FDA-NIH EFFORT TO CAPTURE THE GLOBAL CLINICAL EXPERIENCE OF DRUG REPURPOSING TO FACILITATE DEVELOPMENT OF NEW TREATMENTS FOR NEGLECTED INFECTIOUS DISEASES (INCLUDING NEGLECTED TROPICAL DISEASES AND EMERGING THREATS)

NEEDS AND OPPORTUNITIES

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ASTMH
AMERICAN SOCIETY OF TROPICAL MEDICINE & HYGIENE
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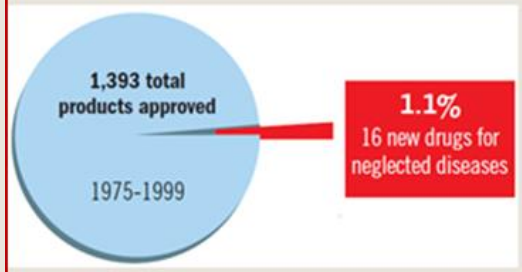
Dr Nathalie Strub Wourgaft – Medical Director

The concept of Neglected Diseases: A R&D gap

A Decade Ago, Pipeline Virtually Empty for Neglected Diseases

Health R&D (1975 – 1999)



A Fatal Imbalance

From 1975-1999:

- 16 of 1393 new products for neglected tropical diseases + malaria and TB (1.1%) despite these diseases representing 12% of global disease burden
- approx. 10% of R&D dedicated to illnesses that affect 90% of global disease burden ('10/90 gap')

Source: Fatal Imbalance: The Crisis in Research and Development for Neglected Diseases, MSF, 2001

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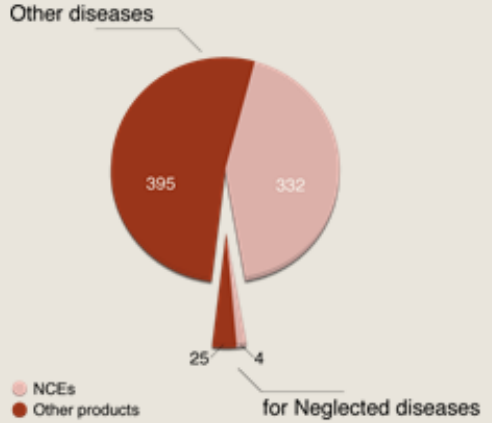
- Poorest of the poor
- Living in remote areas
- Socioeconomic burden on family and community
- Marginalized & voiceless patients

Fatal Imbalance Remains Despite Progress Over A Decade

756 products developed (excluding vaccines) (2000-2011)



- 3.8% of new products for neglected diseases (reformulations, combinations)
- 1.2% of NCEs for neglected diseases
- Only 1.4% clinical trials (of nearly 150,000 trials) focus on neglected diseases
- Only 1% of global health investment for neglected diseases*

Source: "The drug and vaccine landscape for neglected diseases (2000-2011): a systematic assessment" Pedrique B et al. Lancet, Oct 2013

*Source: "Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory?" Rottingen et al. Lancet, May 2013

Many Neglected Diseases at various control stages

WHO NTDs

List of 17
Buruli ulcer, Chagas disease Cysticercosis/taeniasis, Dengue, Dracunculiasis, Echinococcosis, Fascioliasis
Human African trypanosomiasis, Leishmaniasis, Leprosy, Lymphatic filariasis, Onchocerciasis, Rabies, Schistosomiasis
Soil-transmitted helminthiasis, Trachoma
Yaws

Other neglected conditions
Mycetoma, snake bite, scabies, chronic suppurative otitis media, podoconiosis

The «big 3»

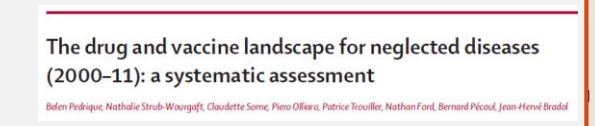
TB, HIV malaria

Diarrheal diseases

Amebiasis, Giardiasis, Cryptosporidium, Cholera, Shigella, E. coli enterotoxigenic, E. coli enteriaggregative enteropathogenic, Campylobacter, Non-typhoidal Salmonella enterica , Typhoid and paratyphoid fever, Rotavirus

