Southern African Pharmaceutical Regulatory Affairs Association

Malaria: *" threats, breakthroughs and the future"*

Dr Fiyinfolu Oladiran

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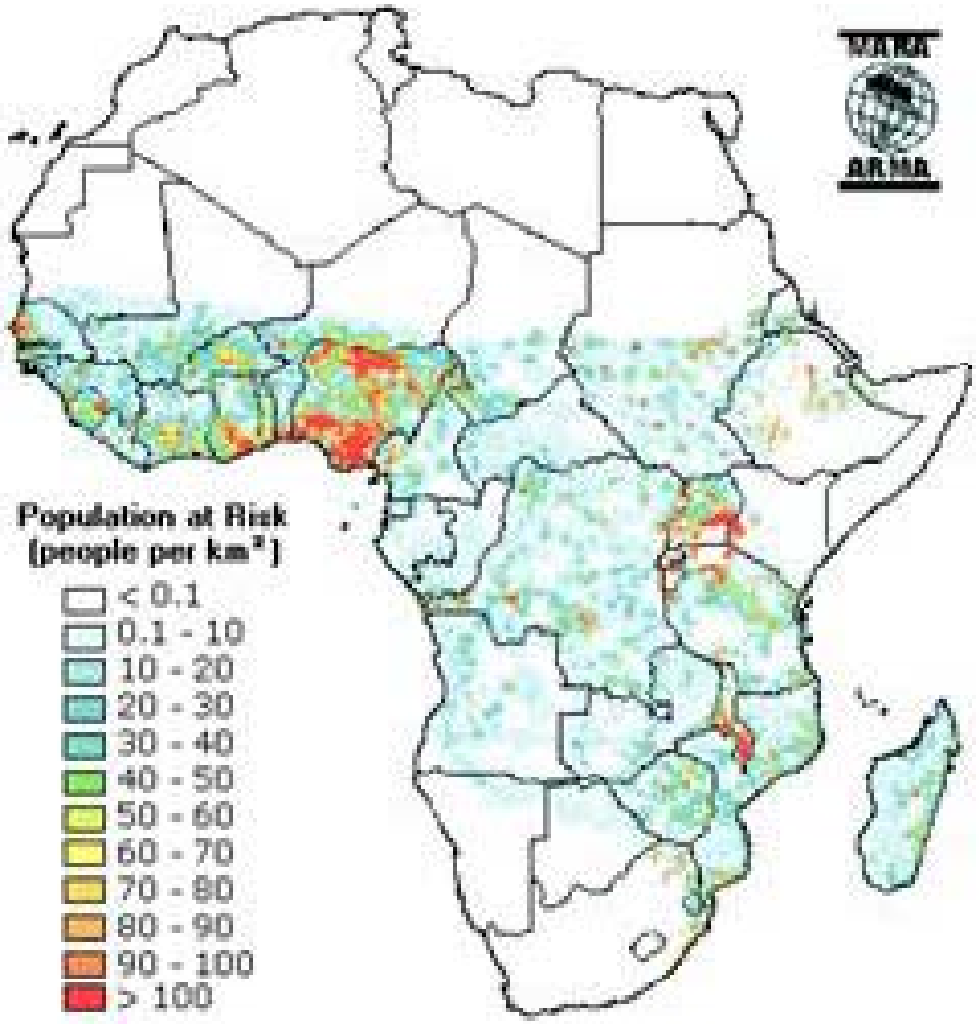
Population at Risk
(people per km²)
< 0.1
0.1 - 10
10 - 20
20 - 30
30 - 40
40 - 50
50 - 60
60 - 70
70 - 80
80 - 90
90 - 100
> 100

