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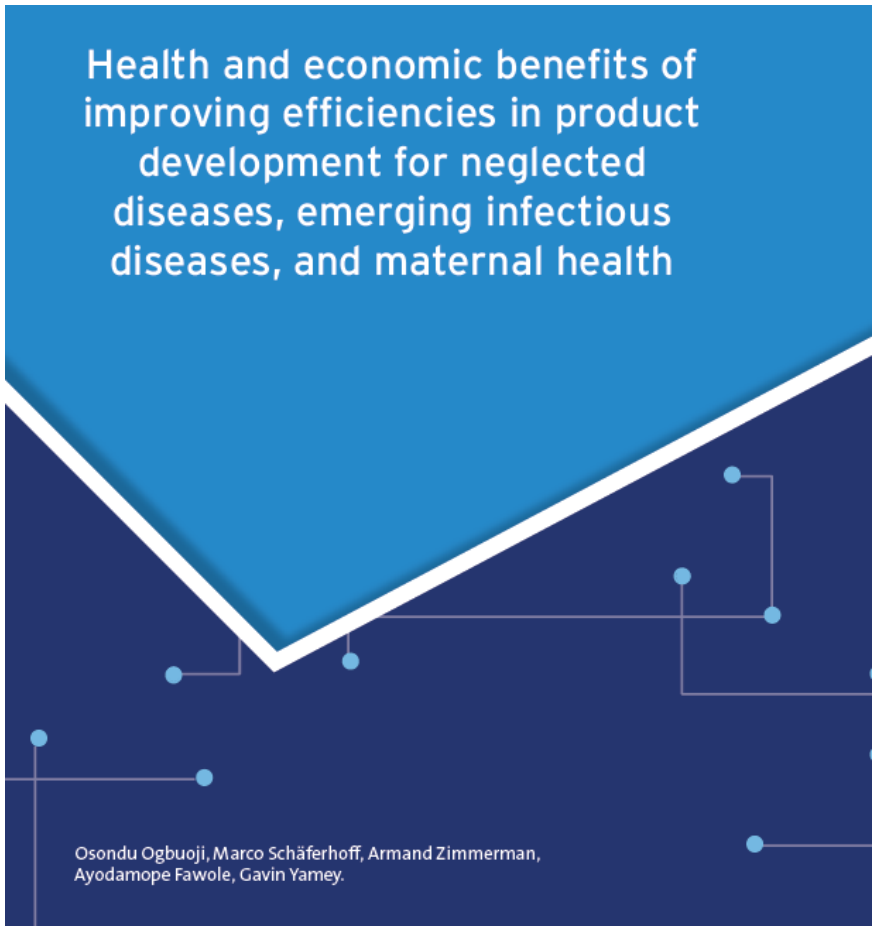
Improving the R&D Ecosystem Over the Next 20 Years

Saving More Lives Through More Effective Innovation

Gavin Yamey, Marco Schäferhoff, Osondu Ogbuoji, Shingai Machingaidze, Delese Mimi Darko

May 21 2024 I Online launch seminar

Two new reports launched today



Today's seminar

1. Introduction to the two reports (Gavin Yamey)
2. R&D ecosystem: Key shifts and efficiency gains (Marco Schäferhoff)
3. Impact of efficiency gains on product launches (Osondu Ogbuoji)

Reflections on the report:

- Shingai Machingaidze, Co-Chair, 100 Day Mission, Science & Technology Expert Group; International Pandemic Preparedness Secretariat
- Delese Mimi Darko, Chief Executive, Food & Drugs Authority, Ghana

Open Q&A with audience (please post questions in the dedicated Q&A box)

1. Introduction

Background: The next 20 years - opportunities and challenges for the R&D ecosystem

- The past 20 years have seen important product launches, but many gaps remain
- New health technologies are needed to accelerate global health progress in the next 20 years
- How can we save most lives, reduce the burden of infectious diseases & maternal health conditions?
- Funding is constrained, costs for clinical trials are rising
- There is a need to make investment more strategic, overcome bottlenecks in the R&D ecosystem, and exploit efficiencies arising from new technologies, approaches, platforms
- “Tools don’t deliver themselves”—need to overcome challenges in access, deployment, delivery

