The drug and vaccine pipeline for neglected diseases, 2000-2011: a systematic assessment

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Introduction

- In 2002, Trouiller and al showed that only 1.1% of all drugs approved over 1975-1999 were for a group of infectious and parasitic diseases despite these diseases are accounting for 12% of the global health burden.
- Predominantly affecting low income countries, often said to be poverty related,
- This study aims to reassess the state of R&D for neglected diseases compared to other diseases over 2000-2011.

Methods (1)

- 49 infectious and parasitic diseases, selected out of existing lists: the WHO list of NTDs, Trouiller et al, Hotez et al, *PLOS Neglected Tropical Diseases* journal disease scope, G-FINDER 2011 report, and BIO Ventures for Global Health 2012 report.
- 5 categories: TB, malaria, diarrheal diseases, neglected tropical diseases according to WHO, and other neglected diseases.

Malaria	
Tuberculosis	
Diarrheal Diseases	
Amebiasis	Giardiasis
Cryptosporidium	Cholera
Shigella	*E. coli* enterotoxigenic (ETEC)
E. coli enteriaggregative enteropathogenic (EaggEC)	Campylobacter
Non-typhoidal *Salmonella* enterica (NTS)	Typhoid and paratyphoid fever
Rotavirus	

Neglected Tropical Diseases (NTDs) – WHO definition	
Buruli ulcer	Chagas disease (American trypanosomiasis)
Cysticercosis/taeniasis	Dengue
Dracunculiasis (Guinea worm)	Echinococcosis
Fascioliasis	Human African trypanosomiasis
Leishmaniasis	Leprosy
Lymphatic filariasis (elephantiasis)	Onchocerciasis (river blindness)
Rabies	Schistosomiasis
Soil-transmitted helminthiasis (ascariasis, trichuriasis, hookworm)	Trachoma
Yaws	

Other Neglected Diseases	
Leptospirosis	Bartonellosis
Bovine tuberculosis in humans	Relapsing fever
Japanese encephalitis	Yellow fever
Other arboviral infections: Chikungunya, Ross River fever, Venezuelan equine encephalomyelitis, Eastern equine encephalitis, Western equine encephalitis, West Nile fever*	Viral hemorrhagic fevers: Ebola, Marburg, Crimean-Congo hemorrhagic fever, Lassa fever, Rift Valley fever, hemorrhagic fever with renal syndrome*
Strongyloidiasis	Loiasis
Toxocariasis and larva migrans	Balantidiasis
Mycetoma	Paracoccidiomycosis
Scabies	Myiasis
Tungiasis	Podoconiosis
Snakebite	

Methods (2)

- All **products approved** across all indications from 1 January 2000 to 31 December 2011 were included.
- Sources for the approved products analysis:
  - EMA and FDA;
  - databases of countries* belonging to the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S);
  - the WHO List of Prequalified Medicinal Products and the WHO Essential Medicines List.
- * Belgium, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Portugal, Spain, Sweden, The Netherlands, United Kingdom, Canada, Australia, Switzerland, Iceland, Argentina; Japan, India, and Brazil.

Methods (3)

- New products were classified into one of the following types:
  - new chemical entity (NCE),
  - new indication (NI),
  - new formulation (NF),
  - fixed-dose combination (FDC),
  - vaccine or biological product.
- The medical benefit of a given product was assessed using inclusion on the WHO Essential Medicines List as a proxy measure.

Methods (4)

- To assess the percentage of new products developed by therapeutic area (or disease), the deviation from the expectation under the assumption of proportionality to DALYs was calculated as the observed number of products in a given therapeutic area minus the expected number under assumption of proportionality.

Methods (5)

- For each registered product, the Marketing Authorization Holder was identified for the application and for the first submission in the regulatory database.
- For prequalified products, this information was available in the WHO database.
- This information was not available for products on the WHO Essential Medicines List.