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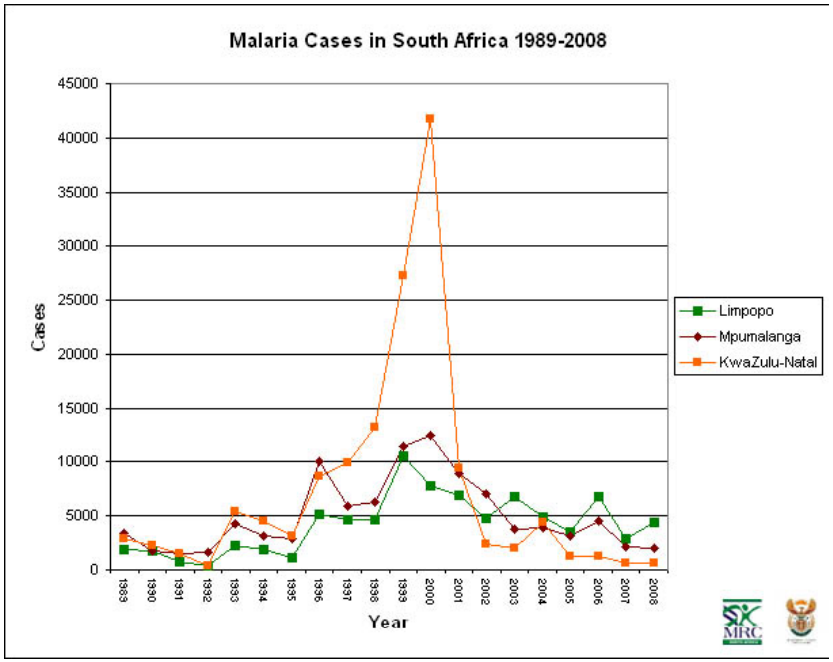
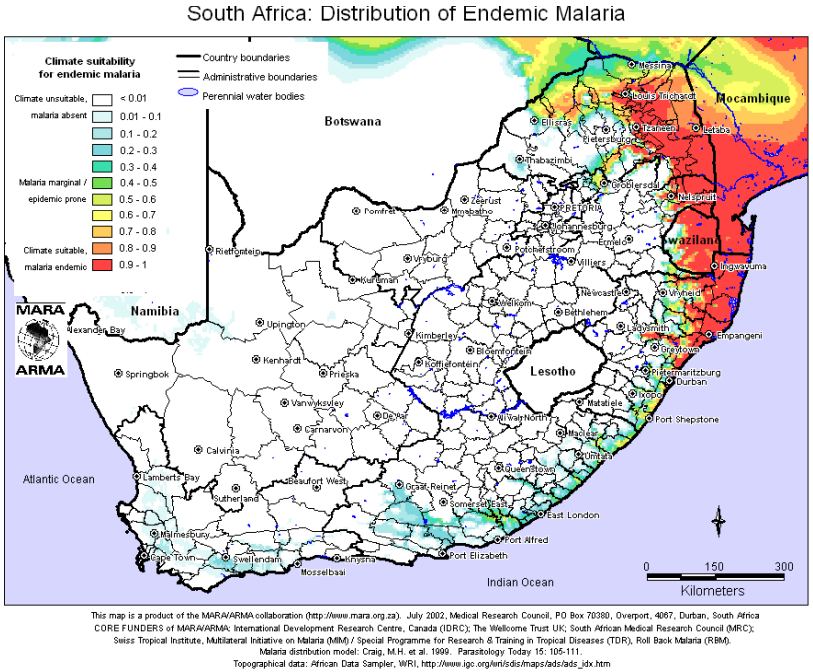
- Burden of Malaria in South Africa





This map is a product of the MARA/ARMA collaboration (http://www.mara.org.za). July 2002, Medical Research Council, PO Box 70380, Overport, 4067, Durban, South Africa
CORE FUNDERS of MARA/ARMA: International Development Research Centre, Canada (IDRC); The Wellcome Trust UK; South African Medical Research Council (MRC);
Swiss Tropical Institute, Multilateral Initiative on Malaria (MIM) / Special Programme for Research & Training in Tropical Diseases (TDR), Roll Back Malaria (RBM).
Malaria distribution model: Craig, M.H. et al. 1999. Parasitology Today 15: 105-111.
Topographical data: African Data Sampler, WRI, http://www.igc.org/iei/sdis/maps/ads/ads_idx.htm

- Economic Burden of Malaria

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Malaria

- A preventable and treatable disease placing about half of world population at risk[2]
  - 80+% of cases in Africa[2]
- Nearly 1 million deaths per year[2]
  - More than 90% in Africa[2]
  - 85% of deaths occur in children <5 years old[2]
- Children and pregnant women are at highest risk[2]
  - Every 30 seconds a child dies from malaria[3]

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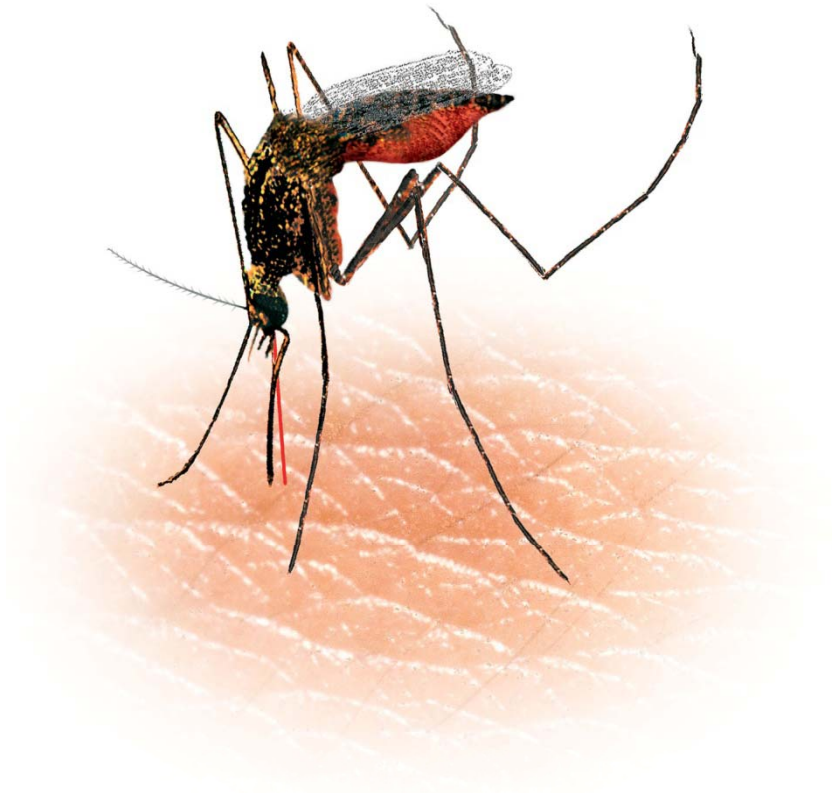
What is malaria?