Context (1): Commission on Investing in Health 3.0, launches in Oct 2024 at WHS

- **CIH 3.0:** pathways for all nations to achieve better health: a 50% reduction in premature mortality (death before 70) by 2050 (“50 by 50”), with an interim 2035 target
- Synergies between CIH 3.0 and our new study on the future R&D ecosystem
  - Game-changing technologies to achieve the 2035 and 2050 targets
  - Pandemic medical countermeasures
  - Innovations in GPG ecosystem, including R&D

GLOBAL HEALTH 2050

Context (2): Our new research builds on previous work conducted by our team

Gates Open Research

Gates Open Research 2020, 2:23 Last updated: 23 MAR 2022

Check for updates

RESEARCH ARTICLE

REVISED **Developing new health technologies for neglected diseases: a pipeline portfolio review and cost model [version 3; peer review: 3 approved]**

Ruth Young[1], Tewodros Bekele[1], Alexander Gunn[1], Nick Chapman[2], Vipul Chowdhary[2], Kelsey Corrigan[3], Lindsay Dahora[4,5], Sebastián Martinez[6], Sallie Permar[4,7], Johan Persson[6], Bill Rodriguez[8], Marco Schäferhoff[6], Kevin Schulman[9], Tulika Singh[4,10], Robert F Terry[11], Gavin Yamey[1]

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Abstract

Background: Funding for neglected disease product development fell from 2009-2015, other than a brief injection of Ebola funding. One impediment to mobilizing resources is a lack of information on product candidates, the estimated costs to move them through the pipeline, and the likelihood of specific launches. This study aimed to help fill these information gaps.
Methods: We conducted a pipeline portfolio review to identify current candidates for 35 neglected diseases. Using an adapted version of the Portfolio to Impact financial modelling tool, we estimated the costs to move these candidates through the pipeline over the next decade and the likely launches. Since the current pipeline is unlikely to yield several critical products, we estimated the costs to develop a set of priority "missing" products.
Results: We found 685 neglected disease product candidates as of August 31, 2017; 538 candidates met inclusion criteria for input into the model. It would cost about $16.3 billion (range $13.4-19.8B) to

Open Peer Review

Approval Status ✓ ✓ ✓

	1	2	3
version 3 (revision) 19 Feb 2020			
version 2 (revision) 22 Aug 2018	✓ view		✓ view
version 1 26 Apr 2018	? view	✓ view	? view

1. **Lloyd Czaplewski**, Chemical Biology Ventures Ltd, Abingdon, UK
2. **Kevin Outterson**, Boston University,

Original research

BMJ Global Health

Investing in a global pooled-funding mechanism for late-stage clinical trials of poverty-related and neglected diseases: an economic evaluation

Armand Zimmerman ,[1] Mohamed Mustafa Diab ,[1] Marco Schäferhoff,[2] Kaci Kennedy McDade ,[1] Gavin Yamey ,[1] Osondu Ogbuoji[1]

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ABSTRACT

Introduction Poverty-related and neglected diseases (PRNDs) cause over three million deaths annually. Despite this burden, there is a large gap between actual funding for PRND research and development (R&D) and the funding needed to launch PRND products from the R&D pipeline. This study provides an economic evaluation of a theoretical global pooled-funding mechanism to finance late-stage clinical trials of PRND products.
Methods We modelled three pooled-funding design options, each based on a different level of coverage of candidate products for WHO's list of PRNDs: (1) vaccines covering 4 PRNDs, (2) vaccines and therapeutics covering 9 PRNDs and (3) vaccines, therapeutics and diagnostics covering 30 PRNDs. For each option, we constructed a discrete event simulation of the 2019 PRND R&D pipeline to estimate required funding for phase III trials and expected product launches through 2035. For each launch, we estimated global PRND treatment costs averted, deaths averted and disability-adjusted life-years (DALYs) averted. For each design option, we calculated the cost per death averted, cost per DALY averted, the benefit–cost ratio (BCR) and the incremental cost-effectiveness ratio (ICER).
Results Option 1 averts 18.4 million deaths and 516 million DALYs, has a cost per DALY averted of US$84 and yields a BCR of 5.53. Option 2 averts 22.9 million deaths and 674 million DALYs, has a cost per DALY averted of US$75, an ICER over option 1 of US$49 and yields a BCR of 3.88. Option 3 averts 26.9 million deaths and 1 billion DALYs, has a cost per DALY averted of US$114, an ICER over option 2 of US$186 and yields a BCR of 2.52.
Conclusions All 3 options for a pooled-funding mechanism—vaccines for 4 PRNDs, vaccines and therapeutics for 9 PRNDs, and vaccines, therapeutics and diagnostics for 30 PRNDs—would generate a large return on investment, avert a substantial proportion of the global burden of morbidity and mortality for diseases of poverty and be cost-effective.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is a substantial gap between current funding for the research and development (R&D) of health products to address poverty-related and neglected diseases (PRNDs) and the funding required to launch these products from the R&D pipeline.
⇒ Most current R&D funding for PRNDs is allocated towards basic and early-stage research.
⇒ This study shows the worldwide health and economic benefits of investing in late-stage R&D for PRNDs.

