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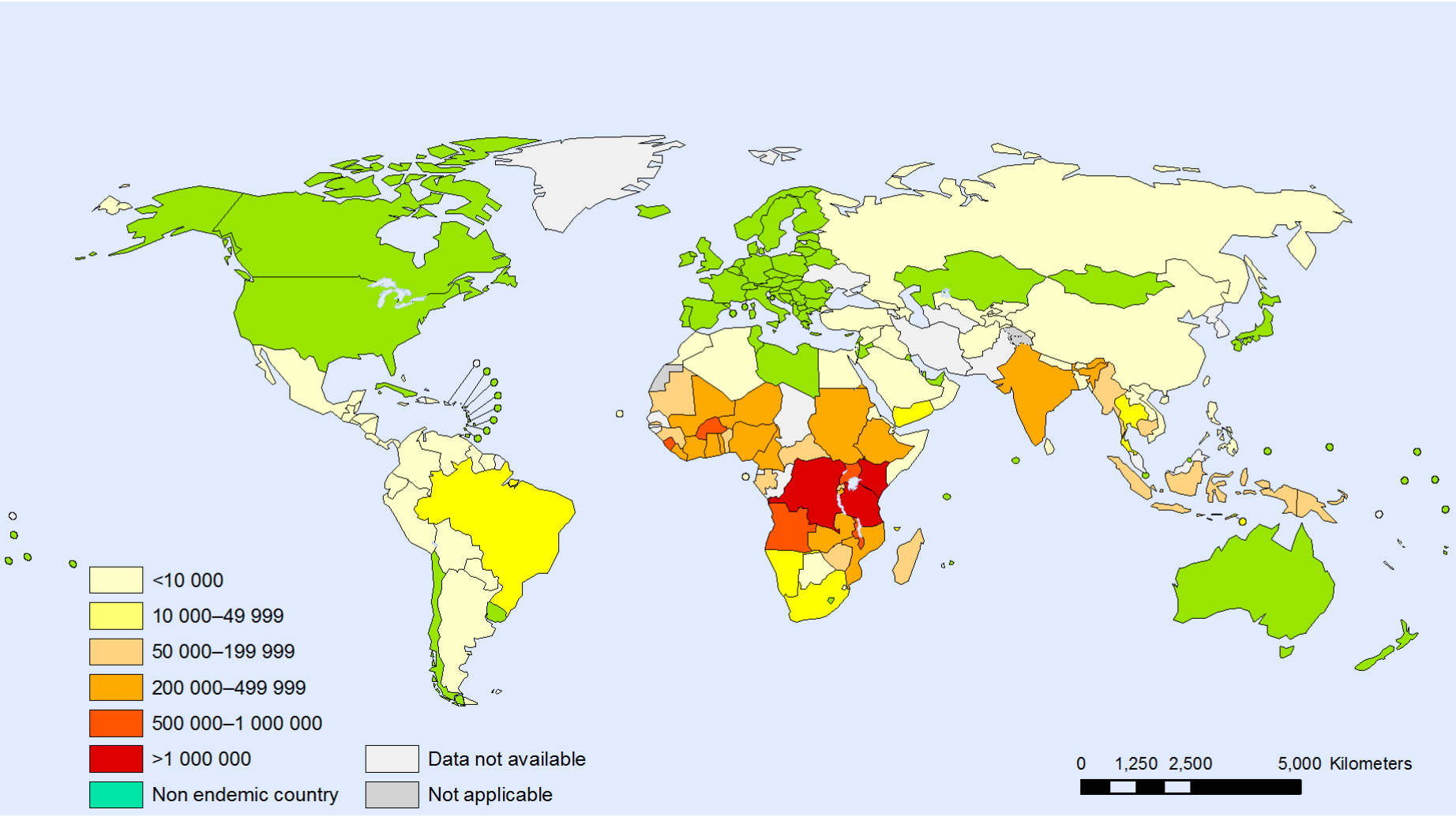
Imperial College London

BARRIERS TO EFFECTIVENESS: ARTEMISININ COMBINATION THERAPIES (ACTS) AND THE HEALTH SYSTEM

Bhargavi Rao

Malaria: global epidemiology

Number of malaria reported deaths, 2010



Malaria and prospects for control/elimination

- Treatable and preventable: but delays in treatment can lead to severe disease and death
  - Mean duration between the onset of symptoms and development of severe complications: 1.8 days
- Initial “vertical” eradication programmes during late 1950s collapsed within 20 years
- October 2007: Bill and Melinda Gates Foundation called for a shift of strategy from malaria control to a new goal of global eradication
- Malaria = not vaccine preventable - so requires integration into a health system to maintain reductions in disease and transmission.

The role of Artemisinin Combination Therapies: ACT

- ACT effects on gametocytaemia and onward infectiousness (transmission)
  - Bousema (2011) : Duration of gametocyte carriage was 55 days with non-ACT (95% CI 28.7 - 107.7) compared with 13.4 days (95% CI 10.2-17.5) following ACT
- Use of ACT for transmission control
  - Evidence for the impact of ACT on transmission from areas where ACT has been deployed as first-line therapy: Zambia, KZN, Ethiopia, Zanzibar, Thailand
  - Zambia: decreases of over 60% in deaths and 90% in severe malaria cases

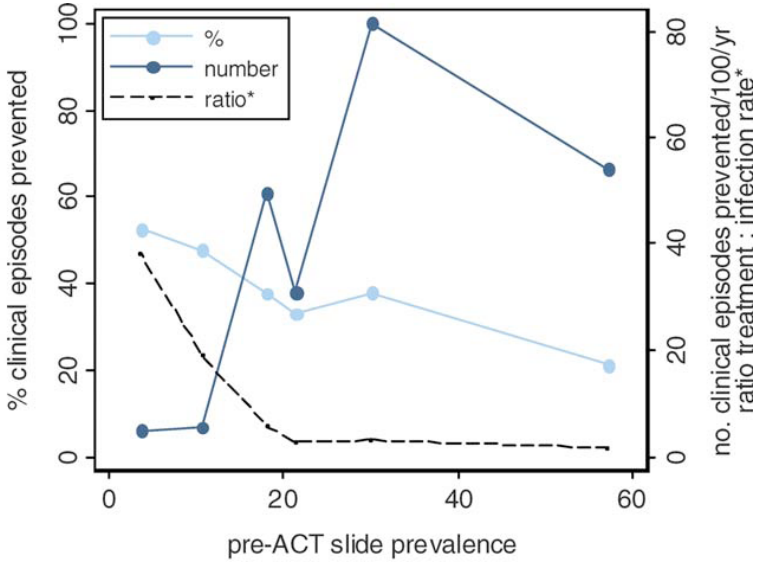
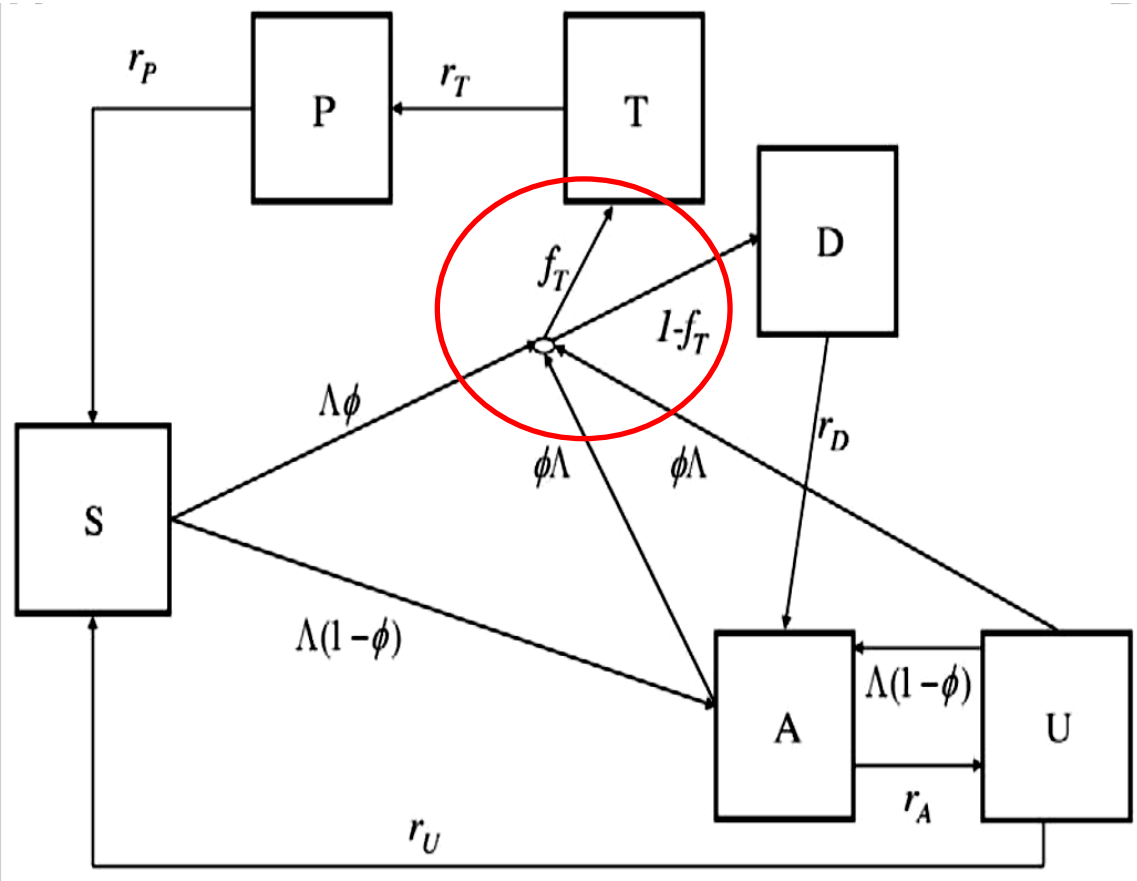


Figure: Okell (2008): predicted reductions in prevalence of infection and incidence of clinical episodes with widespread ACT use in 6 transmission settings in Tanzania



Need to understand how to deliver proven interventions such as ACTs (Artemisinin Combination Therapies)

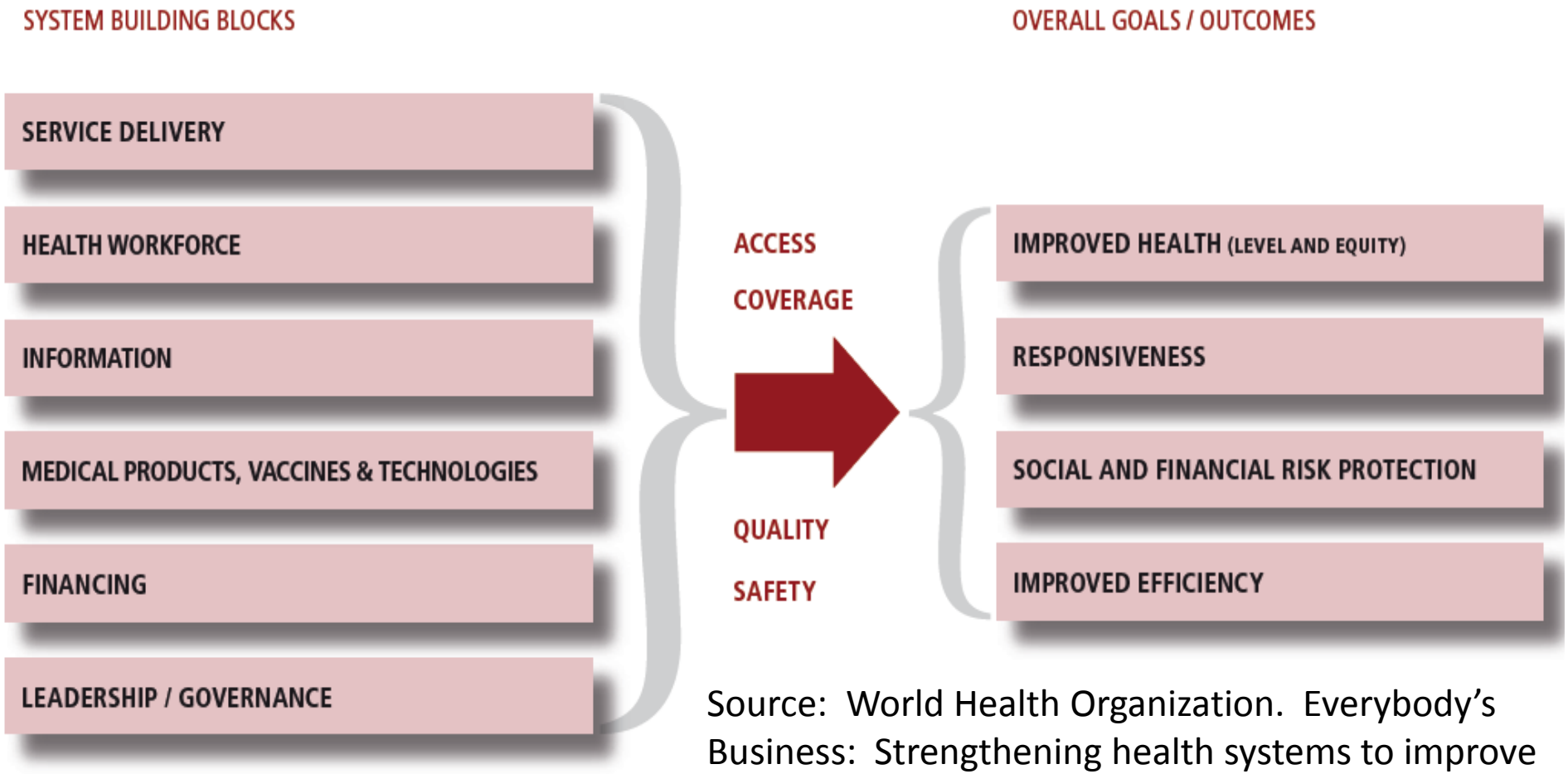
- **at the required levels of coverage and quality,**
- **most effectively through an existing system, and**
- **where the barriers are to achieving its predicted potential**

What is a health system …?