- Parasitic disease
- Transmitted to man via infected Anopheles mosquito
- Most lethal strain is *Plasmodium falciparum*[12]
- Other strains are less virulent: *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*[13]



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Life cycle of the *Plasmodium falciparum* parasite

- Infected mosquito transmits parasite to humans
  - Parasite goes through several stages of its life cycle in the human host
- Parasite invades the blood and liver cells
- Destruction of these cells causes many of the symptoms of malaria

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Clinical symptoms of *P. falciparum* malaria

- Clinical symptoms:
  - Fever and flu-like signs (chills, headache, muscle aches and fatigue)
  - May be accompanied by nausea, vomiting and diarrhea[13]
- Malaria is also a major cause of anemia[13], low birth weight[13], premature birth, infant mortality[3] and maternal death[3]
- If not promptly treated, malaria may cause kidney failure, seizures, mental confusion, coma and death[13]

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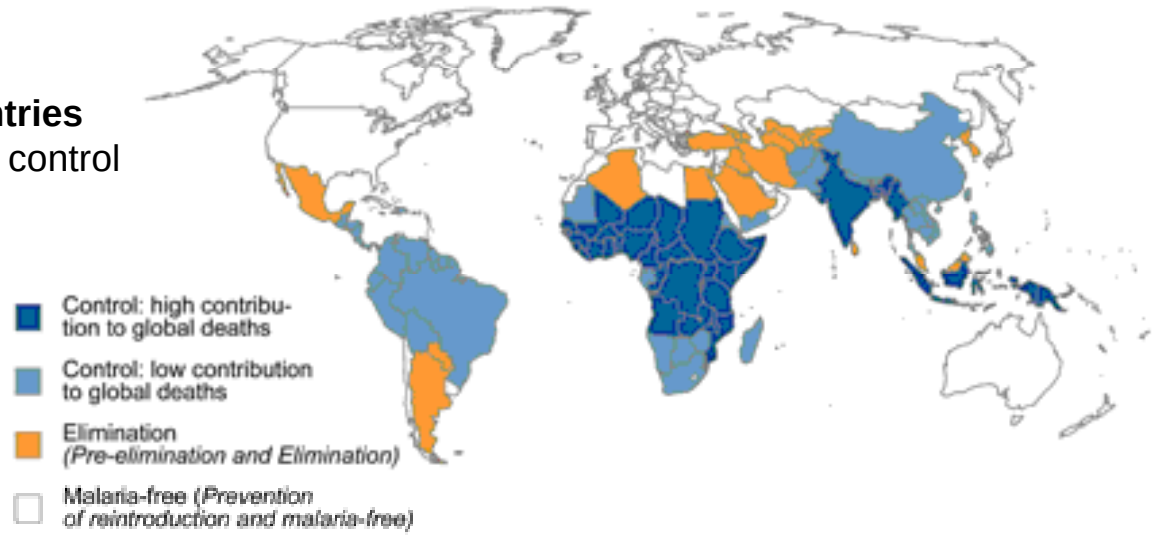
Historically, malaria is a global disease

- Until the 1950s, malaria was present in various countries throughout the tropical and subtropical zones, including Europe and US
- Today malaria is present in Africa and in some areas of South East Asia and Latin America
  - The largest burden of disease morbidity and mortality is in Africa[2]

Malaria endemic countries
Categorized by malaria control status and burden[14]



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Malaria remains an African tragedy!

- About half of the world population (3.3. billion) at risk[2]
- Estimated 247 million clinical cases in 2006[2]
  - 86% of cases in Africa[2]
- Nearly 1 million deaths per year[2]
  - More than 90% in Africa[2]
- Children and pregnant women are most at risk[2]
- A child dies of malaria every 30 seconds[3]
- Malaria causes an average loss of 1.3% of Gross Domestic Product in countries with intense transmission[3]
- Estimated economic burden to African countries of 12 billion USD per year[14]