Methods (6)

- **Clinical trials analysis**: The clinical development pipeline for neglected-disease therapeutics was assessed by examining the number of ongoing Phase I-III clinical trials listed in the US National Institutes of Health (NIH) clinical trials database (ClinicalTrials.gov), and the WHO registry of clinical trials between September 1999 and 31 December 2011. A “snapshot” of ongoing trials was taken in December 2011.

Methods (7)

- For each clinical trial, product type was classified as for approved products (NCE, NI, NF, FDC, or vaccine or biological product).
- Additionally, where approved drugs were combined for a neglected-disease indication but not manufactured as a FDC, they were classified as a “new association” of registered drugs.

Methods (8)

- Analysing the research gaps by diseases within 3 categories :
  - no critical research needs (16%) as either at least 2 field adapted safe and effective treatments existed or prevention measures were largely in place
  - clinical research is ongoing but isn’t covering all prevention and treatment gaps.
  - no research at all was ongoing at the time of the analysis, despite identified needs.

Methods (9)

- Clinical trial sponsors were classified into four categories:
  - public institutions (includes government, academic, and public research institutes);
  - private not-for-profit organisations (PNFPO; includes PDPs, charities, foundations, and philanthropic institutions);
  - private industry/for-profit entity (includes pharmaceutical and biotechnology companies);
  - multiple-sponsors.

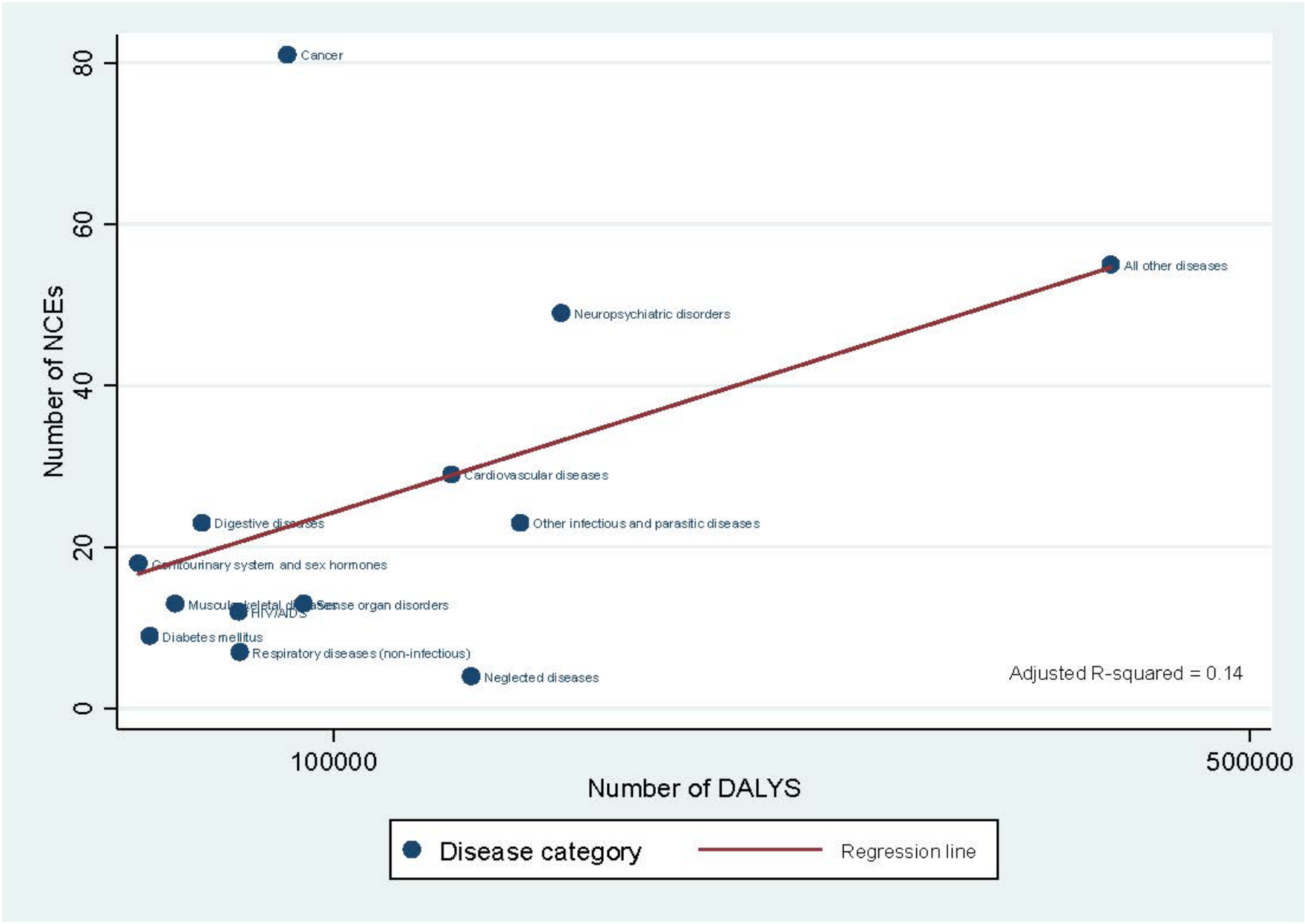
Results (1)