WHO Definitions ….

- A health system is…the sum of all organizations, institutions and resources whose primary purpose is to improve health (WHO)
- Consist of all the people and actions whose primary purpose is to improve health …. They have contributed enormously to better health but their contribution could be greater still – especially for the poor. Failure is more due to systemic failings than technical limitations (Global Fund)
- Health Systems Strengthening (HSS) is defined as…. building capacity in critical components of health systems to achieve more equitable and sustained improvements across health services and health outcomes (WHO)

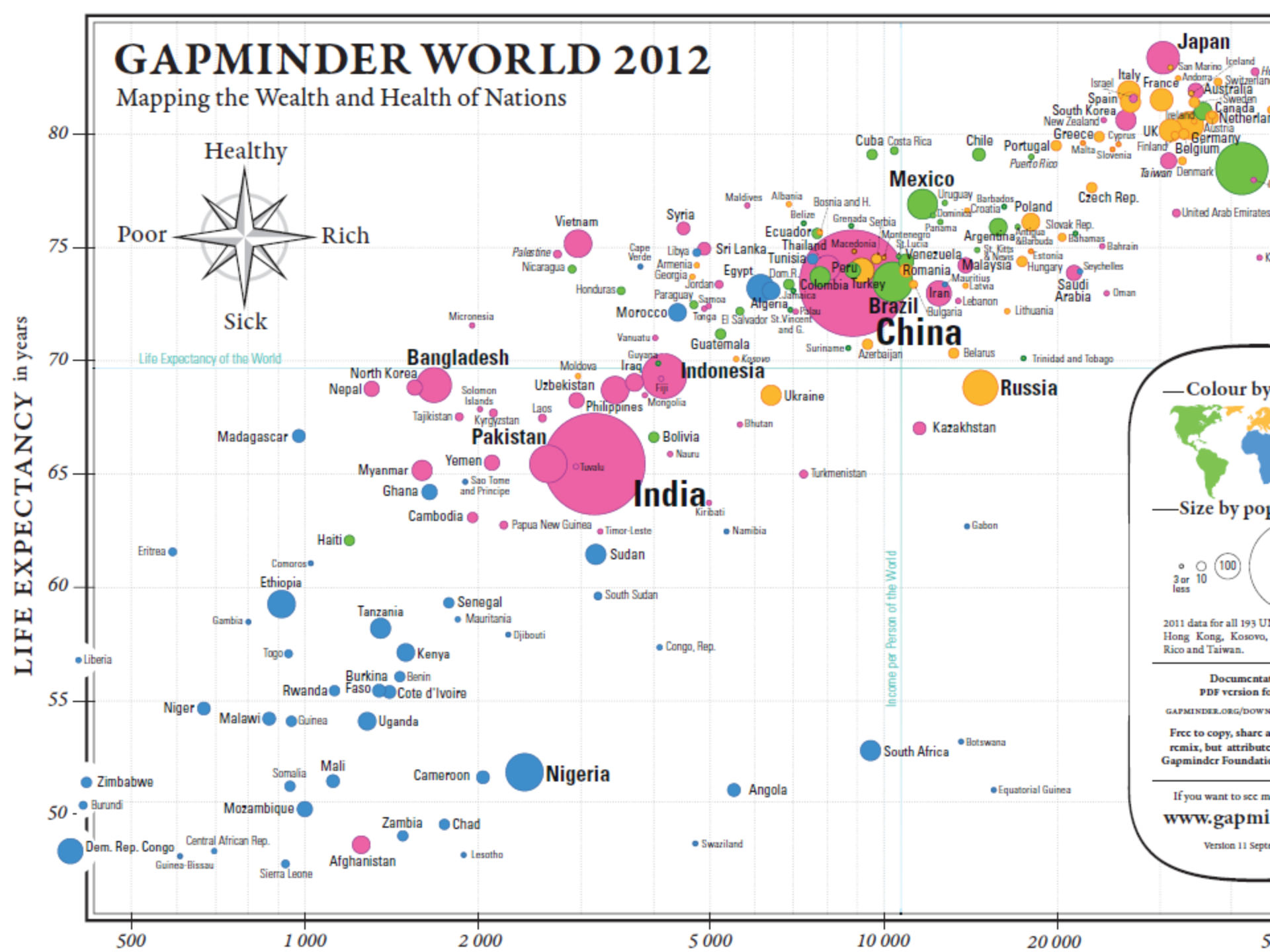
WHO: Six Building Blocks of the health system and link to health outcomes



Source: World Health Organization. Everybody's Business: Strengthening health systems to improve health outcomes—WHO's Framework for Action. Geneva: WHO, 2007, page 3.

The conundrum of health systems

- Erosion of primary health care systems throughout Africa
- Health system factors believed to limit large-scale use of 1st line drugs e.g. ACTs
- "…consensus …health systems too fragile and fragmented to deliver the volume and quality of services…" *Lancet 2004*


GAPMINDER WORLD 2012
Mapping the Wealth and Health of Nations
Healthy
Poor
Rich
Sick
Life Expectancy of the World
LIFE EXPECTANCY in years
80
75
70
65
60
55
50
Income per Person of the World
500
1 000
2 000
5 000
10 000
20 000
Japan
Italy
France
Spain
South Korea
Greece
UK
Germany
Australia
Canada
Mexico
Chile
Cuba
Portugal
Belgium
Czech Rep.
Poland
Argentina
Venezuela
Romania
Malaysia
Hungary
Saudi Arabia
Brazil
China
Iran
Colombia
Peru
Turkey
Ecuador
Thailand
Tunisia
Algeria
Egypt
Morocco
Syria
Vietnam
Sri Lanka
Bangladesh
North Korea
Nepal
Indonesia
Iraq
Uzbekistan
Philippines
Pakistan
India
Russia
Ukraine
Kazakhstan
Bolivia
Yemen
Myanmar
Ghana
Madagascar
Cambodia
Haiti
Sudan
Ethiopia
Tanzania
Senegal
Kenya
Uganda
Nigeria
Cameroon
Angola
South Africa
Zimbabwe
Mozambique
Zambia
Chad
Afghanistan
Dem. Rep. Congo
Somalia
Mali
Niger
Malawi
Rwanda
Burkina Faso
Cote d'Ivoire
Togo
Benin
Guinea
Liberia
Eritrea
Comoros
Gambia
Mauritania
Djibouti
Congo, Rep.
Namibia
Gabon
Botswana
Equatorial Guinea
Swaziland
Lesotho
Sierra Leone
Guinea-Bissau
Central African Rep.
Burundi
Papua New Guinea
Timor-Leste
South Sudan
Kiribati
Nauru
Tuvalu
Fiji
Mongolia
Laos
Bhutan
Turkmenistan
Tajikistan
Kyrgyzstan
Solomon Islands
Sao Tome and Principe
Micronesia
Vanuatu
Guyana
Suriname
Azerbaijan
Belarus
Lithuania
Trinidad and Tobago
Kosovo
Moldova
Honduras
Nicaragua
Palestine
Cape Verde
Libya
Armenia
Georgia
Jordan
Paraguay
Samoa
Tonga
El Salvador
St.Vincent and G.
Jamaica
Palau
Dom.R.
Maldives
Albania
Bosnia and H.
Belize
Grenada
Serbia
Panama
Uruguay
Barbados
Croatia
Dominica
Slovak Rep.
Antigua &Barbuda
Bahamas
Bahrain
St. Kitts & Nevis
Estonia
Seychelles
Mauritius
Latvia
Lebanon
Bulgaria
Oman
Cyprus
Malta
Slovenia
Finland
Iceland
Ireland
Austria
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Puerto Rico
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100
2011 data for all 193 UN
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Rico and Taiwan.
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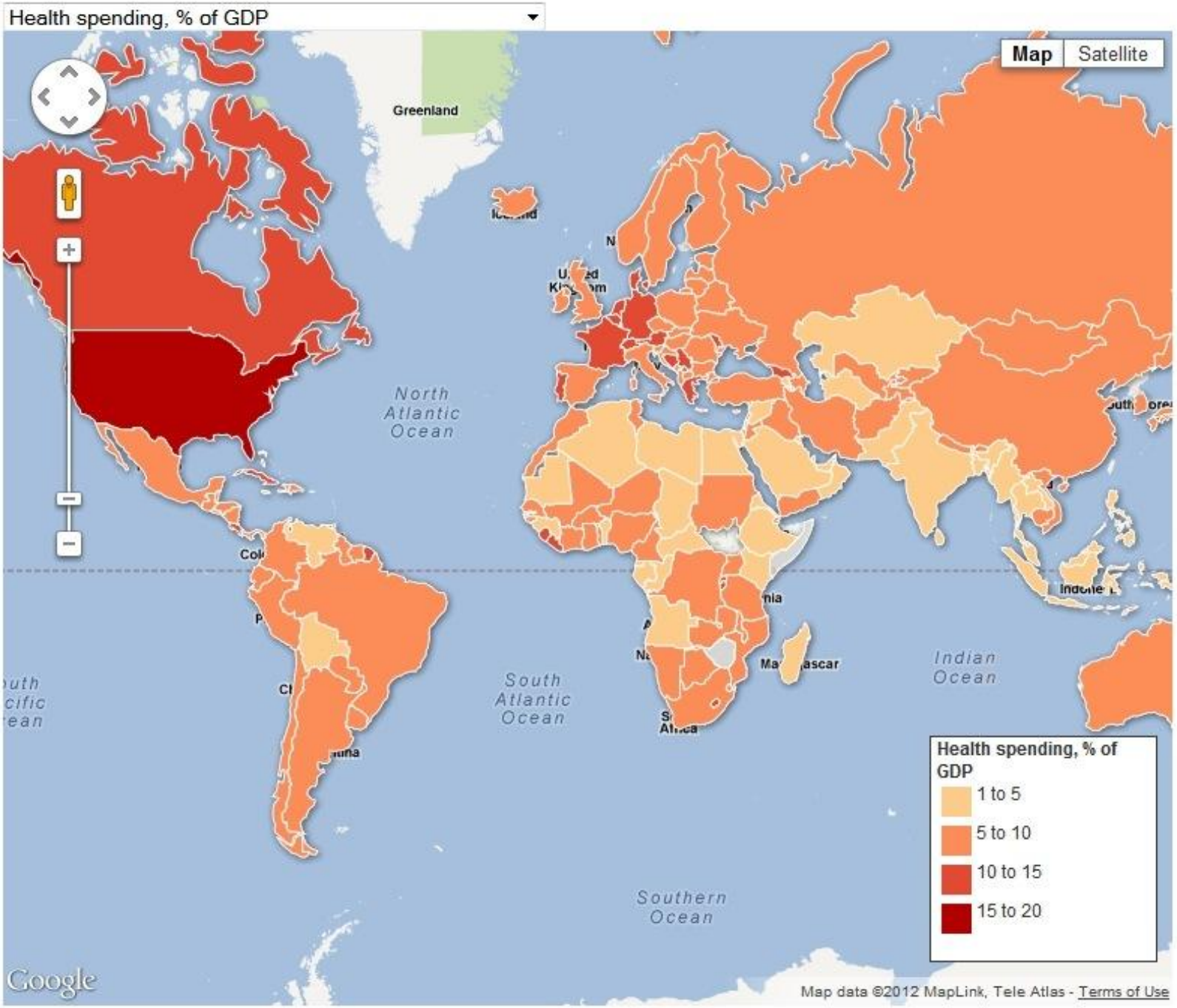
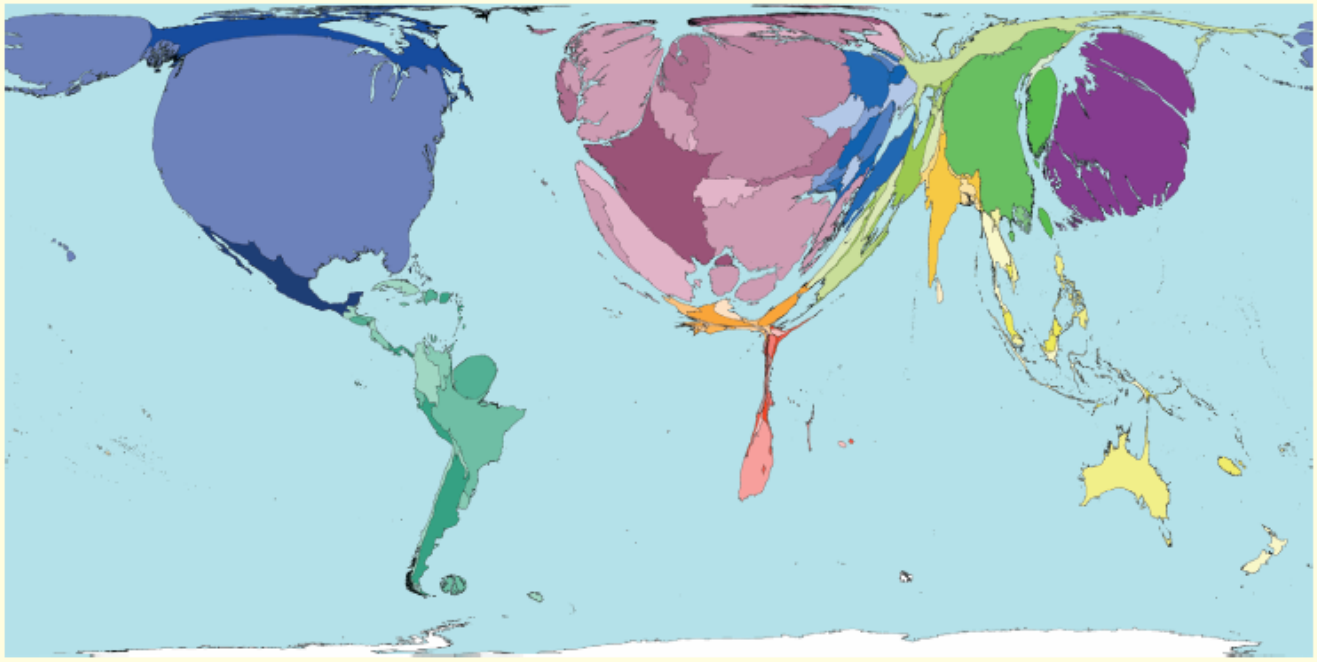