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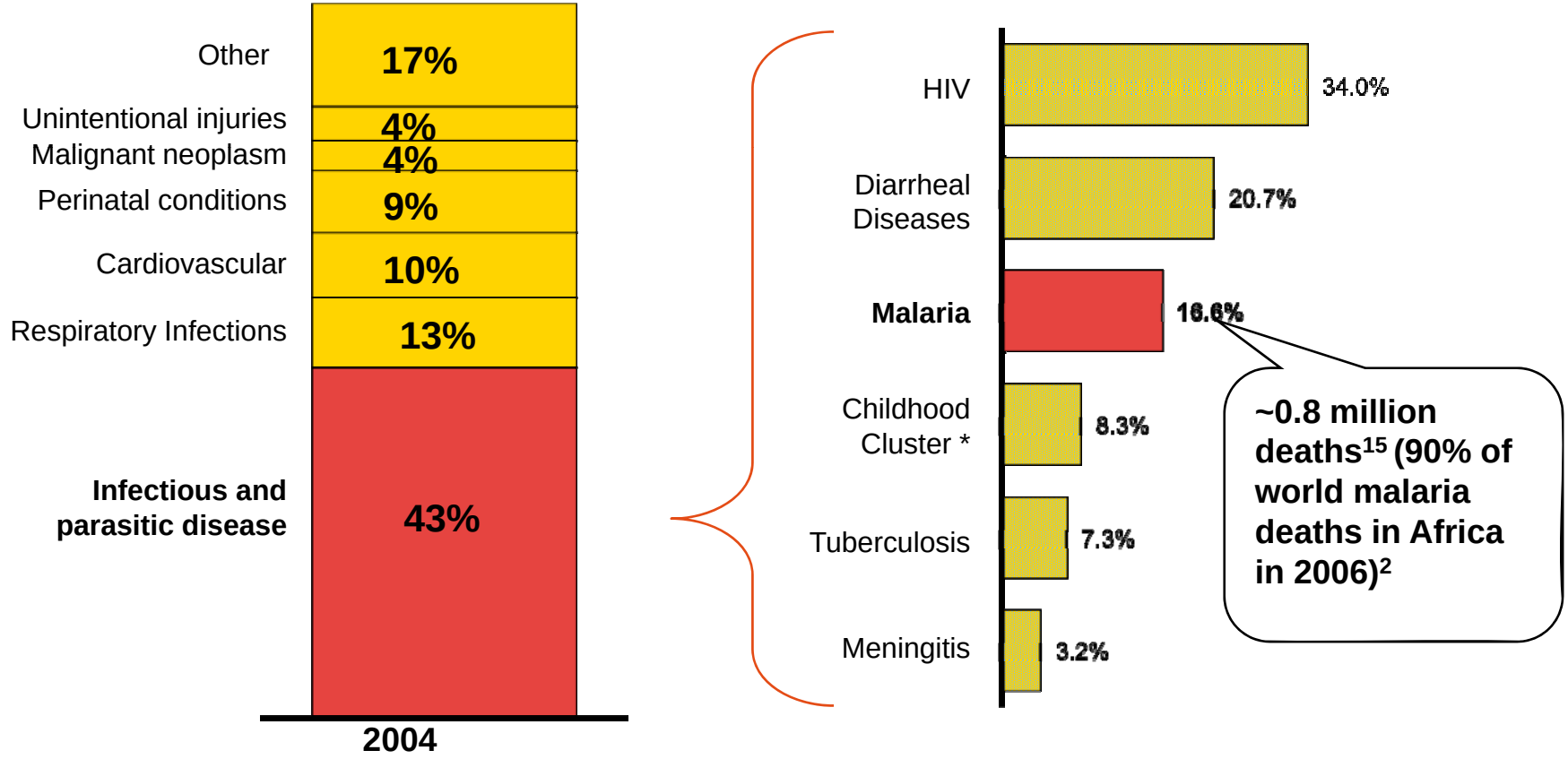
Malaria is responsible for one of every fourteen deaths in Africa