WHAT THIS STUDY ADDS

⇒ Our study estimates the potential impact of a global pooled-funding mechanism to finance late-stage clinical trials of PRND products. Our results show that investments in late-stage clinical trials for PRNDs may avert up to 26 million deaths and 1 billion disability-adjusted life-years globally over the period 2019–2035, with economic returns to society that outweigh the costs of investment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the value of a new financial model to increase coordination and collaboration across R&D initiatives for PRNDs, to mobilise new funding sources for PRND product development, to reduce the financial risk associated with PRND investments and to curate a global portfolio of ideal PRND product investment opportunities. Such a model may avert millions of deaths and billions in treatment costs worldwide.

INTRODUCTION

Poverty-related and neglected diseases (PRNDs) are a major contributor to the disease burden in low-income and middle-income countries (LMICs).[1] These conditions are classified by the WHO as type II diseases that disproportionately affect LMICs or type III diseases that are prevalent exclusively in LMICs.[2] PRNDs include HIV, tuberculosis (TB), malaria, pneumonia, diarrhoeal diseases and all other neglected tropical diseases (NTDs).[3] In 2019, HIV caused 864 thousand deaths globally, TB 1.18 million, malaria 643 thousand,

Articles

Investing in late-stage clinical trials and manufacturing of product candidates for five major infectious diseases: a modelling study of the benefits and costs of investment in three middle-income countries

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See Comment page e944

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Summary

Background Investing in late-stage clinical trials, trial sites, and production capacity for new health products could improve access to vaccines, therapeutics, and infectious disease diagnostics in middle-income countries. This study assesses the case for such investment in three of these countries: India, Kenya, and South Africa.

Methods We applied investment case modelling and assessed how many cases, deaths, and disability-adjusted life years (DALYs) could be averted from the development and manufacturing of new technologies (therapeutics and vaccines) in these countries from 2021 to 2036, for five diseases—HIV, tuberculosis, malaria, pneumonia, and diarrhoeal diseases. We also estimated the economic benefits that might accrue from making these investments and we developed benefit–cost ratios for each of the three middle-income countries. Our modelling applies two investment case perspectives: a societal perspective with all costs and benefits measured at the societal level, and a country perspective to estimate how much health and economic benefit accrues to each middle-income country for every dollar invested in clinical trials and manufacturing by the middle-income country government. For each perspective, we modelled two scenarios: one that considers only domestic health and economic benefits; and one that includes regional health and economic benefits. In the regional scenarios, we assumed that new products developed and manufactured in India would benefit eight countries in south Asia, whereas new products developed and manufactured in Kenya would benefit all 21 countries in the Common Market for Eastern and Southern Africa (COMESA). We also assumed that all 16 countries in the Southern African Development Community (SADC) would benefit from products developed and manufactured in South Africa.

