

The progress in new drug approvals for infective disease of poverty (IDOP) in India

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ABSTRACT

The global burden for infectious disease remains high in the developing and underdeveloped countries like Sub-Sahara Africa, South-East Asia and Latin America. Among them, the three major contributors of mortality and morbidity are HIV/AIDS, tuberculosis and malaria which along with neglected tropical diseases (NTDs) are collectively known as “infectious diseases of poverty” (IDoP). There is the strong pressing need for developing new drug molecules for eradication of these diseases. We did a cross-sectional study as per the STROBE guidelines to compare the disease burden and new drug approved for IDoP in India. The findings of this study show that new drugs approvals in India has restricted to the non-communicable diseases only. This mismatch becomes even more apparent for communicable diseases included under IDOP which had only 2.7% share among the total new drug approved during year 2000 to 2017 and only half of them were true innovator drugs. This shows the urgent need to allocate research resources in sync with the existing burden of disease in India and to promote research and development for diseases which affect poor people of country and are neglected by the world.

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Introduction

Infectious diseases cause significant mortality and morbidity in the developing and underdeveloped countries of the world. Despite the progress in the understanding of the natural history of disease and advancement in the process of drug discovery, the burden for infectious disease remains high. Access to affordable medicines for controlling infectious disease is still a major problem in developing countries. The drug development for most of the infectious diseases was seen in early 20th century during European colonialism. Thereafter, the infectious diseases particularly tropical infectious diseases were progressively neglected and their drug development has virtually stopped. The declining interests of developed world together with low profitability for pharmaceutical industry were some of the reasons for this neglect (1).

Burden of infectious diseases continues to be more among poorer populations inhabiting Sub -sahara Africa, South -East Asia and Latin America. Among them, the three major contributors of mortality and morbidity are HIV/AIDS, Tuberculosis and Malaria, which are priority for the United Nations and enlisted in its Millennium Development Goals (MDG), while other diseases which includes mainly tropical infections have been neglected in terms of global attention and resources, they are collectively referred as “neglected tropical diseases” (NTDs) (2). The World Health Organization (WHO) has made a list of diseases, that includes the three major infectious diseases (HIV, TB, Malaria) along with NTDs,

which are collectively called “Infectious diseases of poverty” (IDoP). As a group, IDoP is among the top ten causes of Disability-Adjusted Life Years (DALY) in the world (3).

India with a population of over 1.3 billion is the second most populous country in the world has high absolute number of cases for IDoP. The country accounts for a quarter of global burden of tuberculosis and with 2.5 million people living with HIV, India has the third highest number of HIV infected cases in the world (4,5). Malaria is another prevalent infection in India and despite the efforts made over the years to eliminate it, over half of the population is still at the risk of contracting malaria and accounts for 6% of all malaria cases and 51% of *P. vivax* cases worldwide (6). WHO enlists 20 communicable diseases prevalent in tropical and subtropical countries as neglected tropical diseases (NTDs) (7). India also harbors the world's largest absolute burden of at least 11 major NTDs (Ascariasis, hookworm disease; trichuriasis; dengue; lymphatic filariasis; trachoma; cysticercosis; leprosy; cystic echinococcosis; visceral leishmaniasis and rabies) and leads in terms of total number of cases for these diseases (8).

In 21st century, India has become an attractive destination for new drug development and conducting clinical trials for global pharmaceutical companies. There has been significant investment towards clinical research and framing of new guidelines to ensure good quality clinical trials (9). The enhancement of our knowledge in

medical technology and research has led to development of effective therapies and many new drugs have been made available to combat various diseases. While these efforts to promote drug research and development is commendable but it is unclear whether these research resources are allocated in a balanced manner and towards the diseases which are the major cause of mortality and morbidity in the country. New drug approvals in a country serve as an important indicator to quantify such research efforts and help us in knowing the priorities of drug manufacturers. This study was designed to quantitatively and qualitatively analyze the new drug approvals for infectious diseases in India over the period of past 18 years, specifically for IDoP. We also assessed the mismatch between the drug approval output and disease burden for IDoP in India.