Breakdown of death by cause

11.2 Million total estimated deaths in Africa in 2004[15]



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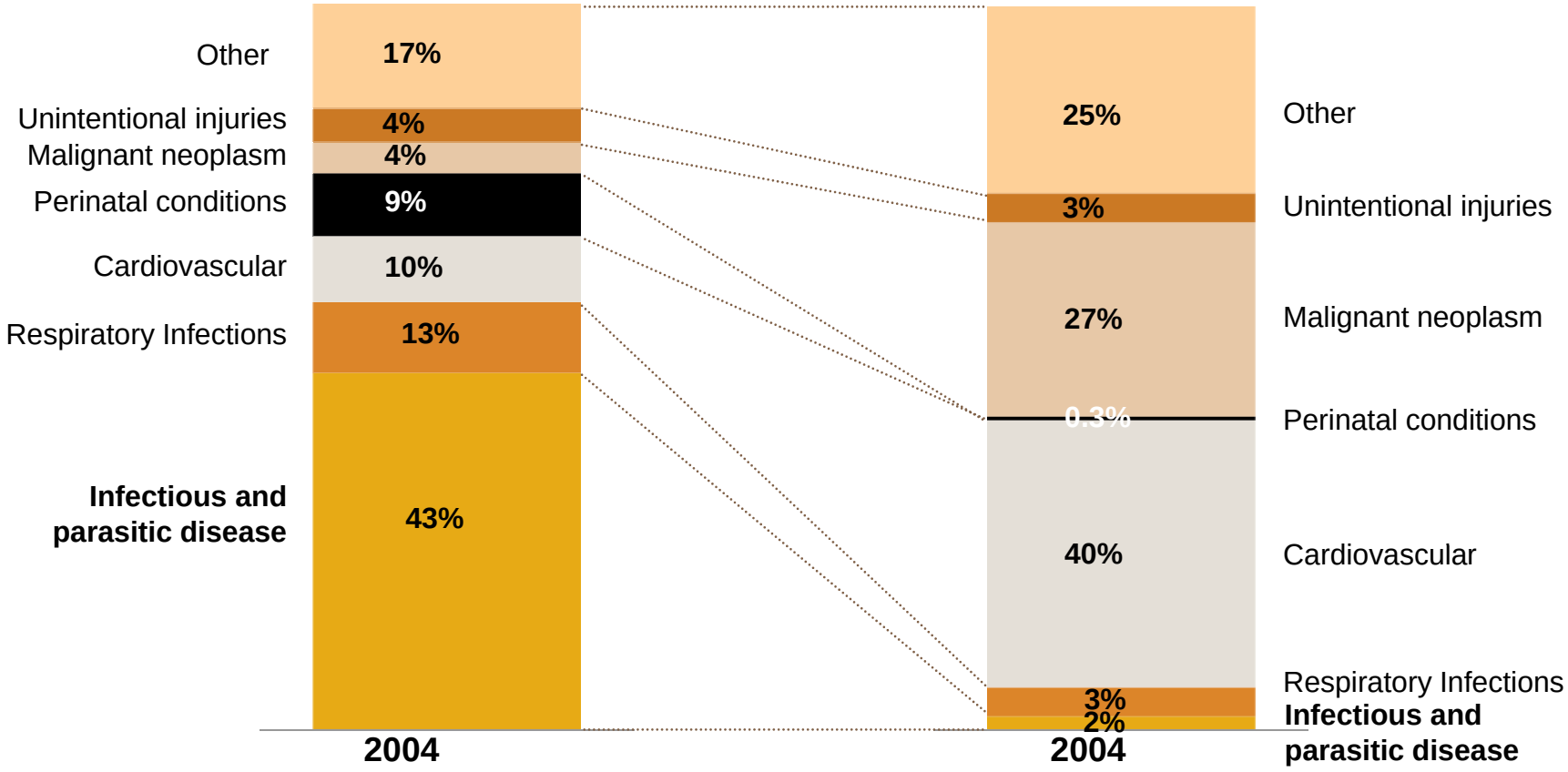
Comparison of mortality per disease in Africa and high income European countries*

11.2 Million total estimated deaths in Africa in 2004[15]

3.8 Million total estimated deaths in high income European countries in 2004[15]



* WHO defines high income European Countries as Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom [15]

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Strategy against malaria in endemic countries
Holistic approach combining prevention and cure

Malaria can be prevented and controlled by three main strategies:

Prevention

Insecticide Spraying

- Control of the mosquitoes by spraying and drainage of areas where they live
- Indoor residual insecticide spraying (IRS)

Insecticide-treated Bed Nets (ITN)

Cure

Drug Treatment

- ACT (artemisinin-combination therapies)
- Artemether–Lumefantrine tablets are included on the WHO's Model List of Essential Medicines[16]

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The issue of resistance…

- Malaria parasite can develop resistance to treatment over time
- Established therapies such as chloroquine and sulphadoxine-pyrimethamine have encountered serious drug resistance in much of Africa and Southeast Asia[17-19] (70-80% treatment failure rates have been reported for chloroquine)[17]
- Increasing drug resistance to amodiaquine[18] has rendered the more recent combination therapy of artesunate and amodiaquine less effective in large parts of East Africa
- Inappropriate use of antimalarial drugs, leading to less than effective drug-load in the human body, contributes to increased resistance[20]
  - Suboptimal dosing
  - Misuse and poor prescribing habits
  - Lack of adherence to the proper dosing regimen by patients
  - Use of poor quality drugs
  - Use of artemisinin-based monotherapies

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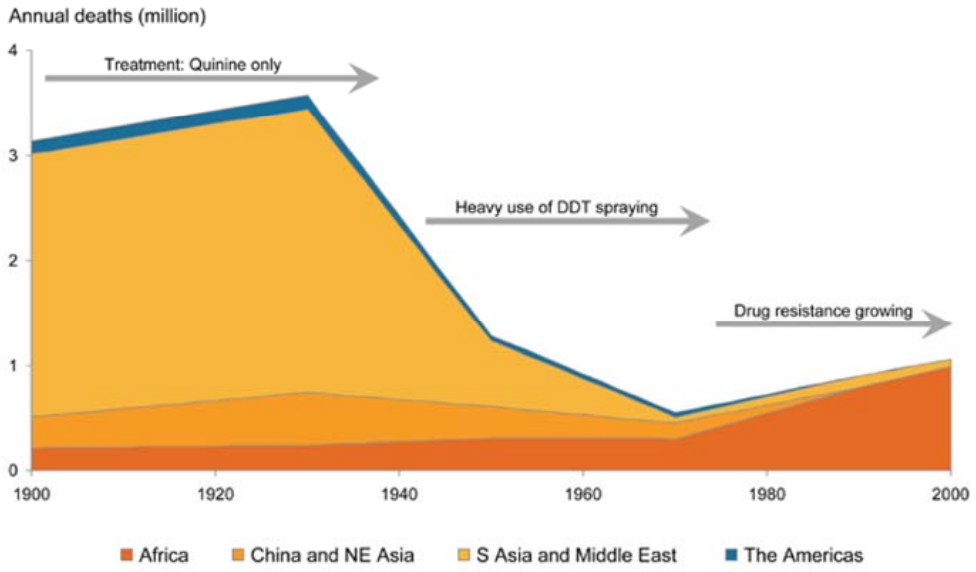
High levels of treatment failure in Africa lead to adoption of ACTs