Health spending, % of GDP
Map
Satellite
Greenland
North Atlantic Ocean
South Atlantic Ocean
Indian Ocean
Southern Ocean
Health spending, % of GDP
1 to 5
5 to 10
10 to 15
15 to 20
Google
Map data ©2012 MapLink, Tele Atlas - Terms of Use

Public Health Spending

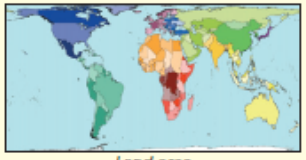
The University Of Sheffield. The Leverhulme Trust Geographical Association
Produced by the SASI group (Sheffield) and Mark Newman (Michigan)



Public health spending is all government spending on health care, plus money from grants, social insurance and non-governmental organisations. Public health spending reduces, or even eliminates, the direct cost of health care to an individual.

The highest public health care spending per person is in the regions of Western Europe, North America and Japan. Luxembourg, Norway and Iceland are the territories with the highest per person spending. As this map of spending is adjusted for purchasing power parity, the size of a territory compares more directly what can actually be funded by this spending. However costs will still vary.

Territory size shows the proportion of worldwide spending on public health services that is spent there. This spending is measured in purchasing power parity.



Land area

Technical notes

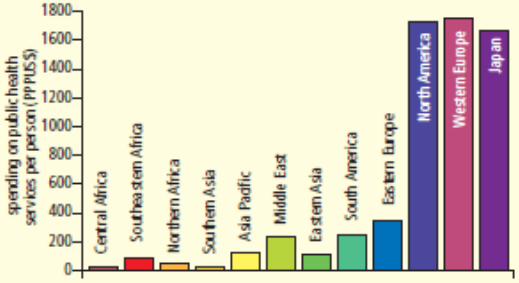
- Data are from the United Nations Development Programme, 2004, Human Development Report.
- Spending is measured in Purchasing Power Parity (PPP) US$. One dollar refers to the purchasing power equivalent of $1 in the United States.
- See website for further information.

MOST AND LEAST PUBLIC HEALTH SPENDING

Rank	Territory	Value	Rank	Territory	Value
1	Luxembourg	3304	191	Burundi	13
2	Norway	2525	192	Sudan	13
3	Iceland	2261	193	United Republic of Tanzania	12
4	United States	2217	194	Niger	11
5	Germany	2195	195	Ethiopia	11
6	Denmark	2166	196	Tajikistan	10
7	Canada	2005	197	Democratic Republic Congo	10
8	France	1965	198	Madagascar	10
9	Sweden	1954	199	Nigeria	7
10	Switzerland	1891	200	Myanmar	4

*spending in 2001 on public health services per person US$ purchasing power parity**

PUBLIC HEALTH SPENDING



"... I brought my little girl to the health center in my district in the south of Bujumbura. But the nurse wouldn't see us as I didn't have any money to pay for the consultation."

Simeon, 2004

	UK	Uganda
Healthcare spending, % of GDP	9.6	9.0
Government spending on health as % of all health spending	84	22
Private spending on health as % of all health spending	16	78
Per capita total spending on health (PPP int. $)	3,480	124
Nurses and midwives per 10,000 population	101	13
Doctors per 10,000 population	27	1

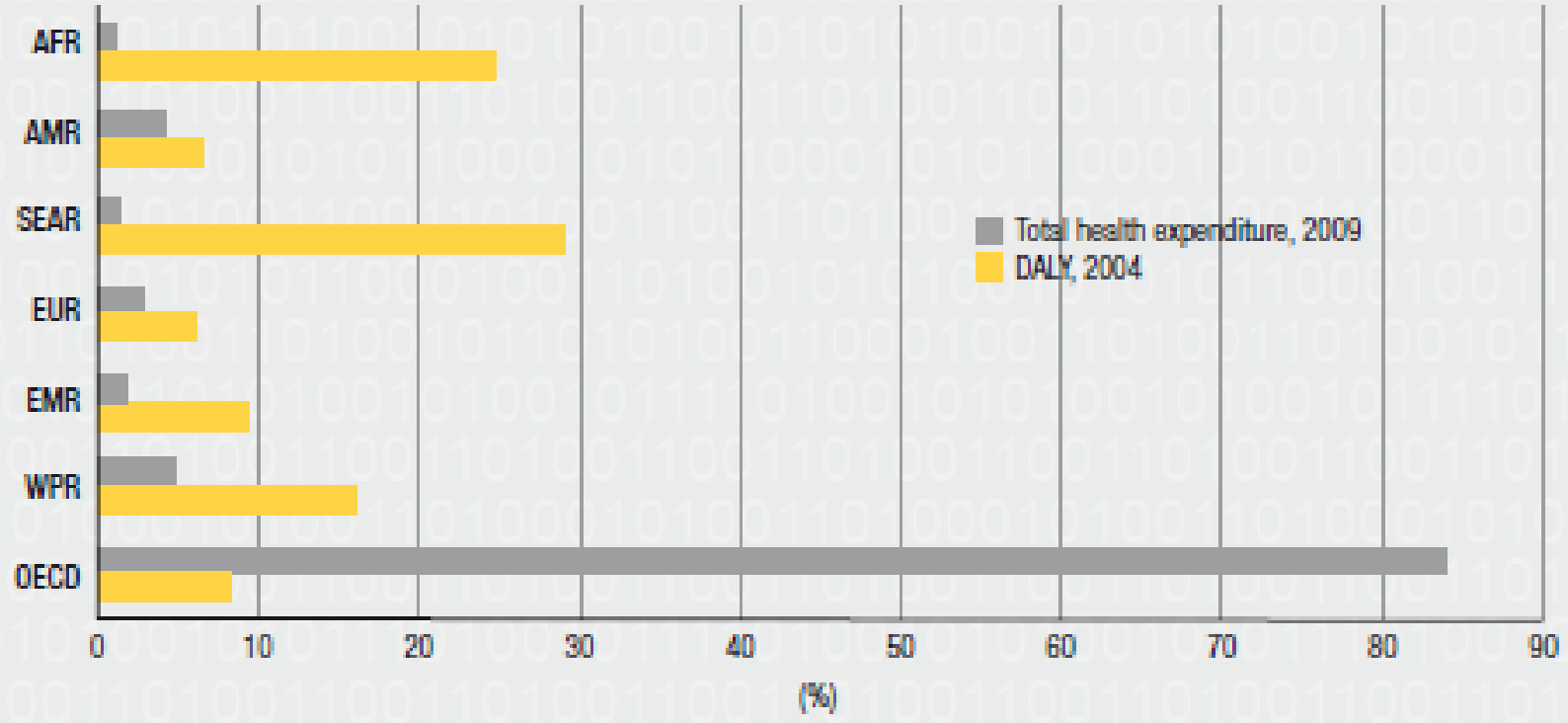
Money for health

The range and quality of health services is largely determined by the money available to improve health in each country. This is influenced by that country's wealth, the proportion of the national budget that it devotes to health and funds from external donors.

Worldwide, the range of money spent on health is extreme: health expenditure from all sources – public, private and external – ranged from US$ 11 per person per year in Eritrea to US$ 8262 per person in Luxembourg. Average per capita expenditures varied substantially from US$ 25 in low-income countries to US$ 4692 in high-income countries. Richer countries with lower disease burden use more health resources than poorer countries with higher disease burden (Figure 5).

The High Level Taskforce on Innovative International Financing for Health Systems suggested that, on average, a low-income country would have to spend a minimum of US$ 44 per capita to ensure all people had access to a set of essential health services focusing largely on HIV, tuberculosis, malaria, and maternal and child health. In 2009, 29 countries spent less than this minimum recommended amount. At this low level, it is not possible to ensure access to even a limited set of health services.

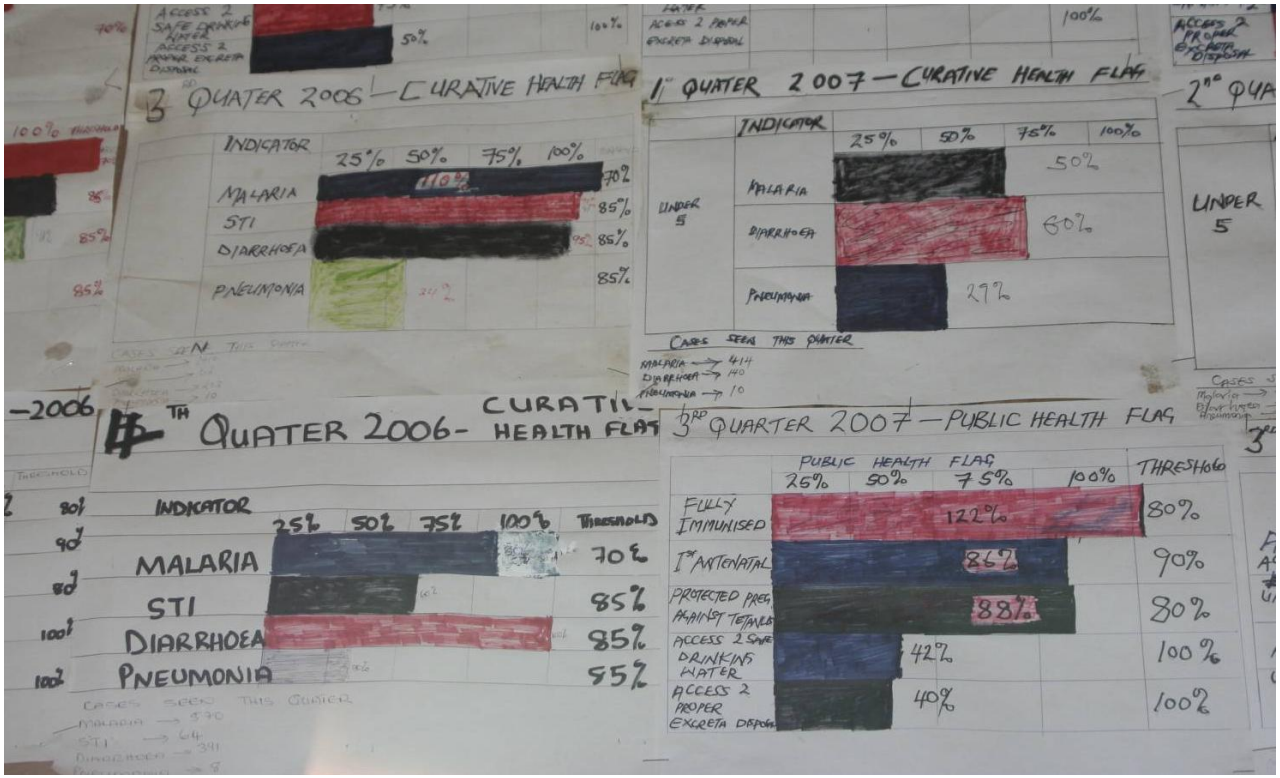
Figure 5. Distribution (%) of disability adjusted life years (DALYs) and total health expenditure per capita (US$) by WHO region* and OECD[c]



Source: National Health Accounts series, World Health Organization (www.who.int/nha).

[c] Organisation for Economic Co-operation and Development (OECD). For this figure, OECD countries are not included in their respective WHO region.