Findings From 2021 to 2036, product development and manufacturing in Kenya could avert 4·44 million deaths and 206·27 million DALYs in the COMESA region. In South Africa, it could prevent 5·19 million deaths and 253·83 million DALYs in the SADC region. In India, it could avert 9·76 million deaths and 374·42 million DALYs in south Asia. Economic returns would be especially high if new tools were produced for regional markets rather than for domestic markets only. Under a societal perspective, regional returns outweigh investments by a factor of 20·51 in Kenya, 33·27 in South Africa, and 66·56 in India. Under a country perspective, the regional benefit–cost ratios amount to 60·71 in India, 8·78 in Kenya, and 11·88 in South Africa.

Interpretation Our study supports the creation of regional hubs for clinical trials and product manufacturing compared with narrow national efforts.

Funding Bill & Melinda Gates Foundation.

Introduction

Investing in late-stage clinical trials, trial sites, and production capacity for new health products could improve access to vaccines, therapeutics, and diagnostics in middle-income countries. Strengthening trial sites and manufacturing will also contribute to pandemic preparedness and strengthening the response to future outbreaks. The COVID-19 pandemic has shown that low-income and middle-income countries have had to rely mostly on donations of COVID-19 vaccines from high-income countries. As a result, there are now multiple efforts to boost vaccine manufacturing in Africa. WHO, for example, is supporting the creation of African COVID mRNA vaccine technology transfer hubs to scale up production and access to COVID vaccines, with South Africa becoming the first hub. Algeria, Egypt, Morocco, Rwanda, and Senegal have also signed agreements for COVID-19 manufacturing or started production.[1]

In this study, we assessed the case for investing in clinical trials and manufacturing capacity for three middle-income countries: India, Kenya, and South Africa. We modelled the health and economic benefits that would

Our research on the R&D ecosystem: 9-month study, Aug 2023 to April 2024

Objectives

- Identify ~20 infectious disease and maternal health tools that have the potential to make the largest impact over the next 20 years
- Assess potential for efficiency gains in the R&D ecosystem to accelerate the development of these tools at lower cost
- Model the impact of efficiency gains (e.g., cost savings; health benefits of accelerated introduction)

R&D areas

- Neglected diseases (NDs)
- Emerging infectious diseases (EIDs)
- Maternal health (MH)

Two interlinked focus areas

R&D ecosystem changes

Paradigm shifts for accelerated, efficient and cost-effective execution of R&D for prioritized high-impact innovations & technologies

- Artificial intelligence
- Clinical trials
- Manufacturing
- Regulation
- New & underused technologies (mRNA, mAbs)
- Governance and financing

Modeling: cost & benefits of R&D

Identification of high-impact products

- Model future R&D pipeline for PRNDs, EIDs, and MH over a 20-year timeframe, with a focus on advancing the late-stage pipeline
- Calculate the costs, funding gaps, and expected product launches
- Estimate the public health and economic impact of new products
- Leverage evidence and regional consultations to identify a list of high impact products

Outputs feed into model: Efficiency gains

Broad project scope

- **Impact analysis:** Public health and economic impact
- **Efficiency gains** through ecosystem changes
- **Mixed methods:** Modeling and qualitative research, including broad consultation process (over 120 key informant interviews)
- **Regional consultations:** Asia Pacific (led by Ming Xu), Sub-Saharan Africa (led by Mosa Moshabela), and Latin America (led by Ernesto Ortiz)

2. R&D ecosystem: Key shifts and efficiency gains

Key efficiencies and ecosystem opportunities

Artificial Intelligence (AI)	Clinical Trials (CTs)	Manufacturing	Regulation	Financing and governance
Discovery ➢ Accelerated drug discovery at much lower costs (e.g., antibiotic-resistant *N. gonorrhoeae* Vx) ➢ Unprecedented opportunity to search across vast chemical spaces for novel compounds ➢ AI-screening → stronger pipeline & higher probabilities of success in clinical phase	***Innovative designs, networks and tools*** ➢ Decentralized CTs using digital tools can reduce physical visits by up to 40% ➢ Cost savings through synthetic control arms ($10-$20m per trial) ➢ Trial networks can lower costs by 23% ➢ AI tool can predict probability of moving to Phase 3 with 79% accuracy	***Optimized production*** ➢ Optimized mRNA production process offers large savings (~60% of annual costs of goods for 100m Vx doses can be saved) ➢ Modular facilities reduce capital costs (e.g., modular facility for seasonal influenza Vx for 25-50m doses at a cost of $20m)	***Regulatory reforms accelerate approval*** ➢ Harmonization and reliance → AMRH reduced approval timelines from 7 to 1-2 years in SSA ➢ Regulatory reforms during pandemic (e.g., review times in EU were reduced from 40-70 days to 20 days)	***Priority Review Voucher (PRV)*** ➢ Introduction of a PRV in Europe could provide an additional incentive of $100-200 million per drug candidate to industry ***Regionalization*** ➢ R&D priority setting ➢ Regional hubs (e.g., CTs; manufacturing)