Materials and methods

This was a cross-sectional study and was performed and reported as per the STROBE guidelines (10). The data on new drugs approved for infective disorders in India was obtained from the website of the drug authority of India, Central Drug Standard Control Organization (CDSCO). Information related to the drug name, drug category, year of drug approval, and drug indications were extracted (11). The disease indications for each drug were extracted from the CDSCO website and reclassified as per the classification of the global burden of disease (12). Information related to the disease burden of India was collected from the WHO website. As per the standard method of the WHO, the disease burden is measured in terms of estimated number of disease-adjusted life years (DALYs) (13).

Data analysis

Descriptive statistics in the form of frequency and percentages were used for disease burden and new approved drugs approved for communicable and non-communicable diseases.

Results

Characteristics of new drugs approved

Between years 2000 and 2017 a total 2265 drugs for human use were approved in India of which 753 (33%) were fixed drug combinations (FDCs). The total single drugs approved were 1512 of which 1297 drugs were meant for treating non-infectious diseases while only 215 drugs (14.28%) were indicated for treating infectious diseases and only 42 (2.77%) drugs were meant for IDOP.

Characteristics of burden of disease in India

As per the Global Burden of Disease study (GBD) 2016, the communicable (Infectious) diseases accounts for about 27.5% of the overall mortality and 32.7% of the disability in India. Out of this about 6% of mortality and disability is contributed by the IDOPs. The non-communicable diseases account for 61.8% of total

mortality and 55.4% of disability in the country, while the remaining 11.9% disability and 10.7% deaths are attributed to traumatic injuries (Table 1).

Table 1 New drugs approved between 2000 and 2017 by diseases and relative to disease burden in India.

Disease	New Drug Approved (NDA) 2000-17 (%)	India DALYs 2016 (%)	NDA by DALY
Communicable Diseases			
IDOP	42 (2.768%)	5.7%	0.35
Tuberculosis	03 (0.198%)	3.1%	0.06
HIV	30 (1.98%)	1.1%	0.60
Malaria and NTDs	09 (0.59%)	1.5%	0.39
Non Communicable Diseases	1297 (85.78%)	55.4%	1.55

Comparison of disease burden and new drug approved in India.

For the period considered only 14.22% share of the new drugs approved were meant for the treatment of communicable diseases while majority of the new drugs approved (85.78%) were indicated for non-communicable diseases. The ratio of the number of drugs approved and their disease burden was also calculated. For the period considered, the number of drug approved per DALY was only 0.43 for communicable diseases, while it was three to four times higher for non-communicable diseases (1.55) (Table 1).

The total 42 new drugs were approved for IDOP (HIV, Tuberculosis, malaria and NTDs) and 22 of them were approved during 2000 to 2005. There was a significant difference between drug approved and the disability caused by these diseases. The average ratio of new drug approved by DALY for IDOP was (0.35) which was lower than that for all communicable diseases (0.43). For individual diseases like tuberculosis, HIV, malaria and NTDs the ratios were 0.06, 0.6 and 0.39 respectively (Table 2).

Out of the total 42 new drugs approved only 20 drugs were new chemical entities (NCE), while others were change in formulation or repurposed drugs. The NCE included 15 anti-retroviral drugs, 3 anti-tubercular drugs (Rifabutin, Bedaquiline and Delamanid) and 2 drugs for NTD's. (Miltefosine and Ivermectin). Out of these 20 NCE's, 15 drugs were included in WHO essential drug list 2017 (Figure-1) (14).

Table 2 List of drugs approved for IDOP diseases in India between years 2000 to 2017