Source: RBM Global Malaria Action Plan[21]

- In September 2005, the World Health Organization (WHO) called for use of artemisinin correctly in combination therapies[22]

➡ ACTs – artemisinin-based combination therapies

- In January 2006, WHO called for termination of the distribution and sale of artemisinin monotherapies[23]

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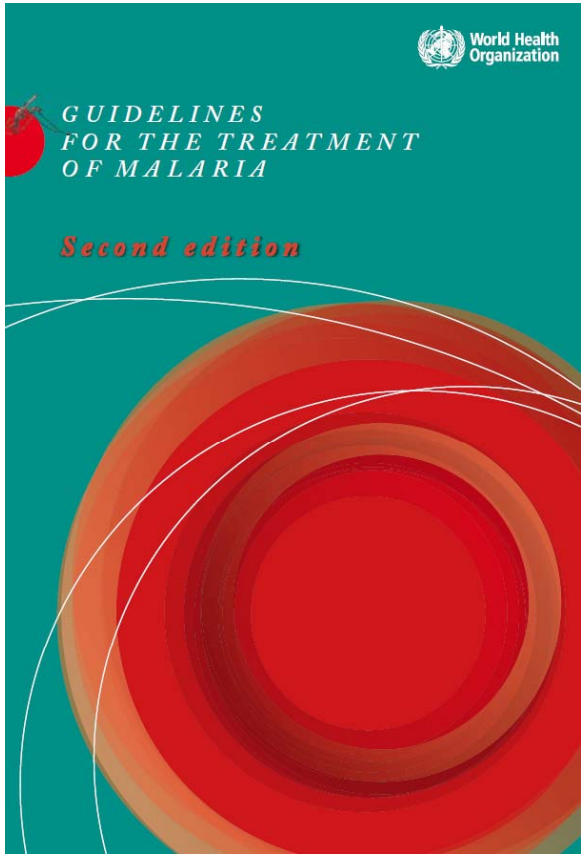
Current WHO Treatment guidelines

- WHO, 2009, Guidelines for the treatment of malaria 2nd edition, Geneva
- Focus on acute uncomplicated *P. falciparum* malaria



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Current WHO Treatment guidelines cont...

- Malaria Diagnosis
  - Microscopy (thick film)
  - Rapid diagnostic testing
  - Presumptive treatment of fever cases should take place only when parasitological diagnosis is not available.

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Current WHO Treatment guidelines cont...

- Chemotherapy
  - ACTs should be used in preference to SP plus Amodiaquine for the treatment of uncomplicated *P. falciparum* malaria
  - ACTs should include at least 3 days of treatment with an artemesinin derivative.
  - Dihydroartemesinin plus piperaquine (DHA PPQ) is an option for first-line treatment of uncomplicated *P. falciparum* malaria
  - Addition of a single dose primaquine (0.75mg/kg) to ACT treatment for uncomplicated falciparum malaria as an antigametocyte medicine, particularly as a component of pre-elimination or an elimination program.

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Important factors in Malaria case management

- Children < 5 years old
- Pregnant patients with malaria
- Asymptomatic *P. falciparum* carriers
- Patients co-morbid HIV infections

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Exploring new frontiers

- Screening and treatment of community members with Asymptomatic malaria
  - Within a geographic area e.g. village, province etc
  - Use of parasitological diagnosis
  - Remove the parasite reservoir from the community
  - Drug must be able to clear gametocytes (sexual forms of the parasite).
  - Informally done in some countries e.g. South Africa, Zanzibar and Zambia (some regions such Macha)
  - Interrupt transmission

ACTs: a highly-effective cure for malaria

- ACTs are highly effective in drug resistant areas[13] and are recommended by WHO as first-line therapy for the treatment of uncomplicated malaria*[13]
- Coartem, a combination of the artemisinin derivative artemether, and lumefantrine, is the first ACT prequalified by WHO[10]

Coartem Features:

- ✓ Rapid fever control[4-8]
- ✓ Rapid parasite clearance stopping spread of disease[4-6]
- ✓ Cure rates > 95%**[4-6]
- ✓ Short therapy duration (three days only)!
- ✓ Good safety and tolerability profile[4-9]

* *P. falciparum* malaria

** 28-day PCR-corrected, calculated on the evaluable population

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Artemisinins

- Extracted from *Artemisia annua*
- Used as herbal remedy for fevers in China for thousands of years
- Artemisinin and derivatives extensively tested in China since late 1970s
- Used widely to treat malaria in Asia since 1980s

Artemisia annua

Artemisinin

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Coartem is the result of unique partnerships with