Selected action points

Area	Action points
AI	• Scale-up adoption of AI for product development for NDs, EIDs and MH • Enable LMICs to take part in AI by building capacity (rather than “augmenting inequalities”) • Support creation of Vx library to strengthen PPR (map antigen designs of priority viruses)
Clinical trials	• Leverage the efficiencies from innovative clinical trial designs in low-resource settings • Unlock the efficiency potential of clinical trial networks
Manufacturing	• Scale-up innovative manufacturing approaches • Support creation of diversified production capacity across regions and product types • Work towards concrete and firm purchasing commitments
Regulation	• Invest in (sub-)regional regulatory harmonization and reliance models • Strengthen NRAs, including through collaborations (e.g., twinning)
New/underused technologies	• Leverage the advantages (speed; versatility) of mRNA platform for NDs, EIDs and MH • Scale-up R&D investments on mAbs that target NDs, EIDs, MH
Financing and governance	• Introduce PRV in Europe • Invest in underlying R&D systems rather than in individual trials • Strengthen regional R&D ecosystems, including priority setting

3. Impact of efficiency gains on product launches

Methods

Analytic approach

- **Unit of analysis**
  - Product portfolio
- **153 product portfolios**
  - Included vaccines, therapeutics, diagnostics
  - Excluded vector control products, devices, nutritional supplements
  - 1,498 product candidates
- **Time horizon**
  - 2023 to 2044
- **Four efficiency gains scenarios**

Perspectives

- **Health systems**
  - Incremental cost per death averted
  - Incremental cost per DALY averted
- **Societal perspective**
  - Net monetary benefits