Malaria and Health systems

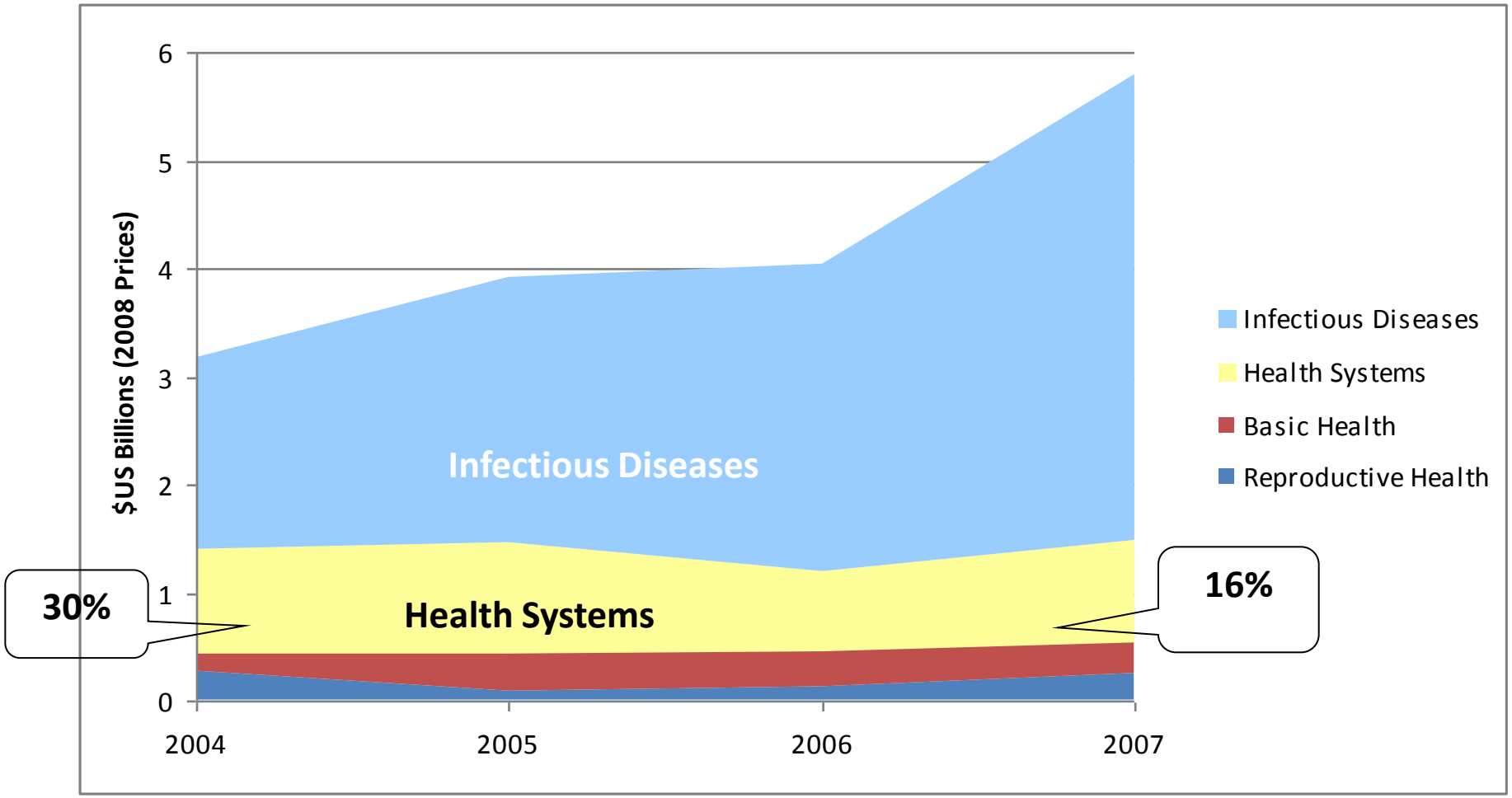


- The challenge of achieving the required rates of drug treatment is complex and remains poorly understood:-
  - Sierra Leone: despite adequate stocks of the recommended drugs for malaria treatment, only 4% of the children with malaria symptoms received appropriate treatment in a timely fashion

Global Attention to Health Systems

As health assistance to Africa has risen, funding for health systems has remained flat

G7 Health ODA to Africa 2004-2007 by sub-category



The Data Report 2009: Monitoring the G8 Promise to Africa. www.one.org.

Research Spending Priorities

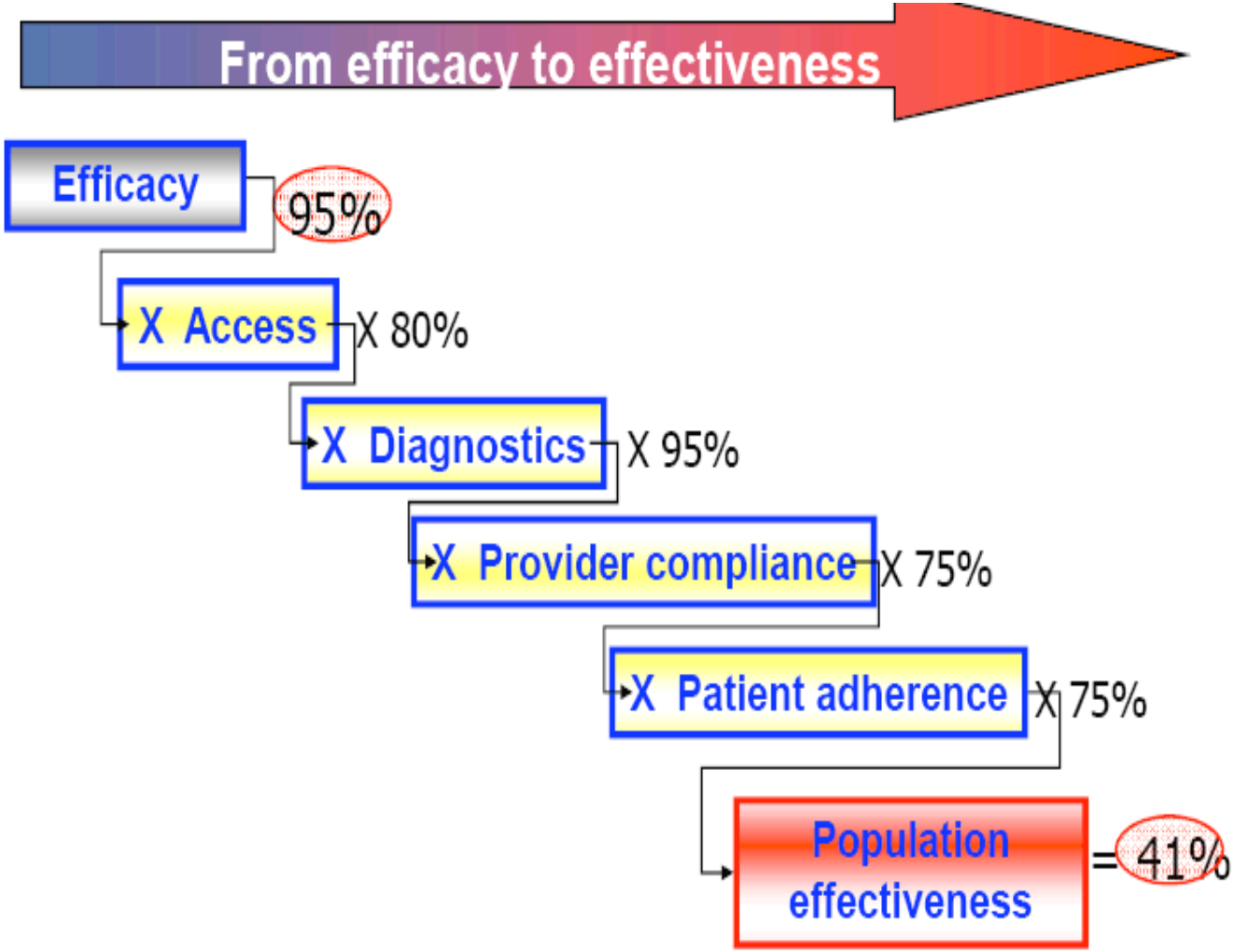
- Spending on product development versus delivery and utilisation
- 97% of grants for developing new technologies
- Potential reductions in child mortality
  - From new technologies: 22%
  - From full utilisation of existing technologies: >60%

Leroy JL et al. Current priorities in health research funding and lack of impact on the number of child deaths per year. Am J Public Health. 2007 Feb;97(2):219-23.

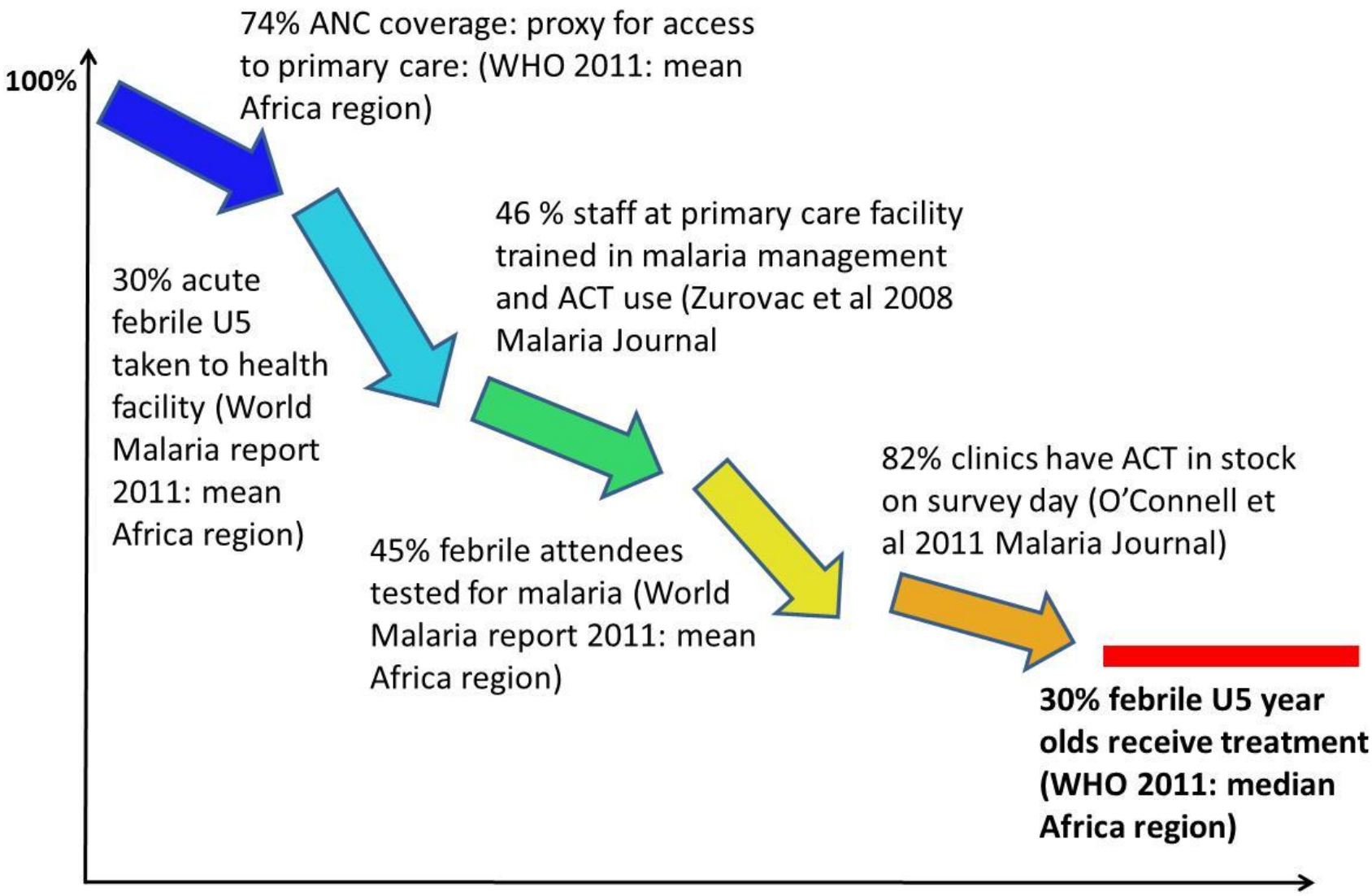
What is needed for treatment ...?

From efficacy to effectiveness: A systems effectiveness framework

(Tanner 1993)



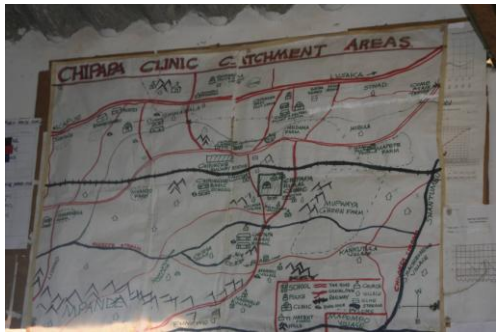
Systems effectiveness framework: ACT treatment



Barriers to effectiveness: Access to healthcare

- Reduction in accessing care with increasing distance to a health facility (13·9%/km - 34%/km): with access declining to low levels (<10%) once the health facility is <5 km from the home (Stock 1983, Feikin 2009)
- Families that live further from primary care facilities wait longer to seek care for their febrile child than those living nearby: two-fold increase in odds of delay if distance to care >3km (Getahun 2010)
- Delay can increase risk of severe disease & death e.g. incidence of hospitalised malaria >2x as travel time to the nearest primary care facility increased from 10 mins to 2 hours in Kenya (O'Meara 2009)
- 2002 Malaria Indicator Survey of Papua New Guinea, the prevalence of infection was significantly lower in communities living within closer reach of a health facility (22·4% vs. 35·6%)

  (Mueller 2005)



Public sector healthcare: barriers to effectiveness

- **Staffing:** 34 facilities surveyed, 10 closed due to staffing: Kenya (Chuma 2010)

