Progress in Neglected Diseases Research and Development: Towards the Elimination of Kinetoplastid and Filarial Diseases

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Summary

The WHO roadmap has set ambitious goals to eliminate a number of neglected diseases (NDs), which will require improved treatments and increased implementation at the primary healthcare level to access remaining patients as numbers decrease.

A "fatal imbalance" between drugs needed by the poor and R&D efforts was previously described, with only 1.1% of drugs approved (1975-1999) for NDs, despite accounting for 12% of the global health burden. A review of the next decade's progress shows that the advent of new models, such as Product Development Partnerships (PDPs), and philanthropic efforts has led to an improvement, but our study shows that still only 4% of the 850 products registered (2000-2011) were indicated for NDs, mostly repurposed drugs.

'The Fatal Imbalance'

Trouiller et al (2002): only 1.1% of all drugs approved over 1975-1999 were for "neglected diseases" accounting for 12% of the global health burden.

Objective

To reassess the state of R&D for neglected diseases compared to other diseases over 2000-2011based on (A) Approved products and (B) Ongoing clinical trials.

The drug and vaccine landscape for neglected diseases (2000–11): a systematic assessment

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Methods

Selection of diseases
49 infectious and parasitic diseases, selected out of existing lists:
5 disease categories
Approved products
- All **products approved** across all indications from 1 Jan 2000 to 31 Dec 2011

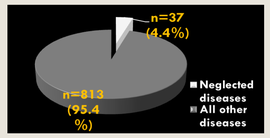
Clinical trials review
Data bases: (Sep 1999-Dec 2011)
- Phase I-III clinical trials listed in the US National Institutes of Health (NIH) (ClinicalTrials.gov)
- WHO registry of clinical trials
- 31 December 2011 "Snapshot" of active trials

Clinical trial sponsors were classified according to organization type

Results

(A) Approved products* : Deficit persists
NDs represented 11% of the global burden of disease in 2004.
But of the 850 new therapeutic products registered in 2000—11, 37 (4%) were indicated for neglected diseases comprising 25 products with a new indication or formulation and eight vaccines or biological products.
Only four new chemical entities were approved for neglected diseases (three for malaria, one for diarrhoeal disease), accounting for 1% of the 336 new chemical entities approved during the study period.
*including vaccines

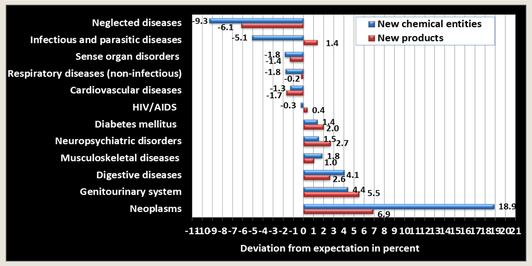
48% of new products for ND in WHO-EML vs 4% for all other diseases



	NCE (n=336)	Other new product (n=420)*	Vaccine or biological (n=94)†	Total (n=850)
Neglected diseases				
Malaria	3 (1%)	9 (2%)	0	12 (1%)
Tuberculosis	0	7 (2%)	0	7 (1%)
Diarrhoeal diseases	1 (<0·5%)	3 (1%)	3 (3%)	7 (1%)‡
Neglected tropical diseases	0	5 (1%)	0	5 (1%)§
Other	0	1 (<0·5%)	5 (5%)	6 (1%)¶
Subtotal	4 (1%)	25 (6%)	8 (9%)	37 (4%)
Other infectious diseases	35 (10%)	48 (11%)	66 (70%)	149 (18%)
All other diseases	297 (88%)	347 (83%)	20 (21%)	664 (78%)

Data are n (%). NCE=new chemical entity. *New indication, new formulation, or fixed-dose combination. †Includes immunoglobulins and other biological products. ‡For diarrhoea, cholera, cryptosporidiosis, and giardiasis. §For human African trypanosomiasis, Chagas disease, and leishmaniasis. ¶For Japanese encephalitis, haemorrhagic fevers, and snakebite.

Table 1: New therapeutic products approved or recommended, by disease category (2000–11)



(B) Clinical trials

Of 148 445 clinical trials registered in Dec 31, 2011, only 2016 (1%) were for neglected disease

	NCE	NF or FDC	NI	NA	Vaccine or biologics	Total
Malaria	6 (38%)	4 (50%)	5 (21%)	1 (14%)	21 (31%)	37 (30%)
Tuberculosis	5 (31%)	0	3 (13%)	3 (43%)	8 (12%)	19 (15%)
Diarrhoeal diseases	0	0	2 (8%)	0	13 (19%)	15 (12%)
NTDs*	3 (19%)	4 (50%)	10 (42%)	3 (43%)	14 (21%)	34 (28%)
Other†	2 (13%)	0	4 (17%)	0	12 (18%)	18 (15%)
Total	16 (100%)	8 (100%)	24 (100%)	7 (100%)	68 (100%)	123 (100%)