Chinese institutions and WHO

- 1994: Unique collaboration starts between Novartis (Ciba-Geigy) and Chinese partners for the development of Coartem
- 1997: Novartis CEO Daniel Vasella remained committed to the project despite negative return-on-investment
- 2001: Novartis committed to make Coartem available *without profit* to public sector agencies and malaria-endemic countries under an unique private-public agreement with WHO
- 2009: The inventor of Coartem, Prof Zhou Yi-qing, awarded the European 'Inventor of the Year' award

Prof Zhou Yi-qing
Academy of Military Medical Sciences, China

Dr Daniel Vasella
Chairman and CEO, Novartis

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Public-Private Partnerships are a key success factor in access to medicines programs from R&D to delivery

Research & Development	Sourcing	Production	Access	Distribution	Impact evaluation
• AMMS • MMV	• 5 strategic Chinese Artemisinin suppliers • Advanced Bio-Extracts (Africa)	• 2 Chinese partner companies	• Ministry of Health, and of Finance • National Malaria Control Programs • MSD (Medical Stores Department)	• WHO • Unicef • UNDP • NGOs, e.g. MSF • JSI • Crown Agents • Mission Pharma • IDA Foundation	• STI • MSF • WHO • Universities: Oxford, London, Liverpool

- Interactions with funding organizations, including Global Fund (e.g. G8 countries), UNITAID, USAID / US President's Malaria Initiative (PMI), World Bank, Bill and Melinda Gates Foundation, Acumen Fund

AMMS: Academy of Military Medical Sciences
IDA: International Dispensary Association
JSI: John Snow Inc.

MMV: Medicines for Malaria Venture
MSF: Médecins Sans Frontières (Doctors without Borders)
STI: Swiss Tropical Institute

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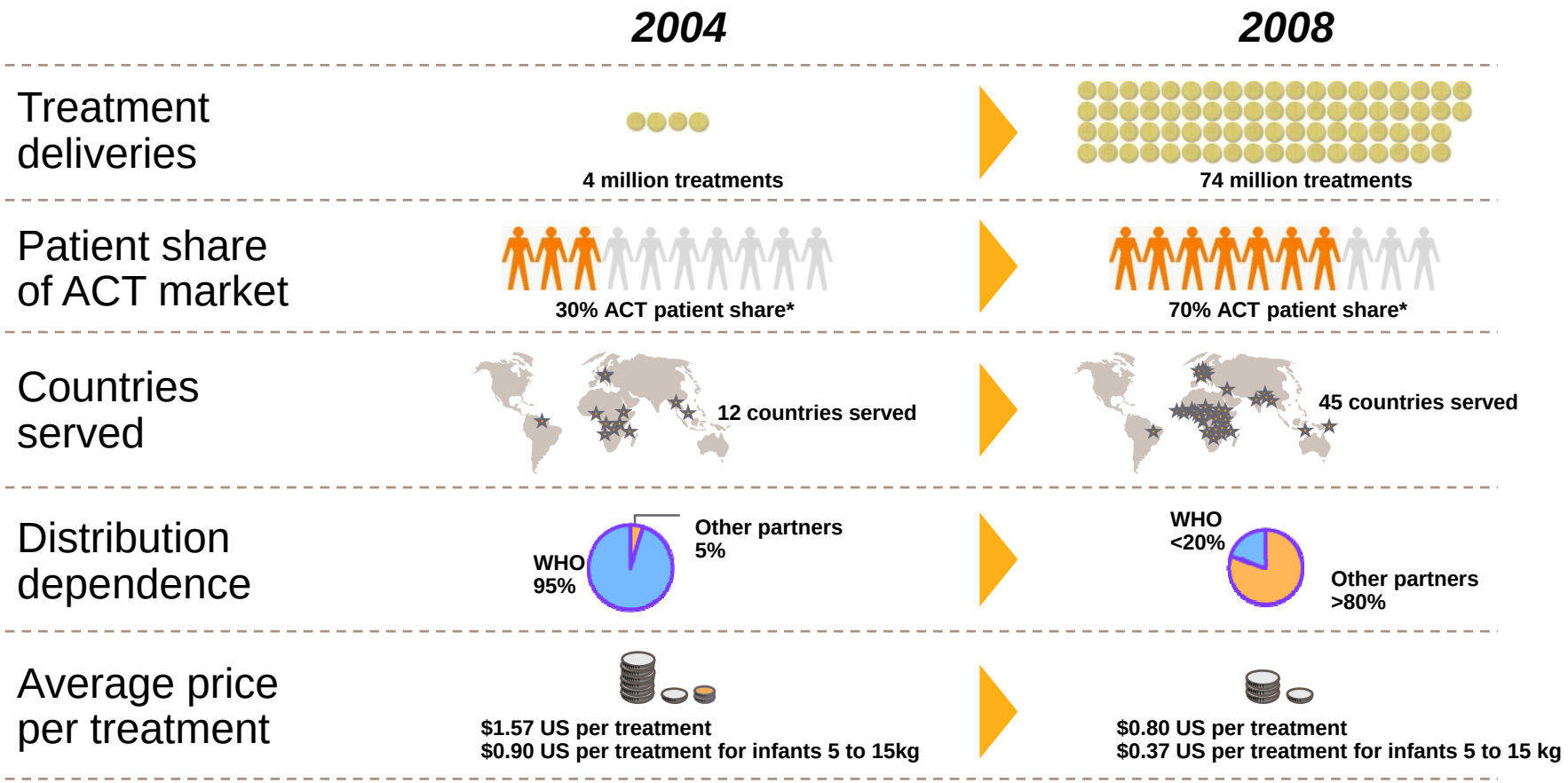
Coartem for the public sector makes great progress
2004 vs. 2008