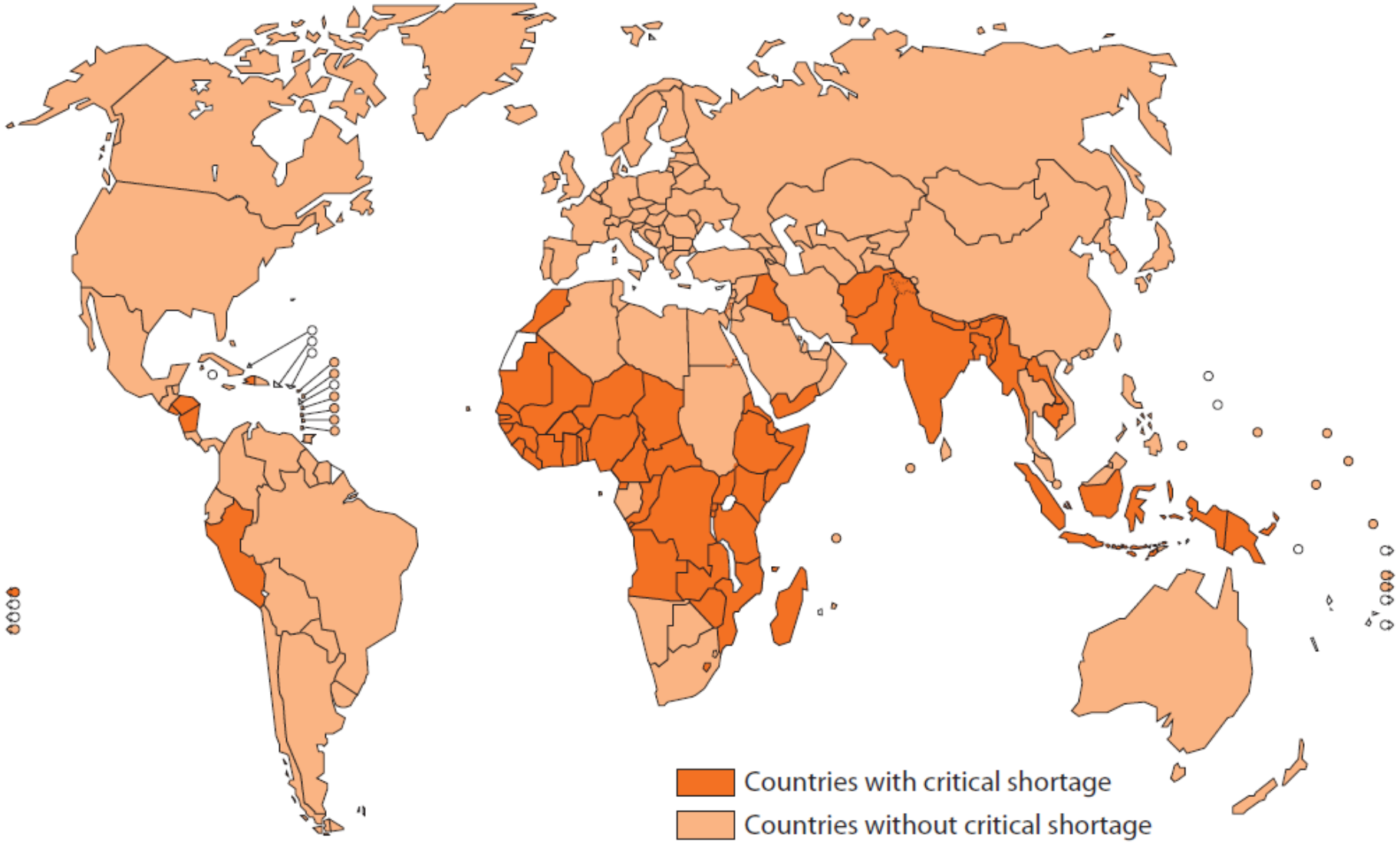
- **Diagnostics**: 25-100% facilities had diagnostic capacity but routine use of testing is limited (median: 35%)

- **Stockouts:** Availability of essential medicines in the public sector: 29·4%
  33%-90% facilities had at least 1 form of ACT in stock (20% had no ACT stock)

- **Prescribing:** Over-prescription of antimalarials (47% - 95% of NMFI): often with non-recommended antimalarials, although 6-63.7% untested or test negative receive first line ACTs

(Zurovac, O'Connell 2011, Nyandigisi 2011, Nankabirwa 2009, Bastiaens 2010)

Countries with a critical shortage of health service providers (doctors, nurses and midwives)



Data source: World Health Organization. Global Atlas of the Health Workforce (http://www.who.int/globalatlas/default.asp).

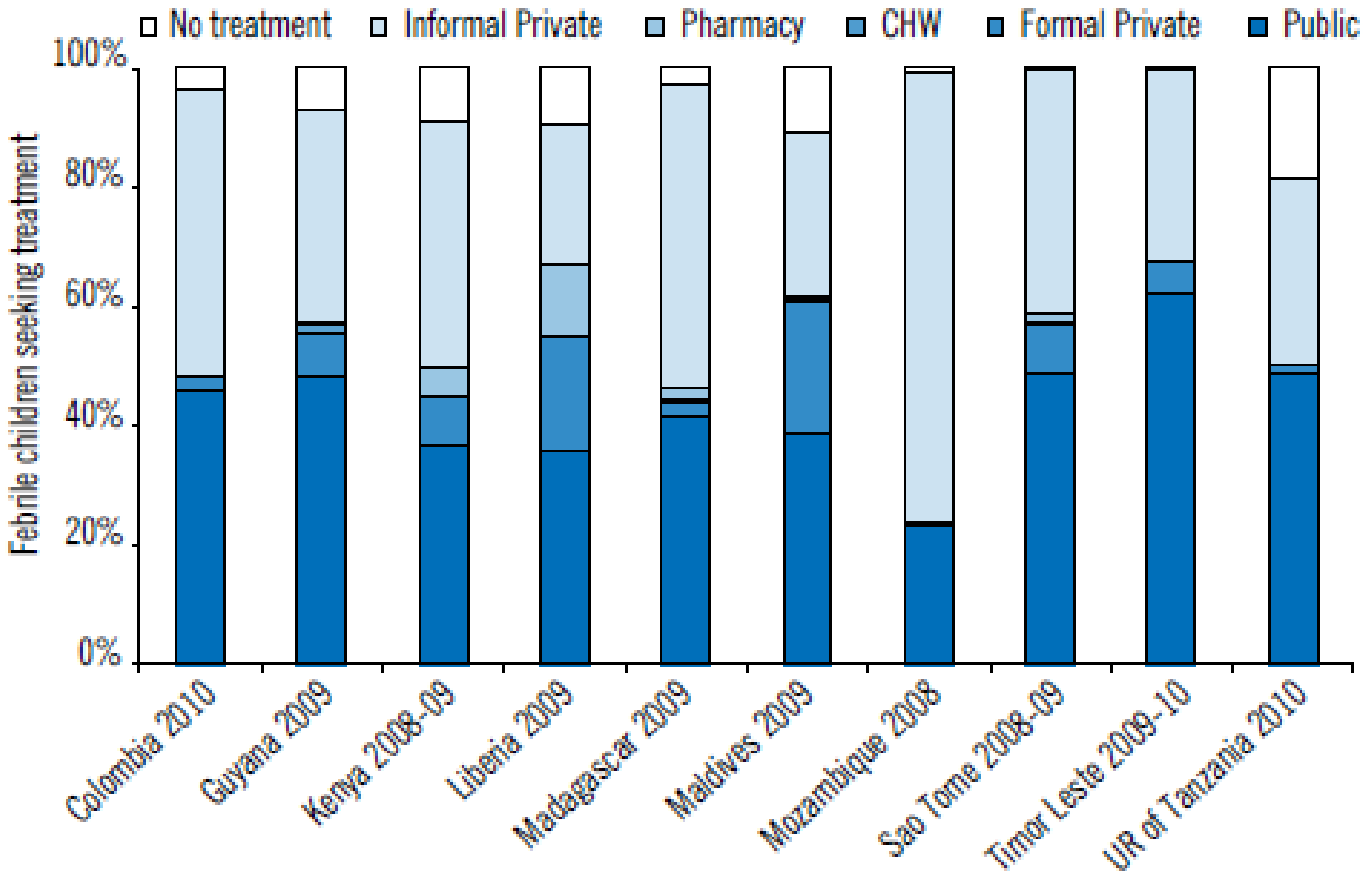
Sources of healthcare

- **Public sector**
  - Health centres
  - Health posts
  - Community health workers

- **Private informal sector**
  - Small drug shops
  - Local general stores/kiosks
  - Itinerant drug sellers

- **“Tertiary” level**
  - Hospitals or higher level clinics
  - In patient facilities

Figure 6.6 Proportion of febrile children seeking treatment from different sources, 2008–2010



Source: Household survey data

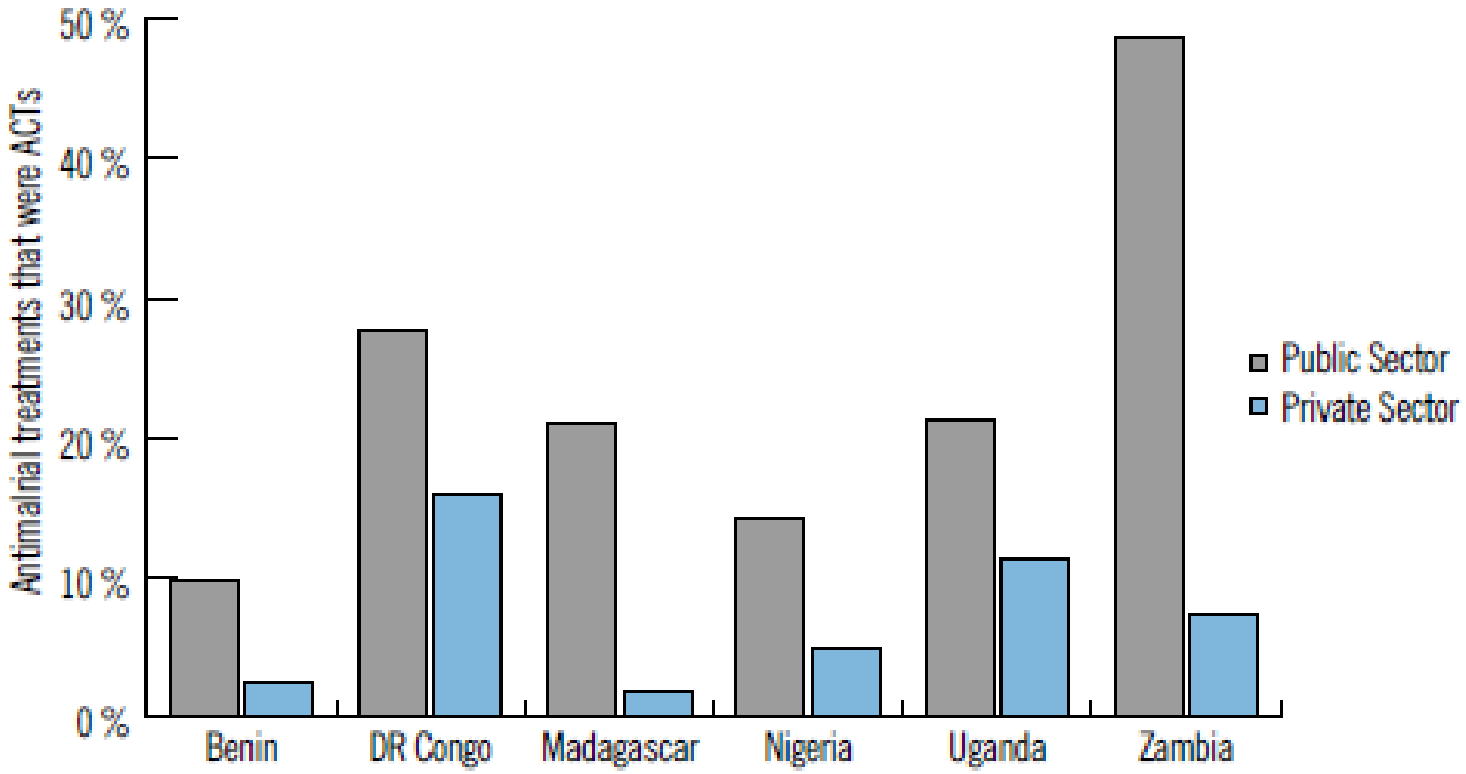
World Malaria Report 2011

Barriers to effectiveness: Private informal sector

- Education and training: often illiterate and untrained
  - Somalia: 53% of private sector facilities surveyed still prescribed chloroquine as a first-line treatment (Noor 2009)
- Poor quality case management: drugs are prescribed, often incorrectly, or over prescribed presumptively on the basis of fever
- Poor quality drugs: poor availability of ACT
  - DRC - 42% traders maintained stocks of artemisinin monotherapy
- Lack of regulation and expense:
  - ACTs are 4 – 22 times more expensive than the most commonly dispensed antimalarial (non ACT)
- Perverse incentives: if diagnostics are used to confirm the diagnosis, sellers lose their profit