Other neglected diseases

Leptospirosis, Bartonellosis, Bovine tuberculosis in humans, Relapsing fever, Japanese encephalitis, Yellow fever, Other arboviral infections, Viral hemorrhagic fevers, Strongyloidiasis, Loiasis, Toxocariasis and larva migrans, Balantidiasis, Paracoccidiomycosis, Myiasis, Tungiasis,


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

Belen Pedrique, Nathalie Strub-Wourgaft, Claudette Some, Piero Olliaro, Patrice Trouiller, Nathan Ford, Bernard Pécoul, Jean-Hervé Bradol

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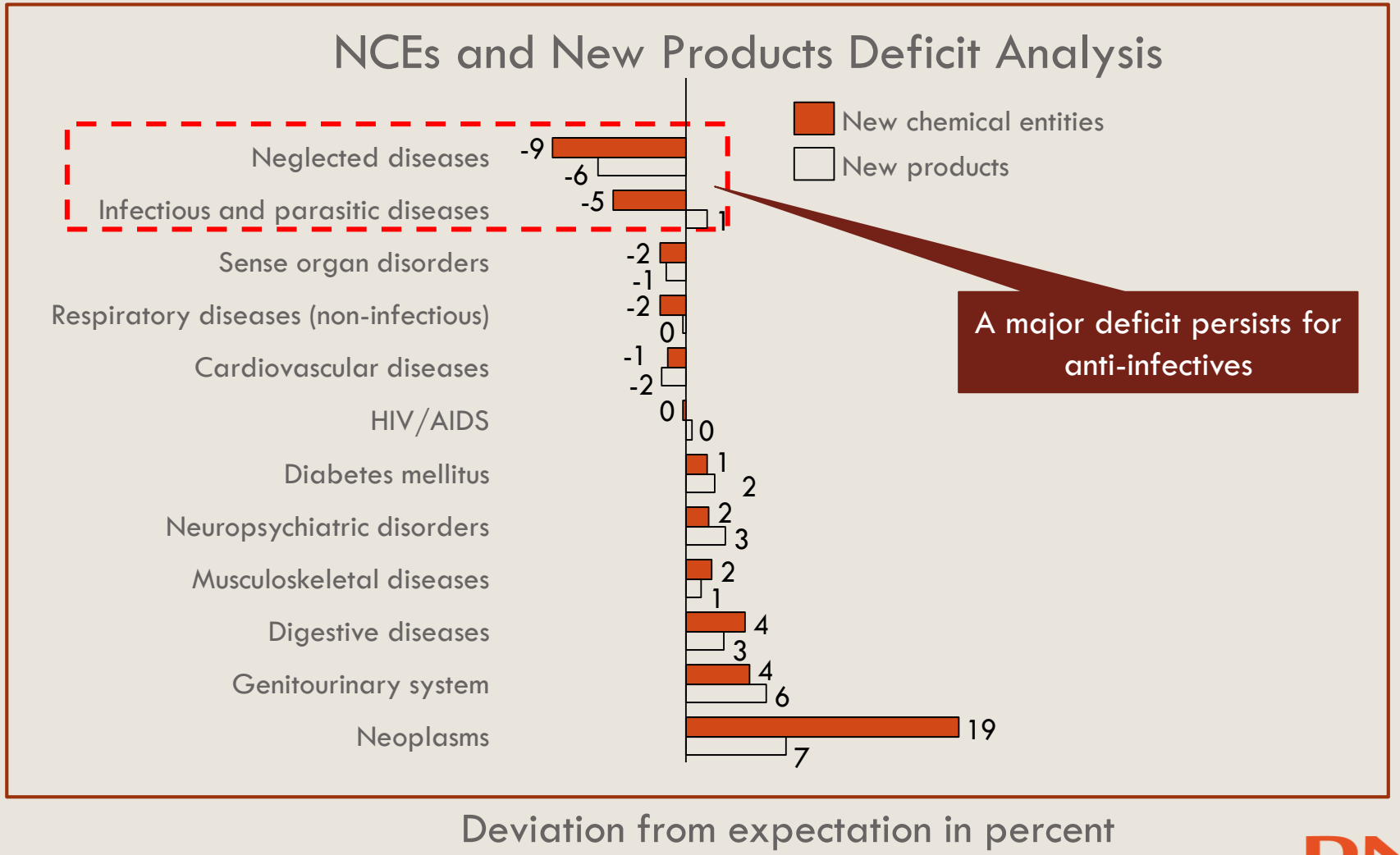
Approved products (2000-2011)
A deficit persists for neglected and infectious diseases



Source: The drug and vaccine landscape for neglected diseases (2000—11): a systematic assessment; Dr Belen Pedrique et al; the Lancet 2013. Deficit analysis was not part of the published version.

