Can India lead the way in neglected diseases innovation?

Nirmal Kumar Ganguly and colleagues call for a comprehensive policy for neglected diseases research in India to foster innovation in drugs, diagnostics, and vaccines, critical for evolving needs of elimination programmes.

India is one of the top global funders of research and development (R&D) into neglected diseases. With a promising scientific base built on the foundation of an expanding science and technology workforce, the country is well placed to make a substantial contribution to innovation in neglected tropical diseases. A third of new drugs (six out of 18) and two thirds of new vaccines (six of 10) for neglected diseases registered since 2000 have had Indian involvement. Nearly 12% of drug, diagnostic, and vaccine candidates for neglected diseases in the R&D pipeline are from India. The world’s first leprosy vaccine was developed in India and is expected to accelerate eradication efforts.

India has successfully eliminated certain infectious diseases—such as guinea worm, trachoma, and yaws—in recent years. Yet, neglected diseases such as leishmaniasis, filariasis, leprosy, snakebite, and soil transmitted helminthic infections still pose a challenge. There persist challenges in the implementation of new technologies and major research gaps. The current model of innovation is driven by market forces and is failing to deliver a steady stream of products that reach patients through adoption into treatment programmes. Neglected diseases predominantly affect poor and marginalised populations and do not constitute a market that is attractive enough to stimulate private sector investment. As such, the Indian government must step in with appropriate policies and investments to support innovation. In this article, we review existing policies and mechanisms, and propose actions to create an enabling environment for neglected diseases research in India.

Current policy scenario

A comprehensive policy to foster research and innovation in drug discovery, diagnostics, and vaccine development in neglected tropical diseases is lacking. Box 1 lists relevant policy statements in India in recent years. While political intent and will are expressed in a few, clear operational plans and funding mechanisms are not specified. Consequently, follow-up action is patchy or absent.

No institutional mechanism exists at a national level to identify gaps in neglected diseases research, set priorities, liaise with research institutions, or monitor research output. There is often no coordination between the various funding and research bodies to prioritise the research agenda and minimise duplication.

Not enough funding for product development

India is the fourth largest government funder of neglected diseases research, and the largest among middle income countries. Yet, funding falls far short of requirements. Few public agencies disburse R&D grants for neglected diseases in India. An analysis of contribution to neglected diseases research globally reveals this shortfall in public funding. The average funding by the Indian Council of Medical Research (ICMR) from 2008 to 2015 was about $26m (£211m; €23m) per year, while the National Institutes of Health in the US contributed over £13bn per year. Indian pharmaceutical companies have filed few patents for new drugs and innovations compared with those in the US or China, which are investing heavily in innovation. A recent trend with involvement of start-ups in diagnostic innovation offers promise.

Slow adoption of novel and innovative technologies

The absence of market intermediaries for commercialisation of products for neglected diseases often results in innovations remaining in laboratories. Few government programmes have supported translational research to facilitate adoption of new drugs and technologies in the real world for treatment and control of neglected diseases. The ICMR has attempted to invite companies to commercialise new technologies such as diagnostic assays, reagents, devices, and vaccines for infectious diseases under a public-private partnership model. It is not clear how well

Box 1: Recent policies on neglected diseases research in India

- The National Health Policy (2017) sets an ambition to stimulate innovation to meet health needs and ensure that new drugs are affordable for those who need them most, but it does not specifically tackle neglected diseases.
- The National Policy on Treatment of Rare Diseases (2018) includes infectious tropical diseases and identifies a need to support research on treatments for rare diseases. It has not yet prioritised diseases and areas for research funding or how innovation would be supported.
- The Science, Technology, and Innovation Policy (2013) does not mention research on neglected diseases.
- The Draft National Pharmaceutical Policy (2017) states that one of its objectives is to create an enabling environment to develop and produce innovator drugs, but the policy does not mention drugs for neglected tropical diseases.
- The National Biotechnology Development Plan (2015-2020) seeks to encourage the preclinical and clinical development of vaccines against rotavirus, cholera, typhoid, rabies (human DNA based), malaria, dengue, tuberculosis, and Japanese encephalitis.
- The National Intellectual Property Rights Policy (2016) states that it will encourage publicly funded R&D institutes and industry to develop affordable drugs for neglected diseases but does not spell out how it will do so. There has been no activity reported in this area.
- The Open Source Drug Discovery programme was set up by the Council of Scientific and Industrial Research for new inventions for the prevention, diagnosis, and treatment of common diseases in India. This programme is no longer being funded. It could have served as a platform to discover new drug targets and drugs for infectious and non-communicable diseases.
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This strategy has worked for neglected diseases technologies. The Biotechnology Industry Research Assistance Council funds translational research and has taken up the development of snakebite antivenom, but this is still in early stages.

It is our observation that national programmes for neglected diseases in India tend to delay adoption of Indian innovations. Quite often products developed in India have been accepted outside the country before their adoption at home. For example, the oral rehydration suspension was jointly developed by scientists working in India and Bangladesh to treat cholera, however it has not been uniformly adopted in these countries. An oral cholera vaccine that was tested and manufactured in India and has been approved by the World Health Organisation is not yet included as part of the national programme, thereby limiting access. Meanwhile, the vaccine was used in Bangladesh during the Rohingya refugee crisis to prevent cholera outbreaks.

Box 2 provides an example of innovations in management of visceral leishmaniasis in India and the need for continually evolving strategies. There is no roadmap for carrying out trials for new drugs and incorporating new innovations as part of the national visceral leishmaniasis elimination programme in India. As such, several innovations have not yet been commercialised.