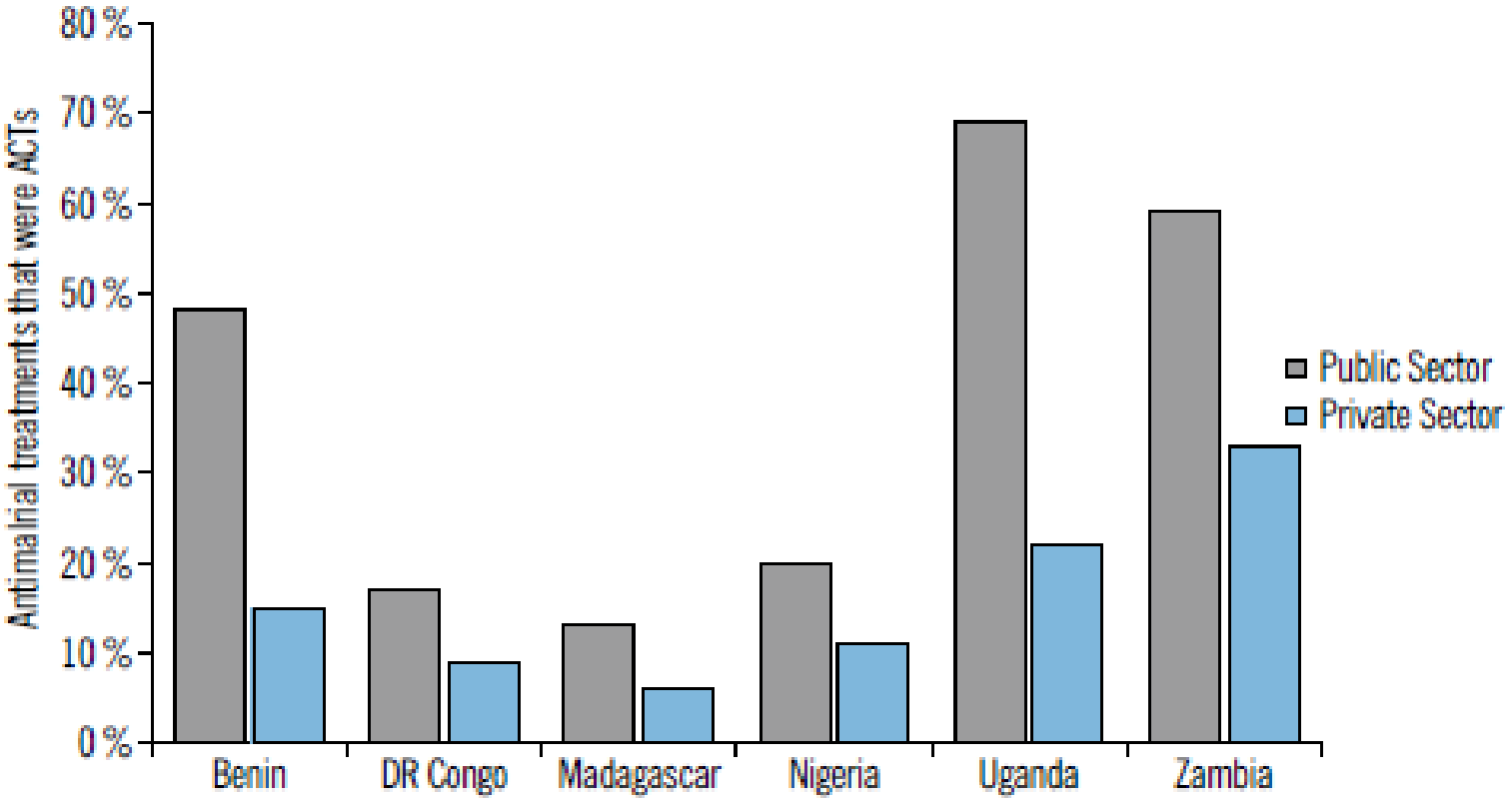
(O'Connell 2011, Littrell 2011, AMFm 2012)

Figure 6.8 Proportion of children under 5 with fever receiving a blood test for malaria



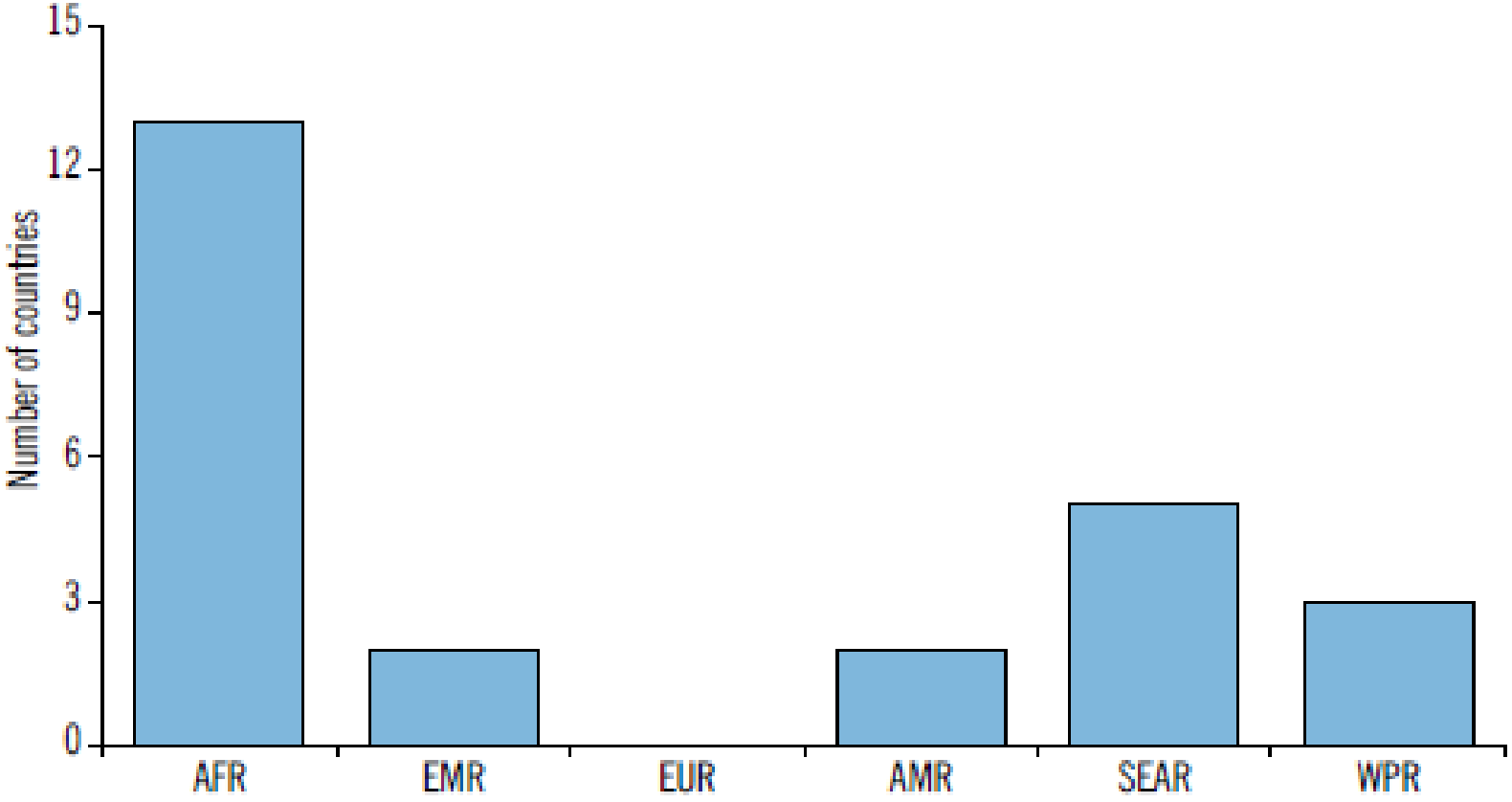
Source: adapted from Littrell, M., et al. Monitoring fever treatment behavior and equitable access to effective medicines in the context of initiatives to improve ACT access: baseline results and implications for programming in six African countries. Malaria Journal, *2011, 10:327.*

Figure 6.13 Proportion of ACTs among antimalarial treatments given to febrile children, by sector



Source: adapted from Littrell, M., et al. Monitoring fever treatment behavior and equitable access to effective medicines in the context of initiatives to improve ACT access: baseline results and implications for programming in six African countries. Malaria Journal, 2011, 10:327.

Figure 6.14 Number of countries allowing marketing of oral artemisinin-based monotherapies, by WHO Region



Source: http://www.who.int/malaria/monotherapy_NDRAs.pdf

Public Sector: improving quality of care

- The widely accepted belief is that improving case management does impact on clinical outcomes and levels of disease: very limited evidence

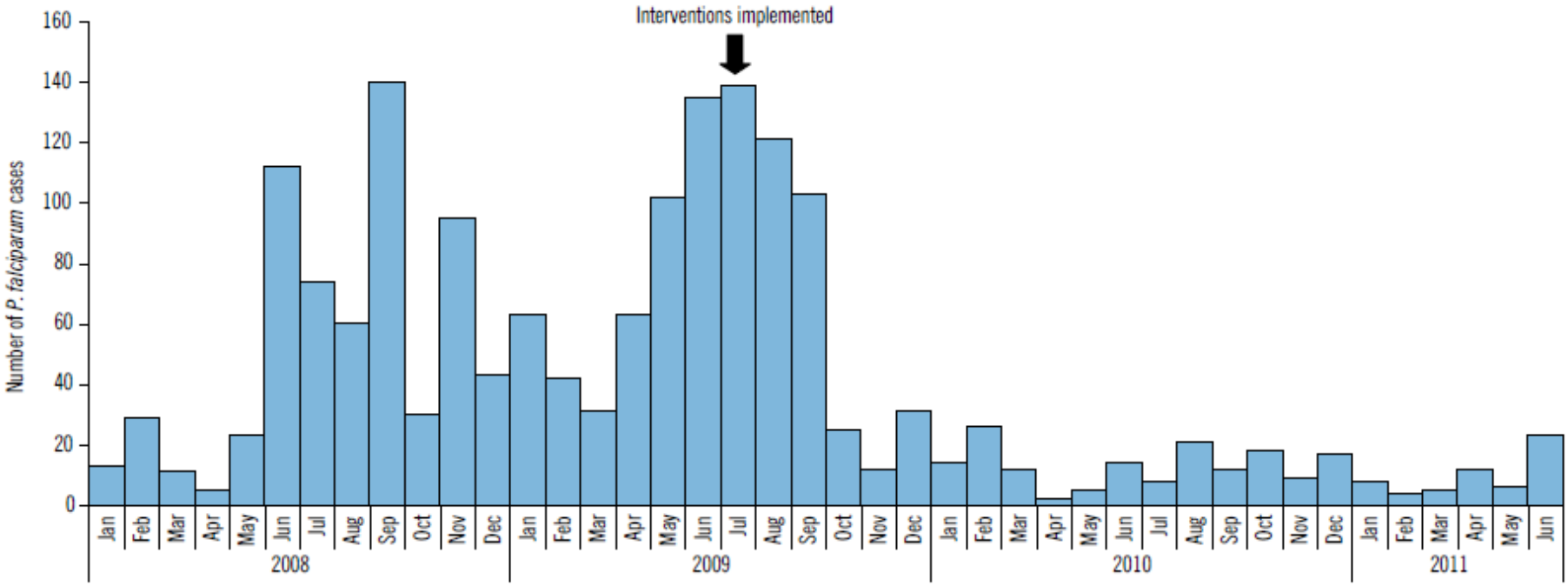
- **Stockouts:**
  - World Bank impact evaluation study in Zambia (2010): estimated that scaling up a well-designed supply chain could reduce child malaria deaths by 37%.
  - SMS potential for stock keeping (Barrington 2011, Asiimwe 2010)
  - Alba (2010): introduction of subsidised AL in health facilities was associated with a decrease in the level of stockouts (drug present > 80%) and an increase in the levels of treatment seeking amongst adults

- **Training:**
  - Systematic reviews of public sector training interventions: not to have much impact and practice deteriorates within a period of 12 months (Smith 2009, Zurovac, Wasunna 2010, Skarbinski 2009)

Public Sector: improving quality of care

- Universal rational case management **:** 2010 WHO guidelines on the treatment of malaria state that whenever possible 'prompt parasitological confirmation by microscopy or alternatively by rapid diagnostic test (RDTs) is recommended in all patients suspected of malaria before treatment is started'.
- Withholding antimalarials in test negative does not result in increased malaria-related deaths or severe morbidity, even in U5s (Mtove 2011, D'Acremont 2010)
- Management of test-negative cases improved: substantial decreases in antimalarial prescription and increases in prescription of antibiotics (Bastiaens 2011, Ansah 2010)
- The cost implication of adding RDTs has been of concern although several studies show little difference compared to clinical diagnosis (Msellem 2009, Mosha 2010, Batwala 2011)
- BUT - Testing levels remain low despite stock and guidelines.
- Cambodia shows promise of what is potentially achievable

Figure Box 6.5 *P. falciparum* cases diagnosed by microscopy and RDT at health facilities in Pailin province, by month 2008–2011



Source: National Malaria Center Cambodia

Improving access to healthcare: CHWs

- Potential role for CHWs has been particularly highlighted by the work of Gomes (2009): pre-referral rectal artesunate for severe malaria.
  - Benefit limited those who had a delay of greater than 6 hours in seeking care (risk ratio: 0.49, 95% confidence interval 0.32 to 0.77)
- CHWs can administer RDT-led care e.g. Zambia - four fold reduction in treatment with ACTs (27.5% vs. 99.1%), and no presumptive malaria treatment in the intervention group (Yeboah-Antwi 2010)
  - Increased treatment seeking (Yeboah Antwi 2010, Elmardi 2009)
  - No progression to severe disease (Lemma 2010, Mubi 2011)
  - Upto 96% adherence to test results (Mubi 2011)
- Reduction: malaria incidence and parasite prevalence - ?causal? (Lemma 2010, Tine 2011)
- Cost effectiveness: cost per case diagnosed and correctly treated was less by CHW rather than facility-level management (Chanda 2011)