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Approved products by category (2000-2011)

	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)

25 (67%) of recently approved products for NDs consisted in New Formulations, New Indications or FDC

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New indications approved products (2000-2011)

Indication (Disease)	Products	Galenic form
Leishmaniasis	Paromomycin (LV)	Inj. 375mg/ml
	Miltefosine (LV)	Capsule 10mg&50mg
	Miltefosine (Additional Indication=Cutaneous L)	Capsule 10mg&50mg
Human African trypanosomiasis	Nifurtimox-Eflornithine Combination Therapy (NECT) Nifurtimox new indication in association	
Leprosy	Thalidomid	Tablets
Acute Diarrhoea	Zinc sulfate	oral liquid, in 10 mg per unit dosage forms; tablet, in 10mg per unit dosage form
Cholera	Tosufloxacin tosilate hydrate	Fine Granules 15% for Pediatric (Ozex)
TB	Moxifloxacin (as hydrochloride)	Tablets 400mg
	Levofloxacin	Tablets 250mg and 500 mg
	Ofloxacin	Tablets 200mg and 400 mg
	Atovaquone&Proguanil	Tablets adults and paediatric tablets for > 11 kg
	Atovaquone&Proguanil	film-coated tablets. (Malarone® Enfants) 5-11kg 2003 FDA

10 (27%) of recently approved products for NDs consisted in New Indications (*including pediatric one) combinig :*

- *Extension of anti-infectives*
- *New indication*

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Neglected Diseases: Treatment Limitations 10 Years Ago

- Ineffective (resistance)
- Toxic
- Expensive
- Painful when delivered
- Difficult to use
- Not registered in endemic regions
- Restricted by patents

We Need Safe, Effective, Easy-to-Use Drugs

DND*i* Portfolio-Building Model:

Address Immediate Patient Needs & Deliver Innovative Medicines

- **New chemical entities (NCEs)**

Long-term projects

- **New formulations (fixed-dose combinations)**
- **New indications of existing drugs**

Medium-term projects

- **Completing registration dossier**
- **Geographical extension**

Short- term projects

Discovery (R, LS, LO) → **Pre-clinical** → **Clinical** → **Implementation**

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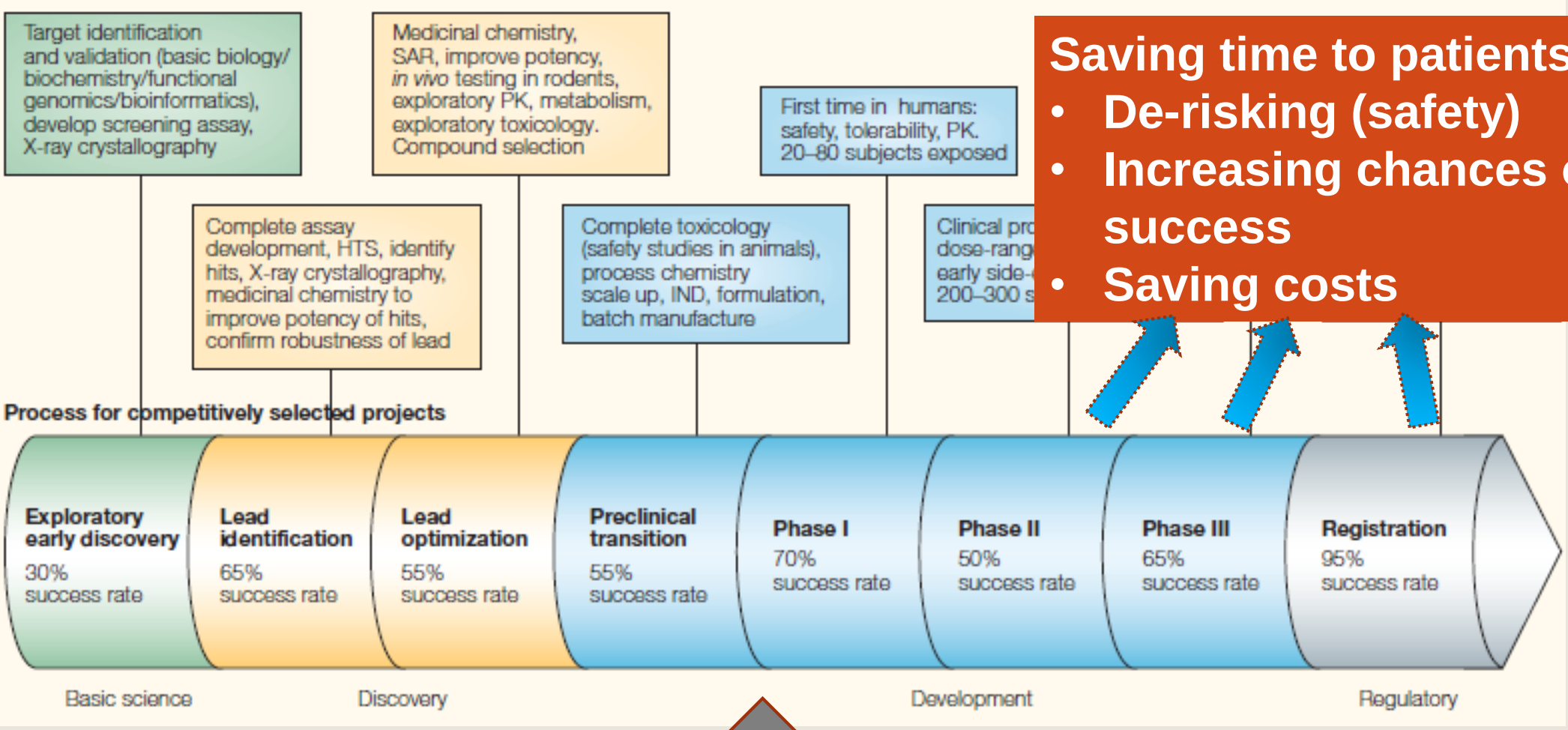
Advantages of repurposing drugs at the clinical stage