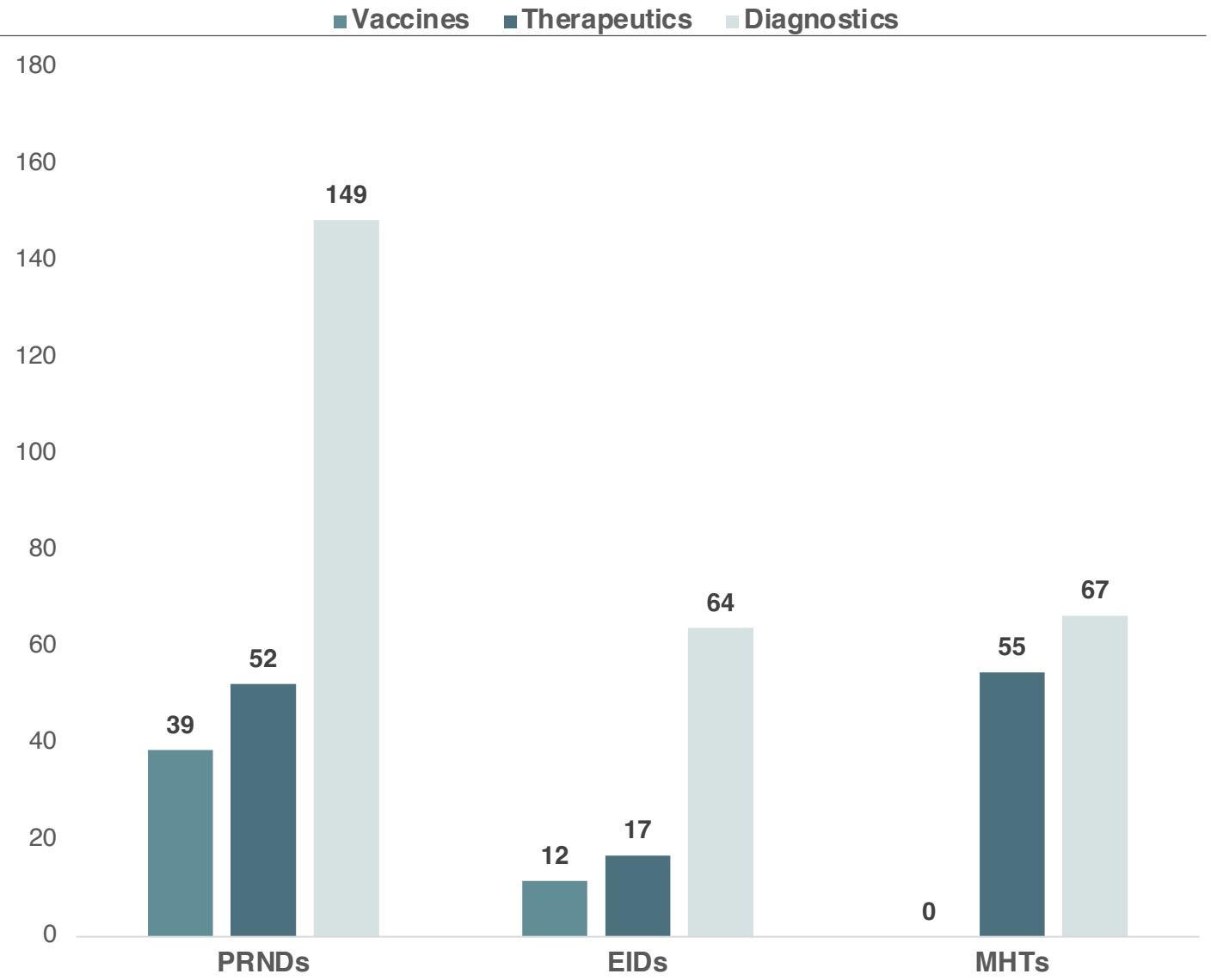
Efficiency gains scenarios

Scenario[1]	Pipeline replenishment[2]	Pre-clinical and clinical trial research costs[3]	Phase time and success rates[4]	LMIC market introduction[5] (In years post-launch)	Production costs[6]
0. Reference case	No	P2I estimates[7]	P2I estimates[7]	3 years	Current costs
1. Coordinated investments in missing products	Yes	P2I estimates[7]	P2I estimates[7]	3 years	Current costs
2. #1 plus improved clinical trial efficiencies	Yes	60% reduction in preclinical research costs[8] 25% reduction in clinical trial costs[9]	10%-point increase in success rates[10]	3 years	Current costs
3. #2 plus shortened market entry and lower production costs	Yes	60% reduction in preclinical research costs[8] 25% reduction in clinical trial costs[9]	10%-point increase in success rates[10]	1 year	20% reduction

59 product portfolios

453 product launches

94 portfolios with missing products



Funding gap – additional $1.4 billion to $7 billion needed annually (depending on product complexity)