- **Approved products**: 850 new therapeutic products were approved by different regulatory bodies between 1 January 2000 and 31 December 2011.
- 4.4% (n=37) were for neglected diseases, including 29 drugs and 8 vaccines.
- Since collectively neglected diseases represent 10.5% of the global disease burden, 89 products would be expected if product development matched disease burden from a quantitative stand point.

Results (2)

- Of all **NCEs approved** between 2000 and 2011, only 1.2% (4/336) were for neglected diseases.
- Of the 37 new products approved for neglected diseases, the largest proportion were for malaria (n=12), including 3 of the 4 NCEs.
- No NCE was developed in 2000-2011 for TB or any NTDs.
- The vaccines and biologics approved were for Japanese encephalitis (n=4), diarrheal diseases (n=3), and one antivenom for snakebite.

New Chemical Entities



New therapeutic products approved or recommended, by disease category, 2000-2011

Disease Category	**NCE n (%)**	**Other New Product[a] n (%)**	**Vaccine or Biologic[b] n (%)**	***Total n (%)***
Neglected diseases				
TB	0 (0)	7 (1.7)	0 (0)	*7 (0.8)*
Malaria	3 (0.9)	9 (2.1)	0 (0)	*12 (1.4)*
Diarrheal diseases	1 (0.3)	3 (0.7)	3 (3.2)	*7 (0.8)[c]*
NTDs	0 (0)	5 (1.2)	0 (0)	*5 (0.6)[d]*
Other	0 (0)	1 (0.2)	5 (5.3)	*6 (0.7)[e]*
Subtotal	**4 (1.2)**	**25 (6.0)**	**8 (8.5)**	***37 (4.4)***
Other infectious diseases	35 (10.4)	48 (11.4)	66 (70.2)	***149 (17.5)***
All other diseases	297 (88.4)	347 (82.6)	20 (21.3)	***664 (78.1)***
TOTAL	**336 (100)**	**420 (100)**	**94 (100)**	***850 (100)***

- NCE, new chemical entity; NTD, neglected tropical disease (WHO definition); TB, tuberculosis
- Source: FDA, EMA, and for neglected diseases, WHO List of Prequalified Medicinal Products and Essential Medicines List, and additional regulatory authorities.

Results (3)

- Assessing medical benefit, 48% (14/29) of the new products (excluding vaccines & biologics) approved for neglected diseases over 2000-2011 were included in the WHO Essential Medicines List, in contrast with only 4% (26/727) for all other diseases.
- A large majority of new product registrations were filed by regional generic or public pharmaceutical companies, including 12 by Indian laboratories. Seven product registrations were filed by large, private pharmaceutical companies.