Private Sector: improving quality of care

- Accredited drug dispensing outlets (ADDO) in Tanzania: to improve access to quality treatment in the private sector (Alba 2010)
  - Between 2004 and 2008 access to malaria treatment greatly improved and was associated with a reduction in unregulated drug shops (68% to 9%)
- Affordable Medicines Facility for malaria - to address the price barrier by drastically reducing the price of ACT.
  - Pilot study in Tanzania: a subsidy applied at the top of a private sector supply chain can significantly increase usage of ACTs and reduce their retail price (Sabot 2009)
- Independent evaluation of AMFm (Phase one)
  - dramatic increases in quality assured ACT availability and affordability in almost all pilot sites (except Niger and Madagascar)
  - reductions in availability of artemisinin monotherapy
  - diagnostics stock remained low
- Worry re: urban-rural equity (Smith 2011) and sustainability/training

Figure 6: Percentage of public health facilities and private for-profit outlets with QAACTs in stock at baseline and endline

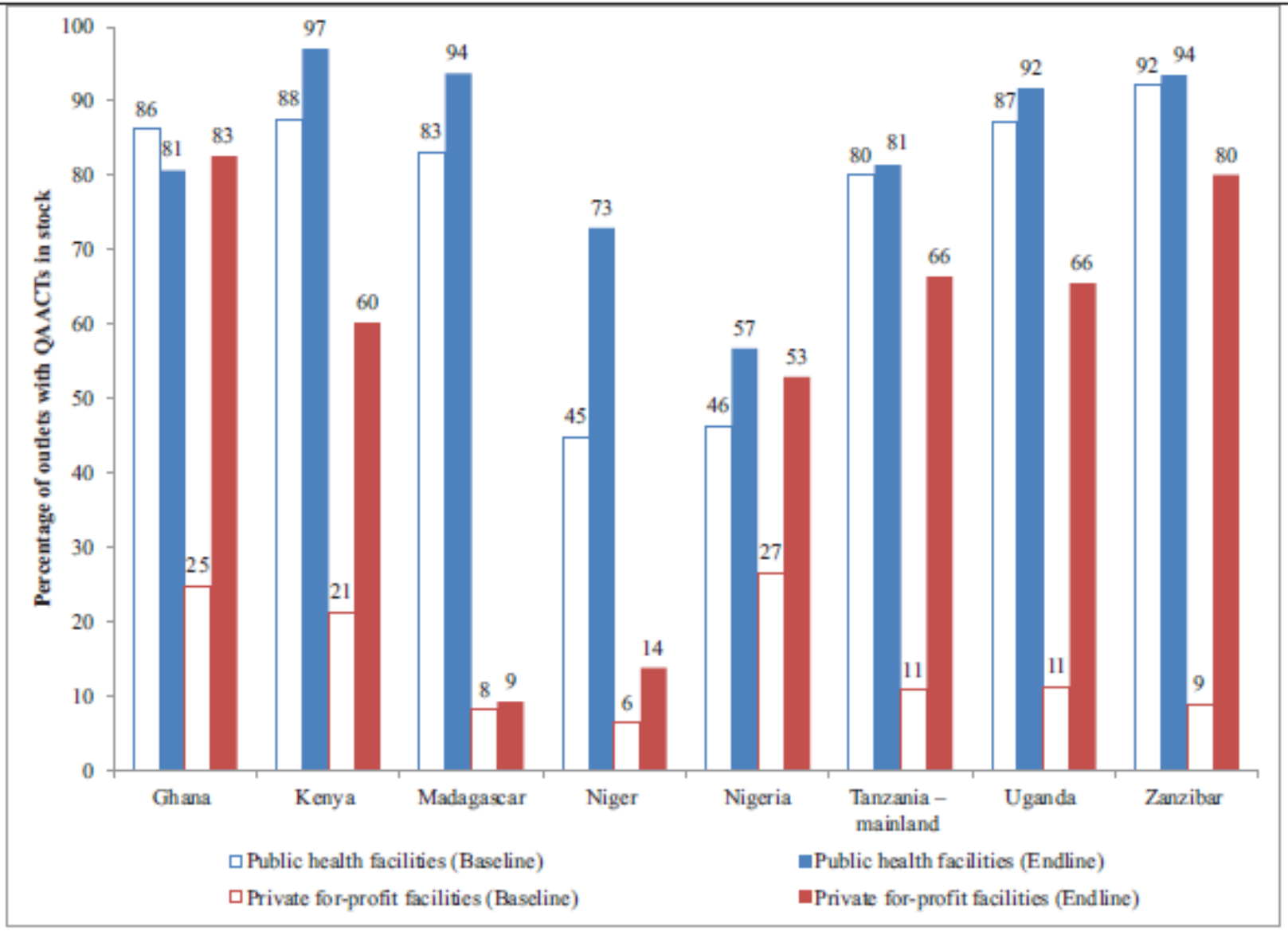


Figure 9: Percentage of outlets with oral AMT and non-artemisinin therapies in stock at baseline and endline

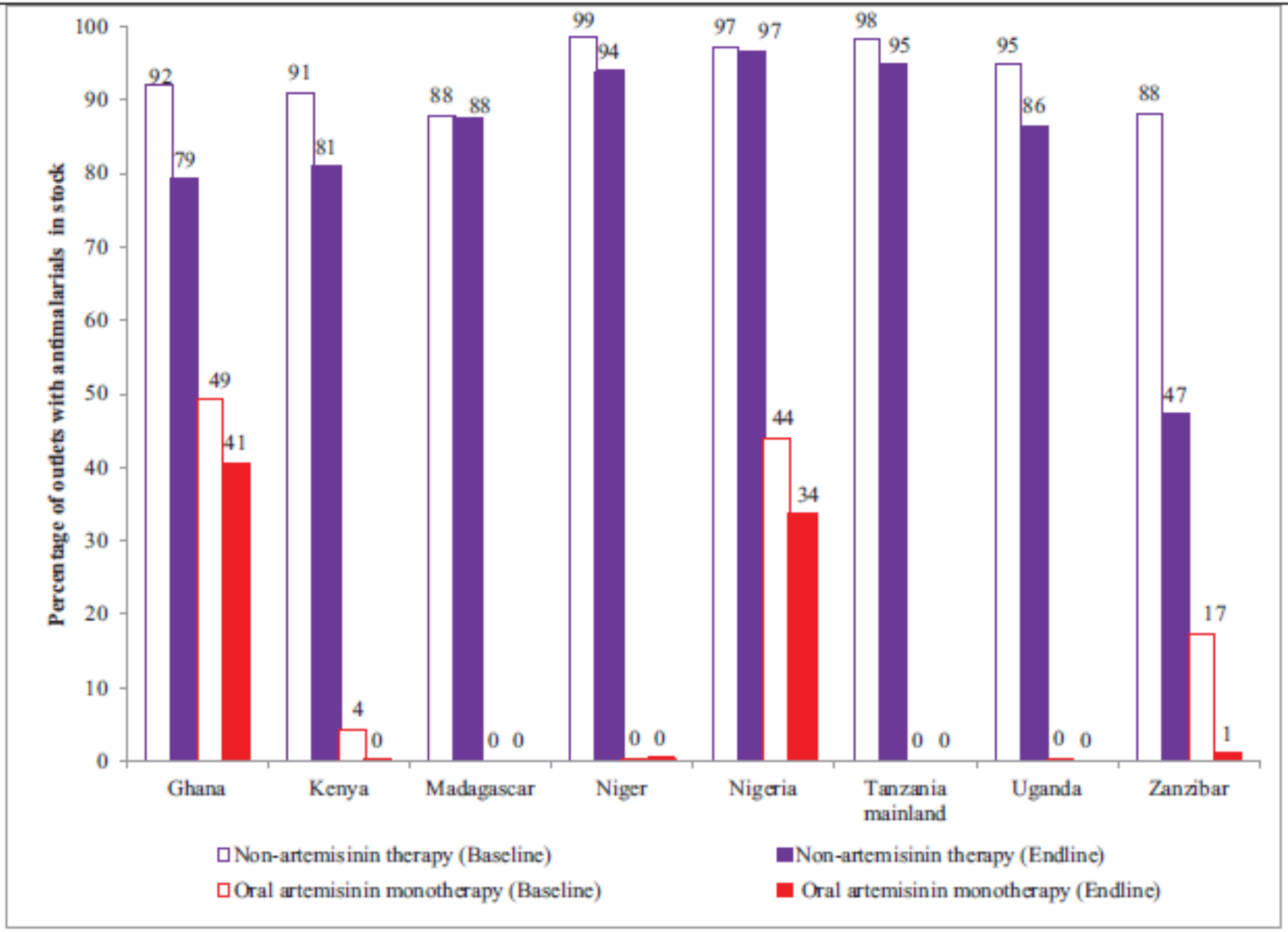


Figure 10. Median cost to patients of one adult equivalent treatment dose (AETD) of QAACTs in public and private for-profit outlets (2010 US dollar equivalent), at baseline and endline

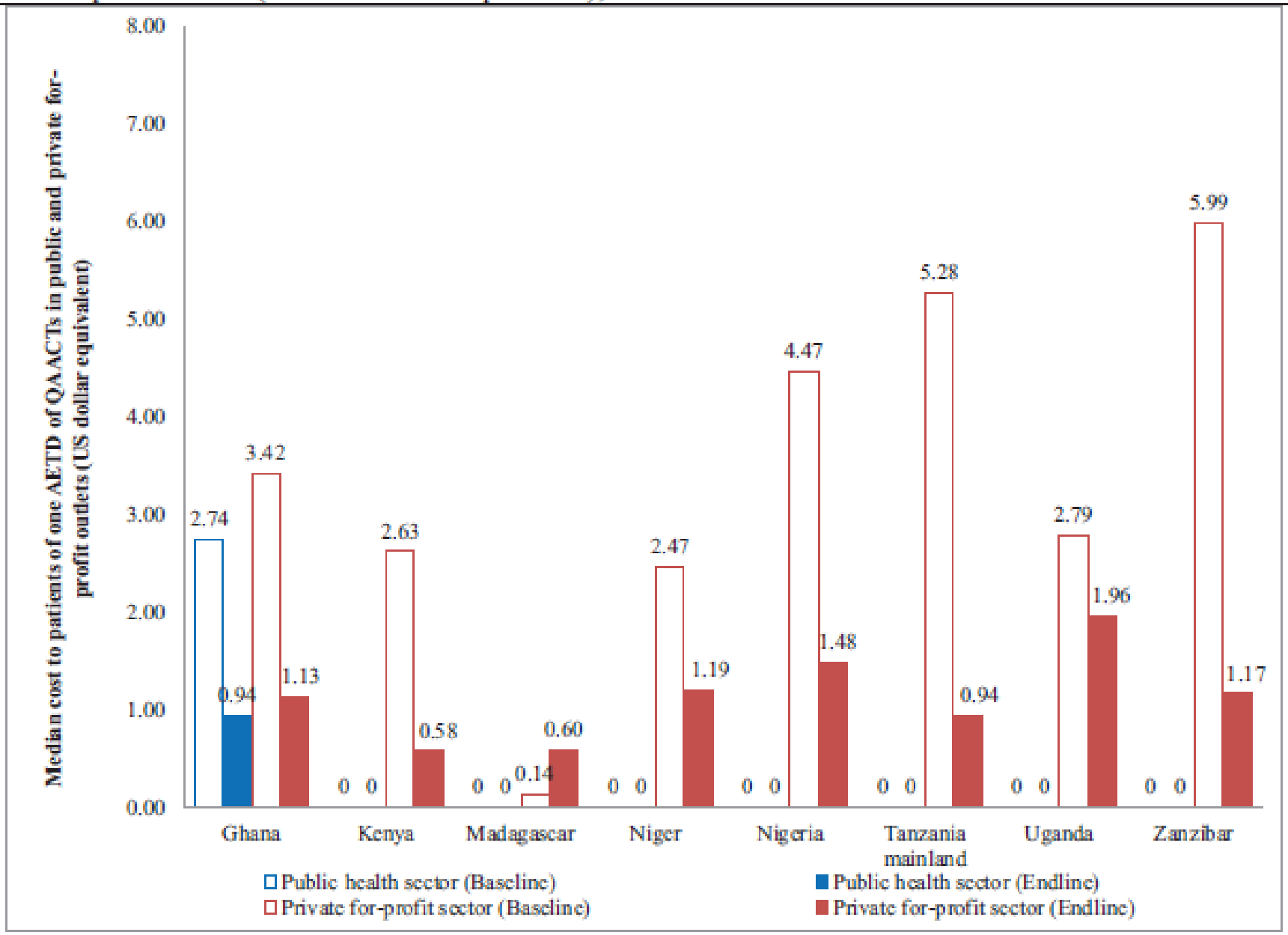
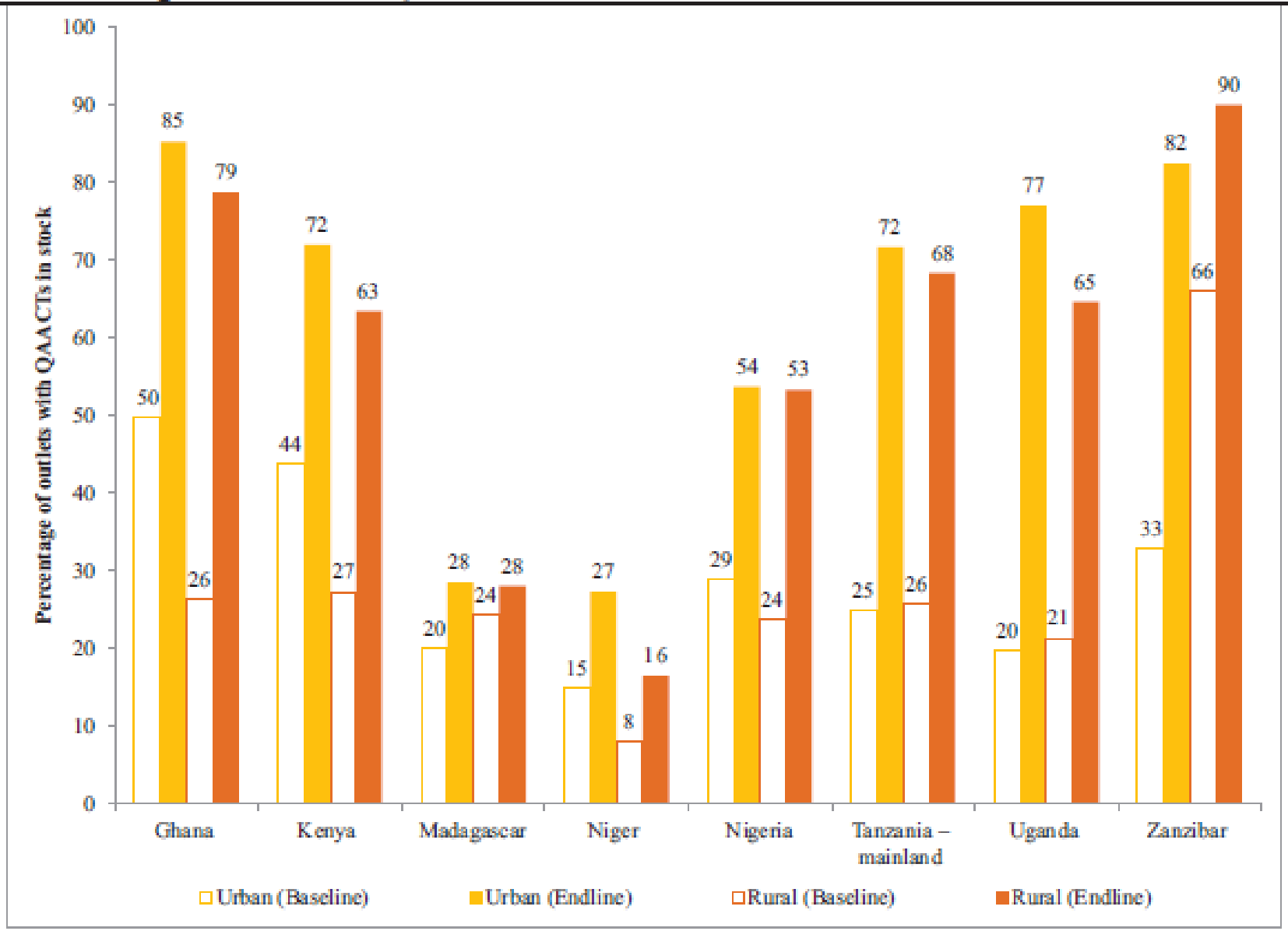
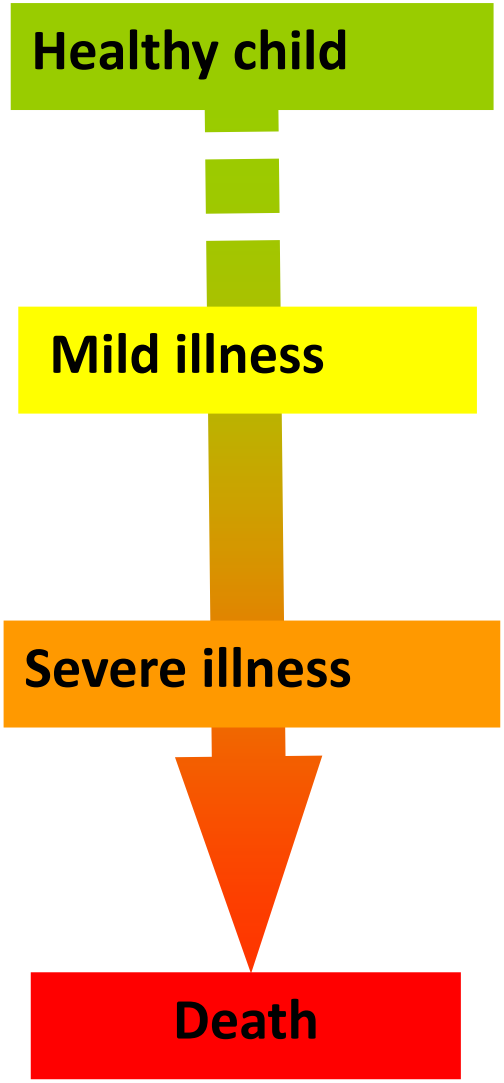