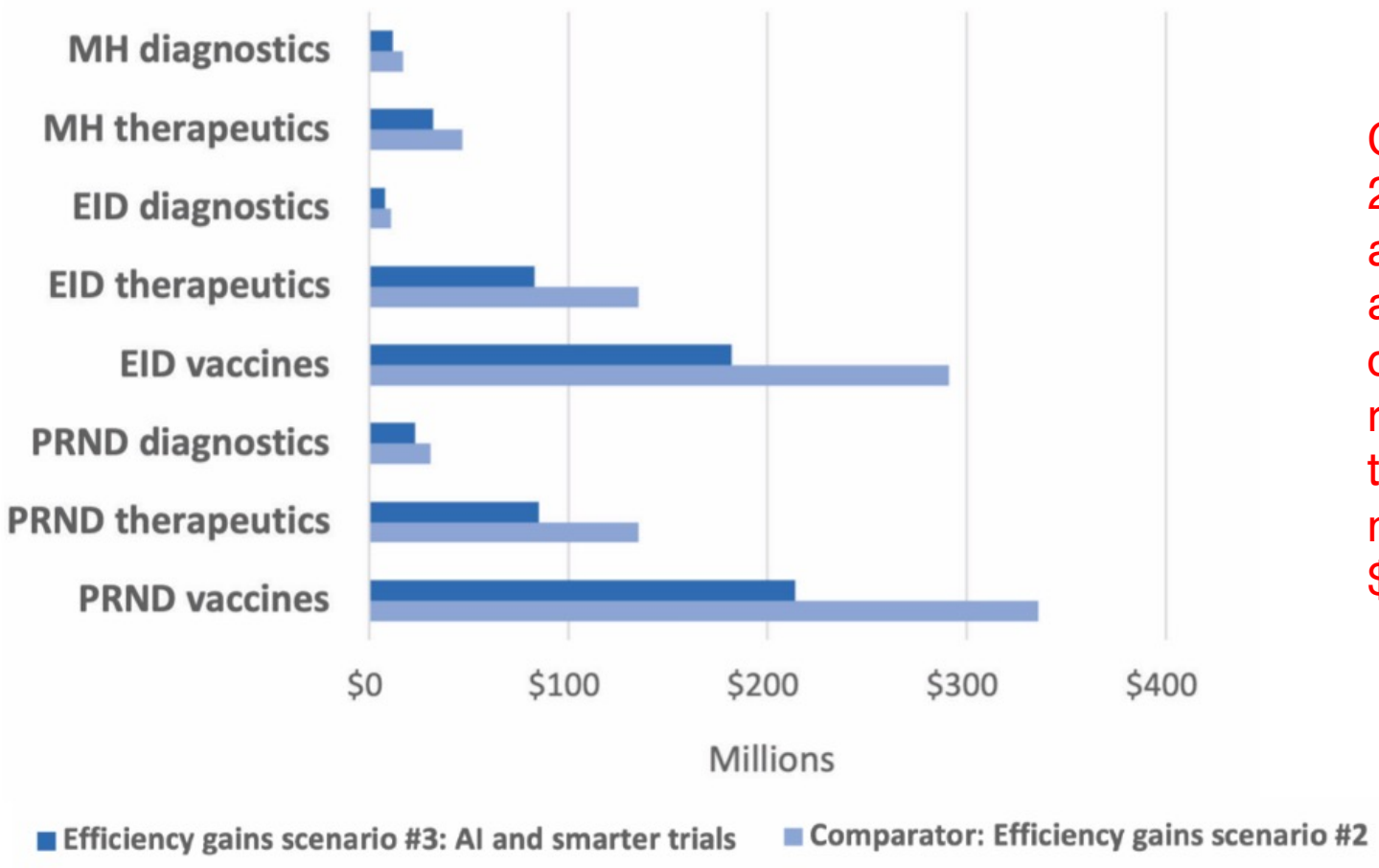
Disease-product-archetype	Available funding (in million USD)	Funding of current pipeline **without** replenishment (in million USD)		**Best-case replenishment:** funding with replenishment of pipeline with **simple products** (in million USD)		**Worst-case replenishment:** funding with replenishment of pipeline with **complex products**	
		Annual need	Funding gap	Annual need	Funding gap	Annual need	Funding gap
All ND products	$2,908	$2,102	-$806	$4,020	$1,112	$8,841	$5,933
All EID products	$742	$586	-$156	$885	$143	$1,536	$794
All MH products	$197	$299	$102	$388	$191	$453	$256
All products	$3,847	$2,987	-$860	$5,293	$1,446	$10,830	$6,983

Efficiency gains

Disease-product-archetype	Positive net monetary benefits[1]			
	#1	#2	#3	#4
	Reference case	#1 + Coordinated investments to include missing products[2] Number (Difference, #2 – #1)	#2 + Improved efficiency of preclinical/clinical trials[3] Number (Difference, #3 – #1)	#3 + shortened market entry and decreased production costs[4] Number (Difference, #4 – #1)
ND vaccines	7	30 (23)	32 (25)	34 (27)
ND therapeutics	3	29 (26)	30 (27)	31 (28)
ND diagnostics	21	30 (9)	30 (9)	30 (9)
EID vaccines	1	2 (1)	2 (1)	4 (3)
EID therapeutics	0	0 (0)	1 (1)	1 (1)
EID diagnostics	3	3 (0)	3 (0)	3 (0)
MH therapeutics	4	6 (2)	6 (2)	6 (2)
MH diagnostics	3	6 (3)	6 (3)	6 (3)

Benefits: monetary benefits of DALYs averted, estimated as a function of DALYs averted and average GDP per capita for LMICs.
Costs: all costs from preclinical to delivery to patients.