HIV			
Abacavir Sulfate Tablet 60mg	2009		
Abacavir sulphate oral solution	2004	Change in Formulation	
Abacavir Sulphate syrup 20mg/ml	2006	Change in Formulation	
Abacavir sulphate tablets & bulk	2002		
Atazanavir (100/150/200mg)	2006		
Darunavir (as ethanolate) Tablet 300mg	2009	Treatment of patients with HIV-1 strains resistant to more than one protease inhibitor when co-administered with 100mg ritonavir	
Didanosine chewable tabs	2000	Change in Formulation	
Didanosine delayed release caps.	2001	Change in Formulation	
Didanosine Powder for oral solution (2gm/4gm per bottles)	2005		
Dolutegravir Tablet 50mg & Bulk	2016		
Efavirenz capsule	2001		
Efavirenz Oral Solution (30mg/ml)	2005	Change in Formulation	
Efavirenz tab	2002	Change in Formulation (higher strength)	
Emtricitabine (200mg) capsule	2005		
Etravirine Tablet 100mg	2012	HIV-1 strains resistant to an NNRTP;	
Indinavir sulphate	2001		
Maraviroc Tablets 150mg/300mg	2009	Treatment of patients infected with CCR5- trophic HIV-1.	
Nelfinavir 625mg tablet (addl.strength)	2005		
Nelfinavir mesylate tabs	2001		
Nevirapine	2000		
Nevirapine Extended release tablet 400mg	2014	Change in Formulation	
Nevirapine oral suspension	2002	Additional strength; neonates	
Nevirapine tablet 50 mg for oral suspension mg	2009		
PEG-interferon alfa-2a	2003	Treatment of kaposi's sarcoma in AIDS	
Raltegravir (as Potassium) film coated Tablets 400mg	2010	Treatment of patients with evidence of HIV-1 replication despite ongoing retroviral therapy.	
Saquinavir (500mg) tablet	2006	Additional Strength	

	Saquinavir (as mesylate) 500mg Tablet	2005	Additional Strength
	Stavudine powder for suspension	2005	Change in Formulation (Infusion)
	Stavudine SR 100mg tablet	2006	Change in Formulation
	Tenofovir Disoproxil Fumarate Tablet (300mg)	2005	
Tuberculosis			
	Rifabutin Capsule 150mg	2007	Treatment of pulmonary T.B only in patients co-infected with HIV
	Bedaquiline Tablet 100 mg	2015	multi-drug resistant pulmonary tuberculosis when an effective treatment regimen cannot otherwise be provided.
	Delaminid Tablet 15 mg	2017	Treatment of pulmonary T.B only in patients co-infected with HIV
Malaria			
	Arteether injection 150mg/mL	2010	Severe malaria including cerebral malaria and as a second line in chloroquine resistant malaria cases
	Artesunate injection. 120mg (Additional strength)	2013	Change in formulation
	Artesunate powder for injection 60mg/vial along with 6ml ampoule of phosphate buffer solution (pH 8.0;0.30M)	2014	Severe falciparum malaria in areas where there is evidence of quinine resistance.
NTDs			
Amoebiasis/ Giardiasis	Tinidazole CDDS tab	2002	Change in formulation
	Metronidazole CR tablet 600mg	2008	Change in formulation
Scabies/Helminth infections	Ivermectin (6mg) tablets	2004	
Visceral Leishmaniasis	Amphotericin B emulsion injection	2003	Change in formulation
	Miltefosin Capsule 10mg/50mg	2002	
Cutaneous Leishmaniasis	Miltefosine capsule	2008	Change in formulation

Discussion

The present study was done to evaluate the research efforts made to address the health problems in India. The developing countries like India are seeing a steep rise in

non-communicable diseases like diabetes, coronary artery diseases, cancer while still struggling to manage the challenge posed by communicable diseases like tuberculosis and malaria adopted to ensure optimal