Saving time to patients by

- **De-risking (safety)**
- **Increasing chances of success**
- **Saving costs**

Ref Nwiaka, Ridley
.Nat Rev Drug Discov 2003 Nov;2(11):919-28

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Miltefosine for Visceral Leishmaniasis (VL)

- Phase 1 showing the need to administer tid to prevent digestive side effects and maximum dose of 150mg/day (planned for oncology)
- 1986: development of a model to infect macrophages with leishmanial donovani (Croft)
- 1987: Alkyl phospholipids identified as possible candidates (Croft et al.)
- 1990s: Initially developed in several cancer indications with insufficient efficacy in phase II trials
- 1992: cure in mice with L donovani and L infantum (Kuhlencord et al)
- 1998, 1999, 2002, 2011: tested in clinical trials for VL, first by Sundar – Policy change for its use in combination in India has now been granted
- Developped by ASTA Medica- Zentaris later Paladin –who applied for NDA in 2013 and was granted the PRV –
  - No new phase 1 – additonal PK data derived from CTs in Leishmanaisis patients

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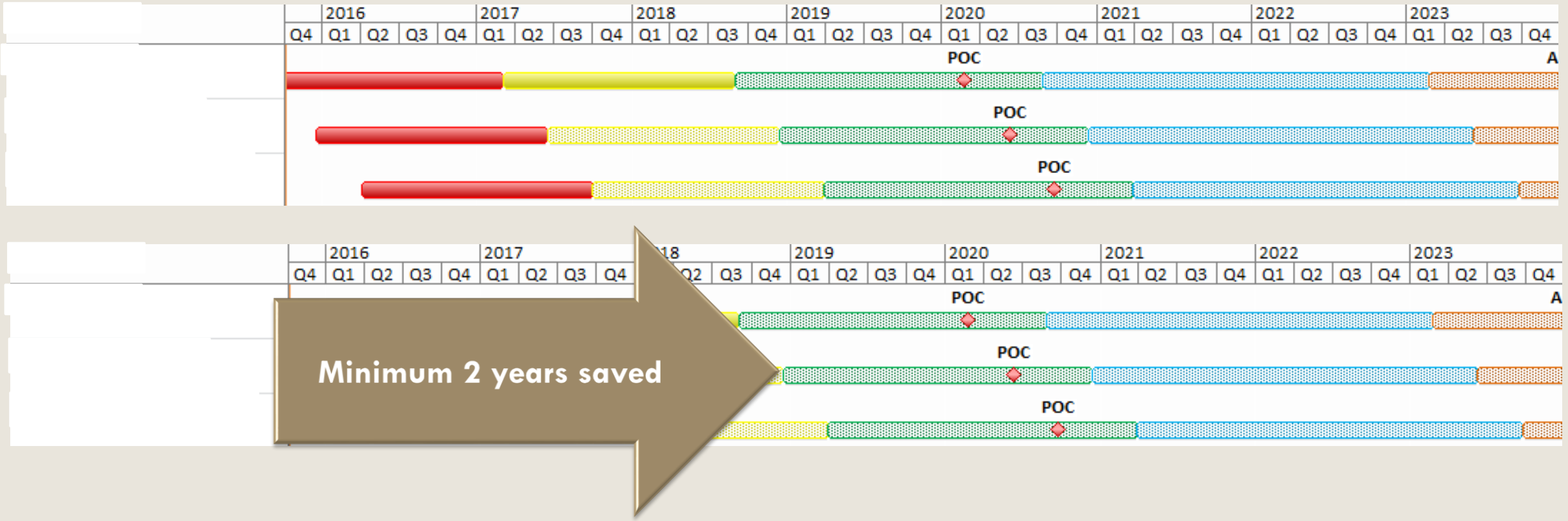
Generic drug development timelines for VL
A significant time gain for repurposed drugs