**Regulatory bottlenecks**

Schedule Y of the Drugs and Cosmetics Rules in India does not permit phase I clinical trials of drugs or vaccines that have been developed outside India. This can act as a disincentive to invest in neglected diseases prevailing in, or exclusive to, India. A favourable provision for neglected diseases is built in, however, which states that toxicological and clinical data requirements may be abbreviated, deferred, or omitted for drugs indicated in diseases of special relevance to India. This provision has not yet been deployed.

An expedited regulatory approval process can facilitate rapid adoption of proved drugs and technologies. The Orphan Drug Act in the US and the Orphan Drugs Regulation in Europe provide examples of creating an enabling policy environment that has stimulated development of new drugs for rare diseases. The priority review voucher (PRV) programme in the US helped promote R&D for new drugs targeting neglected tropical diseases by supporting expedited regulatory review and thereby potentially allowing drugs to reach the market early.

**Box 2: Innovation in visceral leishmaniasis elimination in India**

**Drugs**
- Increasing treatment failures using miltefosine prompted the development of a new treatment regimen for visceral leishmaniasis. New drug trials were conducted through a partnership between government research institutes in India and the Drugs for Neglected Diseases initiative, and led to development of a new treatment—liposomal amphotericin B (Ambisome). A single intravenous infusion of liposomal amphotericin B was found to be effective in treating visceral leishmaniasis and is now recommended as first line treatment in the national programme in India.
- This drug was subsequently tested and introduced in Bangladesh and Nepal.
- Cases of resistance to miltefosine and liposomal amphotericin B have been reported. New drug regimens need to be developed periodically to overcome resistance.

**Diagnostics**
- Indian labs have played a significant role in the development of rK39 and rKE16, which have demonstrated high sensitivity and specificity, good reproducibility, and, most importantly, are heat stable for tropical countries like India. However, the sensitivity is more variable in sample panels from east Africa and South America. A diagnostic probe has been developed in Kolkata but is yet to be commercialised.

**Vaccine development**
- Vaccines against visceral leishmaniasis are at different stages of development. Financial support provided by the Japanese Global Health Innovative Technology Fund has played a vital role.
- A patented innovation from India shows that HbR-DNA from the leishmania parasite coding for HbR protein or fragments thereof is a marker for diagnosis of leishmaniasis. It is immunogenic in humans and could be a vaccine candidate.

**Vector control**
- Research into vector ecology, mathematical modelling of disease transmission, and interventions such as nets treated with insect repellent is essential to control disease transmission. The National Vector Borne Disease Control Programme implements the integrated vector management programme for eradication of neglected diseases and supports research in this area.
- Indoor residual spraying of insect repellent is carried out in endemic districts as part of leishmaniasia control measures. Innovative devices—such as a hand compression pump that is easier to operate, more effective, and less costly than the stirrup pump used in the programme—are being studied.

**Appropriate safeguards must be built in while developing preferential regulatory approval pathways.** There have been challenges in enabling access to these drugs in the long run. For example, miltefosine, which is used to treat visceral leishmaniasis, was registered by the Food and Drug Administration as an orphan drug in 2014 under the PRV programme and received accelerated regulatory clearance. Yet this has had no impact on improving access. Furthermore, serious side effects and treatment failures were noted after the drug was introduced on a large scale.

**Way forward**

It is time for India to establish a comprehensive policy on neglected diseases that paves the way for greater funding and mechanisms to support research and innovation. Box 3 lists the essential elements. A unified programme on neglected diseases encompassing research and elimination measures is likely to have a greater impact in prioritising the matter in the health agenda and streamlining efforts towards disease elimination. Creating an enabling environment for research and innovation will be crucial if India is to achieve the target set in sustainable development goal 3.3 to end epidemics of neglected tropical diseases by 2030.
Box 3: Essential elements of a comprehensive neglected disease policy

**Funding**
- Earmark a proportion of public funds for neglected diseases research and innovation.
- Funding for translational research to support product development.
- The stress on developing internal resources for laboratories has made institutions and scientists shift their research onto diseases with potential market value. Guaranteed public funding would correct this imbalance

**Regulation**
- Develop mechanisms to facilitate priority regulatory pathways for innovations in neglected diseases.
- Capacity building and strengthening of regulators, including institutional ethics committees, in handling regulatory process for neglected diseases.
- Facilitate early adoption of innovations proved effective into national disease treatment programmes. This would incentivise innovation and provide assurance to industry that the products developed will have a market.

**Research environment**
- A National Observatory on Biomedical R&D to prioritise, coordinate, and monitor research output, including on neglected diseases, is needed.
- Such an institutional mechanism would enable efficient allocation of resources and allow policy makers, funders, researchers, and patient groups to identify areas of public investment and existing gaps, and suggest improvements.
- Creating common repositories of biological samples and other materials accessible to researchers, industry, and regulators would facilitate innovation. The absence of a pan-India surveillance data repository on pathogenic strains of neglected diseases poses a hindrance to innovation for vaccines.
- Defining specificity and sensitivity standards for diagnosis of neglected diseases would facilitate diagnostic innovation and help regulatory authorities evaluate these.
- Alternative approaches to R&D based on the principles of open innovation and product development partnerships must be explored.
- A comprehensive national surveillance database for neglected diseases is essential to monitor trends across the country. This could be achieved by strengthening the existing integrated disease surveillance programme. The use of molecular diagnostics at points of care coupled with information technology is the future for robust surveillance. Global positioning systems and mobile technology to track migratory populations are being employed in disease surveillance in Sri Lanka and in the Mekong delta region of SEARO countries, and need to be tested in India.
- The evolving areas of genomics, transcriptomics, and proteomics research can provide a better understanding of the modes of infection and treatment options. More drug and vaccine targets can be identified, and it would provide impetus to biotechnological research and industry.

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