Data are n (%). NCE=new chemical entity. NF=new formulation. FDC=fixed-dose combination. NI=new indication. NA=new association. NTD=neglected tropical disease (WHO definition). *Cutaneous leishmaniasis (10), dengue fever (6), visceral leishmaniasis (4), Chagas disease (3), schistosomiasis (3), rabies (2), one each for echinococcosis, hookworm, human African trypanosomiasis, lymphatic filariasis, onchocerciasis, and cysticercosis or taeniasis. †Viral haemorrhagic fevers (6), other arboviruses (6), Japanese encephalitis (3), one each for yellow fever, scabies, and snakebite.

Table 6: New products in clinical trials by neglected disease and product type (as of Dec 31, 2011)

Conclusions

- **A persistent imbalance between disease burden and product development for neglected diseases.**
- Positive advances are primarily based on
  - ➢repurposed products
  - ➢vaccines (majority of ongoing clinical trials)
- 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 and in some cases no focus at all on other neglected diseases.

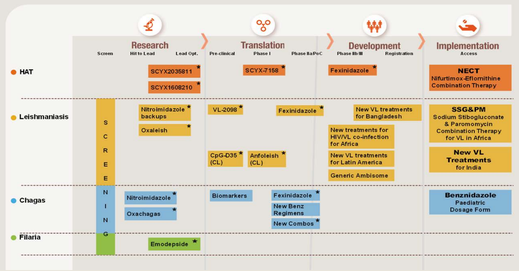
Targets and milestones for elimination and eradication of NTDs 2015 -2020

WHO 2020 targets include the global elimination of human African trypanosomiasis (HAT,) and lymphatic filariasis (LF), and regional elimination of visceral leishmaniasis (VL) (India) and onchocerciasis in selected African countries and Yemen by 2020 and Latin America by 2015.

DISEASE	2015				2020			
	Eradication	Global eliminat ion	Regional elimination	Country elimination	Eradicat ion	Global eliminat ion	Regional elimination	Country elimination
Chagas Disease			✓ Transmission through blood transfusion interrupted				✓Intra-domiciliary transmission interrupted in the region of the Americas	
Human African Trypanosomiasis				✓In 80% of foci		✓		
Visceral Leishmaniasis							✓Indian subcontinent	
Lymphatic Filariasis						✓		
Onchocerciasis			✓Latin America	✓Yemen				✓Selected countries in Africa
Cutaneous leishmaniasis	70% of all cases detected, and at least 90% of all detected cases treated in E.Mediterrean region							

* *adopted from WHO Neglected tropical diseases Roadmap 2012*

DNDi's portfolio for kinetoplastid and filarial diseases – a mix of existing drugs and NCES



NCE's for HAT

- **Fexinidazole,** identified from compound mining efforts, entered a pivotal Phase II/III study in 2012 and is currently recruiting patients with advanced *T.gambienese* HAT in the DRC and the CAR. Two complementary studies will examine efficacy and safety in adults with stage 1 and early stage 2 HAT, and children aged 6-14 years.
- **SCYX-7158** successfully progressed through pre-clinical development, entering Phase I clinical development in early 2012, which is nearing completion.

NCE's for Leishmaniasis

Visceral leishmaniasis (VL)
- **Fexinidazole** in Proof of Concept for VL in East Asia
- **VL 2098** – First class of compounds to show sterile cure in animal models of VL. Scheduled for first-in-man in 2015

Cutaneous leishmaniasis (CL) :
- **Anfoleish:** ointment containing Amphotericin B in Phase I testing in Columbia
- **CPG-D35:** Immune-modular therapy based on a 35 base oligonucleotide that stimulates the innate immune system via toll-receptor activation in pre-clinical testing

New treatments for Chagas Disease

- **Fexinidazole Monotherapy (NCE)**
  - Phase II Proof of Concept trial in Bolivia – to test efficacy and safety of 6 dosing regimens
- **Benznidazole - New Regimens**
  - Proof of Concept – Phase IV
  - Improve safety, tolerability and compliance
  - Maintain efficacy compared to current regimen
  - Select the optimum combination of dose, dosing frequency and treatment duration
- **Combination Therapy of Azole E1224 (NCE) and BZN**
  - Proof of Concept – Phase II
  - Reduction of dose and duration of therapeutic regimen
  - Improvement of safety and tolerability
  - Potential reduction of resistance development for the individual components of the combination

NCE for Filariasis

- **Emodepside is** a natural product in veterinary use is under pre-clinical evaluation and due to enter the clinic in 2015

DNDi
Drugs for Neglected Diseases *initiative*

RSTMH Biennial: "Measuring Progress", Oxford. September 2014