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The process of repurposing … example 1: HAT
A pragmatic and opportunistic scientific approach

- 1922: suramin
- 1941: pentamidine
- 1949: melarsoprol (effective but toxic)
- mid-1970s: nifurtimox (registered for Chagas disease)
- 1981: eflornithine (developed for cancer – nor efficacy but promising in reducing hair growth - developed as a topical cream for hirsutism) – shown effective in HAT- registered in 1990 for HAT and cream for hirsutism in 2000
- 2002: study in Uganda with MSF on 3 combinations
- 2009: Epicentre, and DNDi test nifurtimox-eflornithine combination in a non inferioritiy trial against eflornithine – NECT added to the WHO essential list and 1st line treatment
- 2009: fexinidazole, rediscovered after datamining of 700 nitroimidazole compounds, now in development in Man for stage 2 HAT

Janssens PG, De Muynck A (1977) Clinical trials with "nifurtimox" in African trypanosomiasis. Ann Soc Belg Med Trop 57: 475–480.
Moens F, De Wilde M, Ngato K (1984) [Clinical trial of nifurtimox in human African trypanosomiasis]. Ann Soc Belg Med Trop 64: 37–43.
Pepin J, Milord F, Meurice F, Ethier L, Loko L, et al. (1992) High-dose nifurtimox for arseno-resistant *Trypanosoma brucei gambiense* sleeping sickness: An open trial in central Zaire. Trans R Soc Trop Med Hyg 86: 254–256.

OPEN ACCESS Freely available online
PLOS CLINICAL TRIALS

Three Drug Combinations for Late-Stage *Trypanosoma brucei gambiense* Sleeping Sickness: A Randomized Clinical Trial in Uganda

Gerardo Priotto[1*], Carole Fogg[1], Manica Balasegaram[2], Olema Erphas[3], Albino Louga[3], Francesco Checchi[1], Salah Ghabri[1], Patrice Piola[1]
1 Epicentre, Paris, France, 2 Médecins Sans Frontières, Paris, France, 3 National Sleeping Sickness Control Programme, Arua, Uganda

Arm	Cured (*n*)	Cure Rate (%)	Relative Risk	Exact 95% CI	*p*-Value
M+N (*n* = 18)	8	44.4	—	—	—
M+E (*n* = 19)	15	78.9	1.78	1.01–3.13	0.045
N+E (*n* = 17)	16	94.1	2.12	1.25–3.60	0.003

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The process of repurposing … example 2
A pragmatic and opportunistic scientific approach

Mycetoma

+ advocacy work + industrial partner

A very neglected condition with a single possible low hanging fruit treatment approach

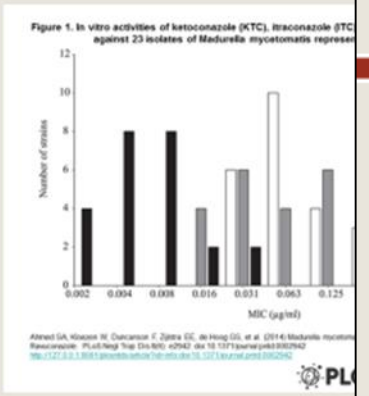
- chronic infection c
  failure results in p