Figure 7: Percentage of outlets with QAACTs in stock in urban and rural areas at baseline and endline



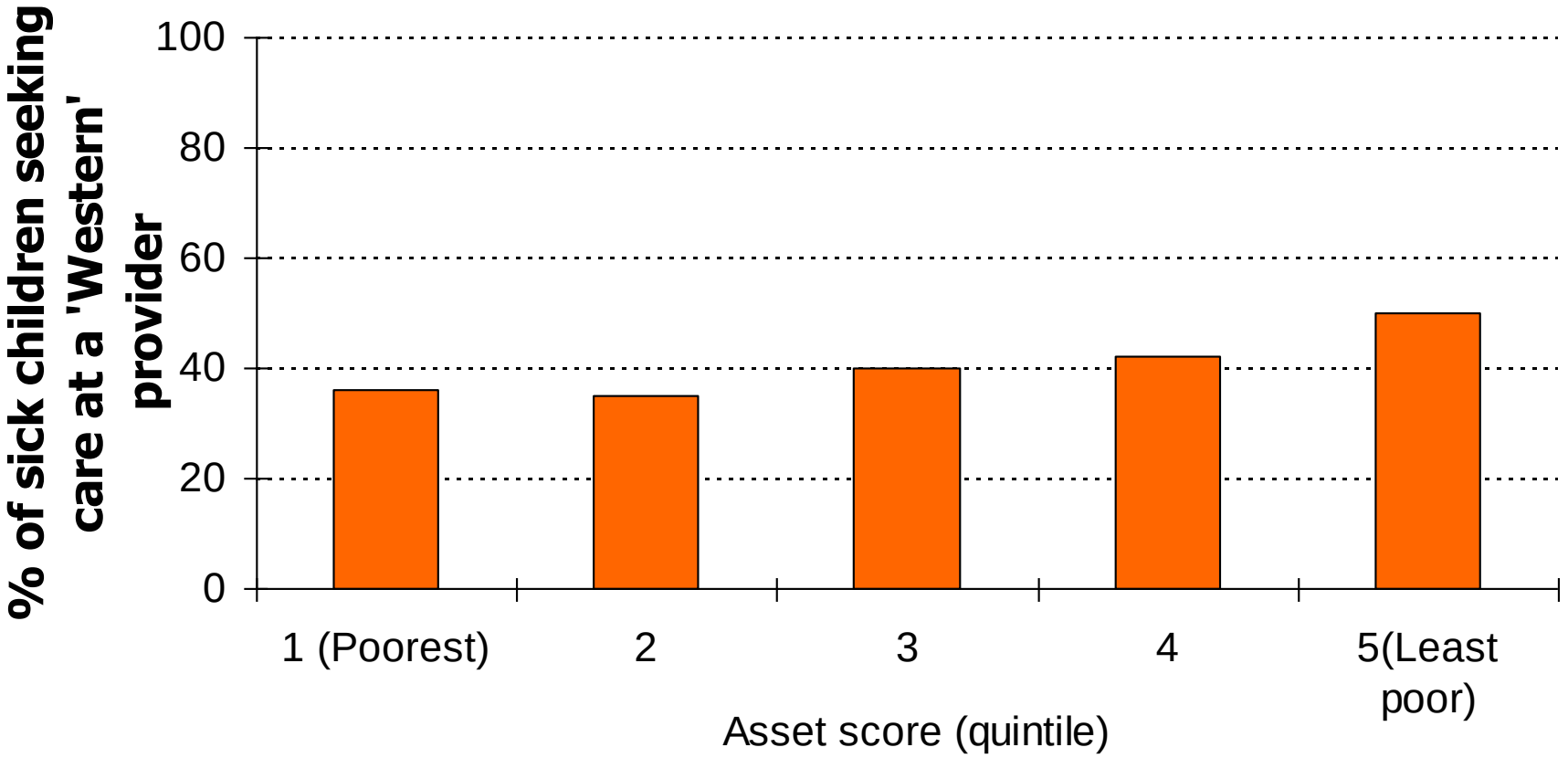
Why is the equity perspective important?



- More likely to be exposed to disease
- Less likely to receive preventive interventions
- More likely to acquire disease
- Lower resistance to disease
- Lower access to health facilities
- Less likely to be managed appropriately in health facilities
- Less likely to get life-saving drugs
- Lower access to secondary and tertiary care

Victora et al Lancet 2003

Inequities in seeking care: any illness in last 2 wks

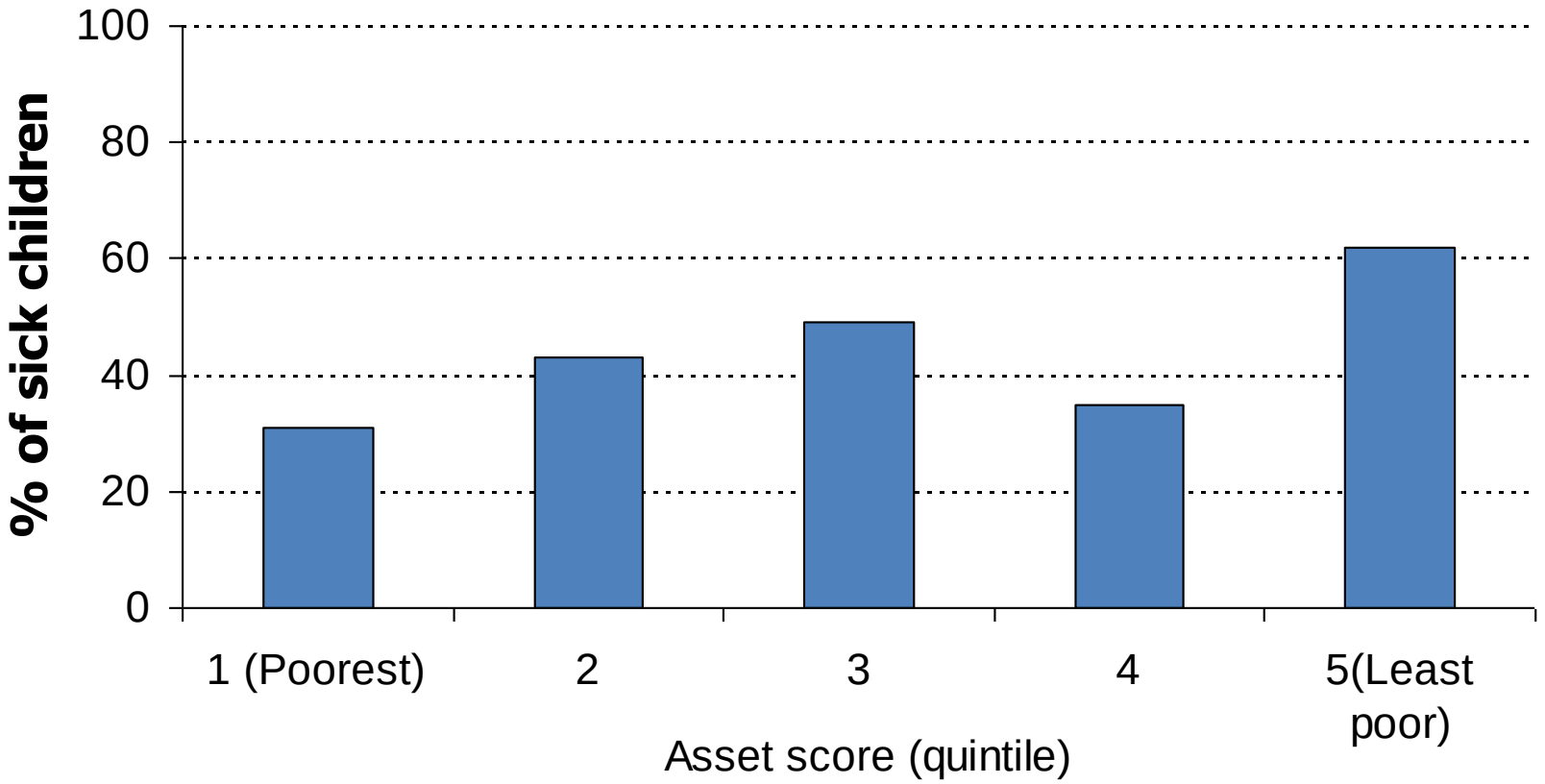


Reaching the poorest:
36% of those who were sick sought & obtained care

Equity:
Poorest/least poor ratio
All-cause care-seeking* - 0.72

* P<0.05

Inequities in antimalarials for fever



Reaching the poorest:
31% received antimalarials

Equity:
Poorest/least poor ratio: 0.5

* P<0.05

Discussion & Future work

- The health system can exert an important effect on the potential impact of an ACT treatment programme.
- Key to reducing malaria mortality is to ensure diagnosis-led, first-line treatment in a timely fashion, before infections progress to severity.
- The relationship between improving delivery through health systems and the resulting impact on health outcomes of infectious diseases is not straightforward.
- Traditional approaches to strengthening the health system such as staff training have had a less sustained impact than hoped
- Novel strategies e.g. the use of mobile phones to ease stockouts, task-shifting to community health workers, and inclusion of the informal sector appear more promising.

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