necessary.[7]

In silico methods are still in development and rapidly evolving, but have been successful in identifying potential candidates for various diseases and the risk of using such methods are very low. Their ability to affect, at scale, drug development processes, costs, and timelines is unknown but likely to be considerable given the private sector's strong interest and investment in this area. Equally likely is that these approaches will be able to affect a wide range of diseases. Although these approaches are currently directed towards diseases with clear revenue streams (eg, inflammatory bowel

disease and cancer), such approaches could be used for unprofitable diseases that affect the most underserved populations of the world.

The inequities already posed by a disease of poverty such as Ebola become further exacerbated when novel technologies are used first to explore diseases that are viable commercial opportunities. This does not have to be the pattern moving forward, and Ebola might provide the opportunity to apply new technological approaches to drug development (such as in silico methods) for traditional "market failure" diseases. If the global community is truly committed to rapidly developing a new drug for Ebola, multiple novel approaches, methods, and technologies will need to be used to beat the inherent hurdles of drug development.

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RG's academic work is the area of global health technologies. He also works for Otsuka Pharmaceuticals in the area of drug development. This Comment strictly reflects the independent personal opinion of RG. The company was not involved in the conception or review of the Comment, nor in the development of the various technologies outlined herein. RG has published a letter in *The New York Times* which is related to some of the information in this Comment (http://www.nytimes.com/2014/08/28/opinion/in-ebola-crisis-hope-and-heroism.html?_r=0).

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