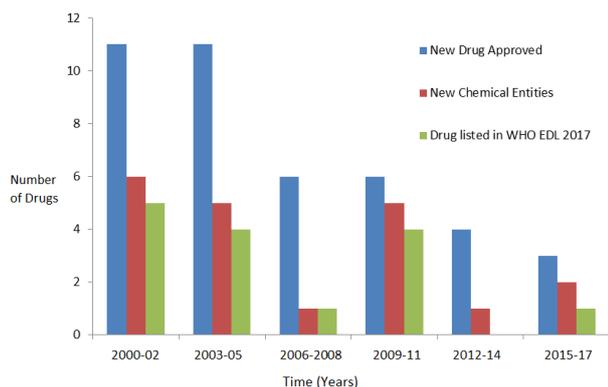


Figure 1 Trends in drug approval for IDOP diseases in India

utilization of research resources to address this dual burden of communicable and non-communicable diseases in India. The substantial disease burden of communicable diseases must invoke research opportunities to address the unmet health needs for developing and underdeveloped countries. The various strategies to combat IDoP are developing of new drugs and vaccines, new diagnostics and vector control measures. New safe and effective medicines are especially required on priority basis for IDOP. New drug approvals in a country serve as an important indicator to quantify such research efforts. We perform a qualitative and quantitative analysis of new drug approved in India over the last 18 years focusing especially on diseases included under IDoP. It was observed that the quantitative distribution of new drugs approved in India has a bias towards non-communicable diseases. This imbalance is more pronounced for diseases like tuberculosis, malaria and NTD's, which are of primary concern for developing country like India. We found that out of 42 new drug approvals for IDoPs 33 drugs were approved for the treatment of HIV/AIDS and malaria. Of the remaining, 3 drugs were for tuberculosis and only 6 drugs for remaining diseases. So it can be concluded that new drug development for IDoP is mainly seen in HIV/AIDS, malaria, and tuberculosis. For the NTDs hardly any new drug development occurs. This disproportionate new drug development indicates shifting of focus from diseases of public importance to the few selected ones.

To further quantify the level of imbalance for drug approved for infectious diseases we calculated the ratio of the number of drugs approved and the respective disease burden in India. This ratio was only 0.43 for communicable diseases while it was 3-4 folds higher for non-communicable diseases. Further, this ratio calculated collectively for IDOP was similar to that calculated for communicable diseases, this is mainly due to the fact that 70% of drug approved for IDOP indication was meant for treatment of HIV/AIDS and for other diseases like tuberculosis, malaria and NTD's the ratio was extremely poor. These findings are in agreement to

those reported by Trouiller *et al.* in their analysis for global trends in drug development during the period of 1975 and 1999 (15). Similarly Cohen *et al.* also observed that 60% of the drug approvals for IDoP diseases during 2009-2013 were for HIV/AIDS and malaria (16).

We specifically examined the new drugs approved for diseases included under IDOP. Out of the 42 new drugs approved for marketing in India only half of them were new chemical entities (NCE). The remaining drugs were mostly approvals sort for change in formulation or repurposing of old drugs, which cannot be considered as true innovation. Out of these 21 NCE, 17 were for treatment for HIV/AIDS and 3 were indicated for Tuberculosis. There were no NCE for malaria and only two new drugs approved for NTD's. This outcome is not surprising considering overall drug development closely follow the existence of viable markets. The new drugs development for HIV/AIDS is a result of serious efforts made by developed nations combined with the major investments from global pharmaceutical industry in these countries motivated by high profit potential (17). The paucity of new drugs for IDOP like Tuberculosis and Malaria is a major setback in the face of emergence of resistance to the existing drugs. The growing neglected disease crises despite significant advances in medicine is a social failure to allocate sufficient resources to prioritize drug development that meet the needs of poor countries (18). The importance of innovator drugs can be deciphered from the fact that 75% of NCE approved for IDOP were included in the essential drug list published by WHO.

The significant burden of IDOP would require a paradigm shift in country's health and research policy, without which the health needs of poor people will continue to be ignored by profit driven pharmaceutical industry. Government across the world should promote need-driven research and development for diseases which are currently ignored. Measures like encouraging public-private partnership and providing market incentives to drug manufacturers as in case of drugs for orphan diseases like tax credit, patent exclusivity, fast track approvals, grants and study design assistance may also help in correcting this imbalance between drug supply and disease burden in poor countries (19).

Lack of effective, convenient and radical curative therapies for IDoPs is a greater menace to public health. All those preventable deaths in absence of effective therapies and increased disease burden of these infectious diseases is a case of mismatched priorities. Apart from running the public health programmes for diseases of national importance, Government needs to incentivize, promote and invest in drug development by all means.

Conclusion

This study shows that new drugs approved approvals in India shows greater inclination towards the non-

communicable diseases. This mismatch is becomes even more apparent for communicable diseases included under IDOP which had only 2.7% share among the total new drug approved during year 2000 to 2017 and only half of them were true innovator drugs. Measures must be taken to allocate research resources in sync with the existing burden of disease in the country. Moreover a priority must be given to promote research and development for diseases which affect poor people of country and are neglected by the world.

Conflict of interest

Authors had declared no conflict of interest.

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