Results (4)

- **Clinical trials:** between 1 September 1999 and 31 December 2011, a total of 148,445 for all diseases were found in the NIH and WHO registries, with only 1.4% (n=2,021) directed at neglected diseases.
- A total of 123 new products are being tested. Vaccines and biological products represent the majority of products in development (55.3%, 68/123), 21 of which are directed against malaria.
- A total of 34 (27.6%) of the 123 products in development are for NTDs, but only 3 of these are NCEs (for onchocerciasis, Chagas disease, and human African trypanosomiasis) and 2 for other neglected diseases (Ebola and Marburg viruses).

Results (5)

- When analysing the research gaps by diseases :
- 8 had no critical research needs (16%) as either at least 2 field adapted safe and effective treatments existed or prevention measures were largely in place like in the case of dracuncunliasis.
- 25 diseases clinical research was ongoing but not covering all prevention and treatment gaps (51%,) such as snake bite, Buruli ulcer for example.
- For 16 diseases (33%) no research at all was ongoing at the time of the analysis, despite identified needs, such as mycetoma, toxocariasis, loasis for example.

Results (6)

- Study sponsorship, as listed in the NIH and WHO clinical trials registries, for the 123 products, shows:
  - public organizations in 55% of cases,
  - private not-for-profit organization (PNFPO) in 15%,
  - private industry in 22%,
  - the remainder (8%) involving a mix of sponsors.

- About half of all the new products in development by PNFPOs are for NTDs (10/19), and all three NCEs for NTDs are being developed by PFNPOs.

New products in clinical trials by neglected disease and product type, December 2011

Neglected Disease	Products in Clinical Trials by Type, N (%)					
	NCE	**NF/FDC**	**NI**	**NA**	**Vaccine/ biologics**	***Total***
Malaria	6 (37.5)	4 (50)	5 (20.8)	1 (14.3)	21 (30.9)	*37 (30.1)*
TB	5 (31.3)	0 (0)	3 (12.5)	3 (42.9)	8 (11.8)	*19 (15.4)*
Diarrheal diseases	0 (0)	0 (0)	2 (8.3)	0 (0)	13 (19.1)	*15 (12.2)*
NTDs	3 (18.8)	4 (50)	10 (41.7)	3 (42.9)	14 (20.6)	*34 (27.6)*
Other	2 (12.5)	0 (0)	4 (16.7)	0 (0)	12 (17.6)	*18 (14.6)*
TOTAL	**16 (100)**	**8 (100)**	**24 (100)**	**7 (100)**	**68 (100)**	***123 (100)***

- Abbreviations: NCE, new chemical entity; NF, new formulation; FDC, fixed-dose combination; NI, new indication; NA, new association; NIH, National Institutes of Health; NTD, neglected tropical disease (WHO definition); TB, tuberculosis.
- Source: US NIH ClinicalTrials.gov registry; WHO International Clinical Trials Registry Platform.

Discussion (1)

- Limitations:
  - broad definition of neglected diseases was applied but HIV, bacterial meningitis and pneumonias, and rheumatic fever were excluded;
  - underestimation of neglected diseases related DALYs;
  - exclusion of Chinese and South-African databases.
  - the bias of WHO Essential Medicines List as a proxy metric for medical in favour of infectious diseases and low-cost products.

Discussion (1)

Sources	Period	New products per year
Trouiller & al / Cohen & al	1975-1999	0.6 to 1.3
Cohen & al	2000-2009	1.5
Perdrique & al	2000-2011	2.4
Perdrique & al	2012-2018	5

Conclusion

- A persistent imbalance between disease burden and product development for neglected diseases.
- In the last 12 years, positive advances for neglected disease therapeutics were based primarily on the number of newly approved drug reformulations, repurposed products, and vaccines, and the number of ongoing clinical trials, especially on vaccine.
- Nevertheless, to this day a major R&D gap remains in NCEs for neglected diseases, both in terms of new approvals and ongoing clinical development.
- Malaria, TB, and diarrheal diseases remain the primary focus of product-development research, with little focus on other neglected diseases.