- existing treatment

Clinical data for eumycetoma treatment

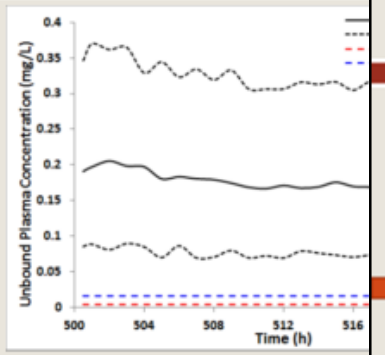
Drug	Organism	N	Dose
Ketoconazole	M. mycetomatis	13	200-400 mg OD Mean treatment 1 year
	M. mycetomatis	50	200 mg BD
	M. mycetomatis (4) Other (4)	8	400 mg OD 8-24 months
Itraconazole	M. mycetomatis	13	400 mg OD 3 months, then 20 9 months
Terbinafine	M. mycetomatis (10) L. senegalensis (3) Other (3) Not known (7)	23	500 mg BD, 24-48 weeks
Voriconazole	S. apiospermum	1	400 mg OD, 18 months
	S. apiospermum	1	Dose not specified, 6 months
	M. grisea	1	Dose not specified, 6 months
	M. mycetomatis	1	200 mg, 3 months, then 300 m 13 months
	Madurella spp	1	200 mg, 12 months
	S. apiospermum	1	200 mg BD, unknown duration
Posaconazole	M. mycetomatis (2) M. grisea (3) S. apiospermum (1)	6	800 mg OD
Liposomal amphotericin B	M. grisea (2) Fusarium (1)	3	Total dose 3.4, 2.8, 4.2 grams max. daily dose 3 mg/kg

Madurella mycetomatis highly susceptible to ravuconazole



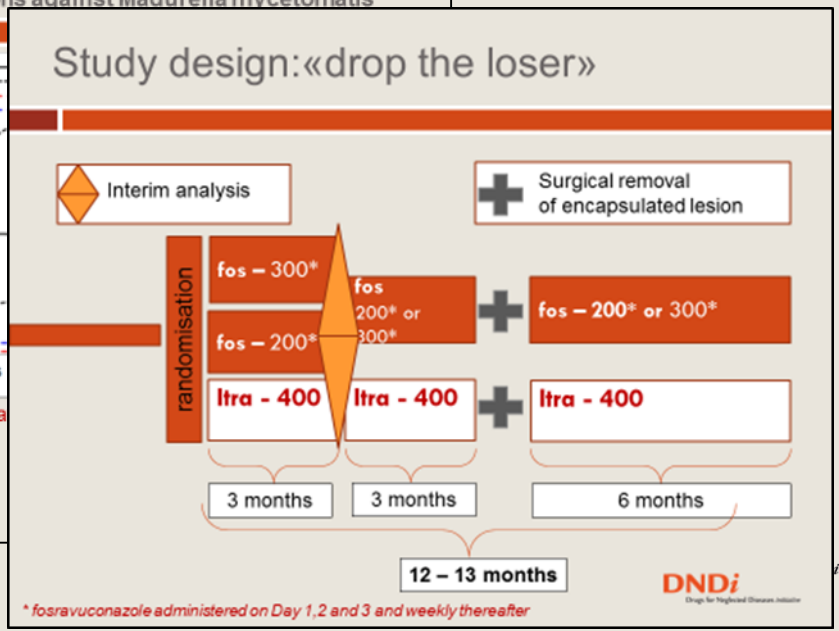
Fosravuconazole dose rationale

Modeling of plasma concentrations against Madurella mycetomatis



Dosing: fosravuconazole 200 mg on Da

Study design:«drop the loser»



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But are there any risks?

- *Scientifically* : … if data from the repurposed compound are not solid … (but this can be evaluated) – especially regarding the safety documentation
- *Regulatory*: … acceptability of the NDA dossier will depend on the stage from "repurposing"
  - Different for a licensed drug vs non licensed vs licensed since a long time
- *For the Industry*: emergence of new safety signals (e.g due to different population)
- *For the patient and public health system*: affordability and sustainable production

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In conclusion …

The gap for safe and effective treatments for NDs or Neglected patients exist !

Accessing clinical candidates is an opportunity to shortcut the R&D process and accelerate therefore access to needed treatments

Anticipation of regulatory needs and access plan are crucial

Repurposing has already shown its benefit for NTDs, and should be encouraged

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