Efficiency gains – Cost savings and reduction in cost-per launch



Cost savings would translate to a 26% to 39% reduction in the average cost-per-launch (CPL) across all product portfolios, with diagnostics portfolios seeing CPL reductions of up to $8 million, therapeutics portfolios up to $52 million, and vaccines portfolios up to $122 million

Global ranking of priority product portfolios

- 16 vaccine product portfolios are cost saving to the health system and also yield positive net monetary benefits
  - 15 ND portfolios
  - 1 EID portfolio
- Net monetary benefits (NMBs): $0.25 to $48,679 billion.
- Regional rankings differ. Driven by prevalence and GDP per capita.

Societal perspective (Positive net monetary benefits)	
Rank	Disease Portfolio (Vaccines)
1	*S. pneumoniae* vaccine ($48,679 B)
2	Multiple diarrheal diseases vaccine ($6,518 B)
3	Typhoid and paratyphoid vaccine ($2,740 B)
4	*P. falciparum* vaccine ($311 B)
5	Multiple / other malaria strains vaccine ($126 B)
6	Tuberculosis vaccine ($118 B)
7	Rotavirus vaccine ($96 B)
8	*N. meningitidis* vaccine ($63 B)
9	HIV/AIDS vaccine ($53 B)
10	Dengue vaccine ($39 B)
11	Hepatitis B vaccine ($28 B)
12	Multiple Salmonella infections vaccine ($17 B)
13	Strongyloidiasis and other vaccine ($15 B)
14	Cryptococcal meningitis ($9 B)
15	Rheumatic fever ($7 B)
16	Zika ($0.25 B)

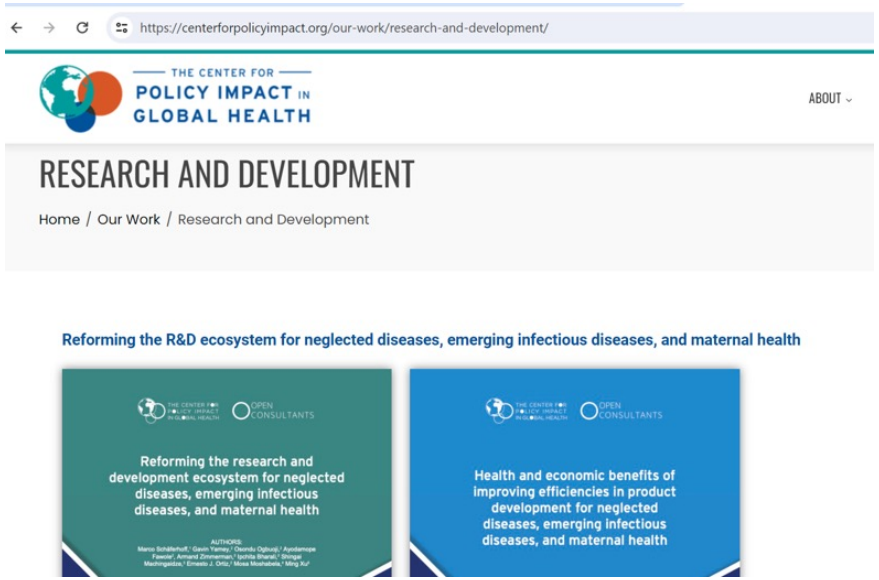
*Vaccines assume 0% coverage at baseline.
* Zika yields positive NMB based on the latest (2019) GBD global prevalence estimates. At lower prevalence estimates, it yields negative NMBs. Prevalence has reduced since 2019 but there are no global estimates.

Reflections on the two reports

Shingai Machingaidze
Co-Chair, 100 Days Mission, Science & Technology Expert Group; International Pandemic Preparedness Secretariat

Delese Mimi Darko
Chief Executive, Food and Drugs Authority, Ghana

The two reports are now online: see QR codes and URL



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