*Based on internal Novartis estimates of global public sector ACT procurment

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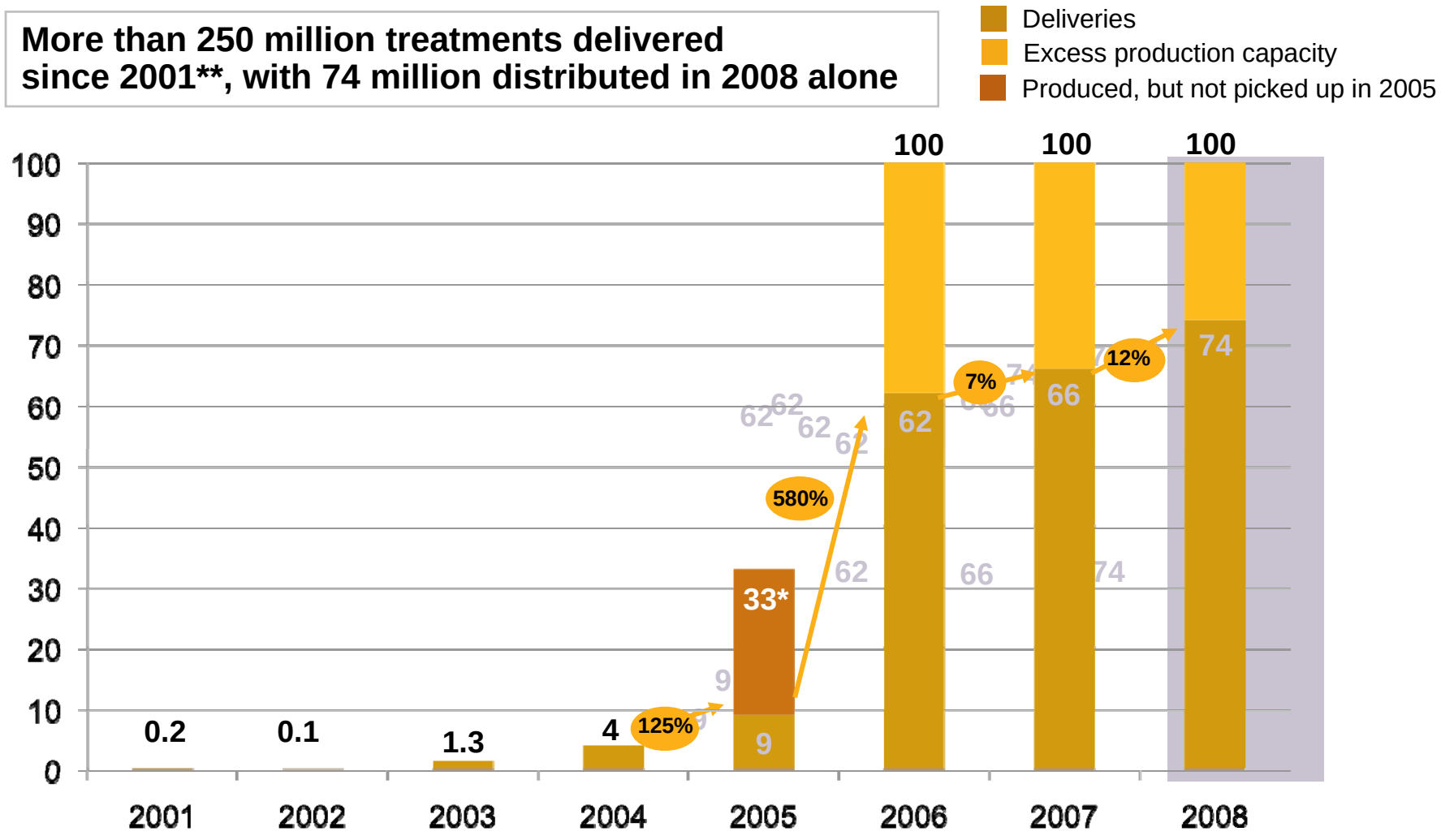
Unprecedented scale-up coupled with consistently high number of Coartem treatments delivered

More than 250 million treatments delivered since 2001, with 74 million distributed in 2008 alone**



*14 mio Tx were ordered for delivery in 2005, but only 9 mio were picked up

** Includes YTD sales for 2009

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Putting 74 million treatments into perspective

- 20 jumbo cargo planes full in 2008
- >95% cure rate*[4-6]

- Potential to cure 70 million patients

*28-day PCR-corrected, calculated on evaluable population

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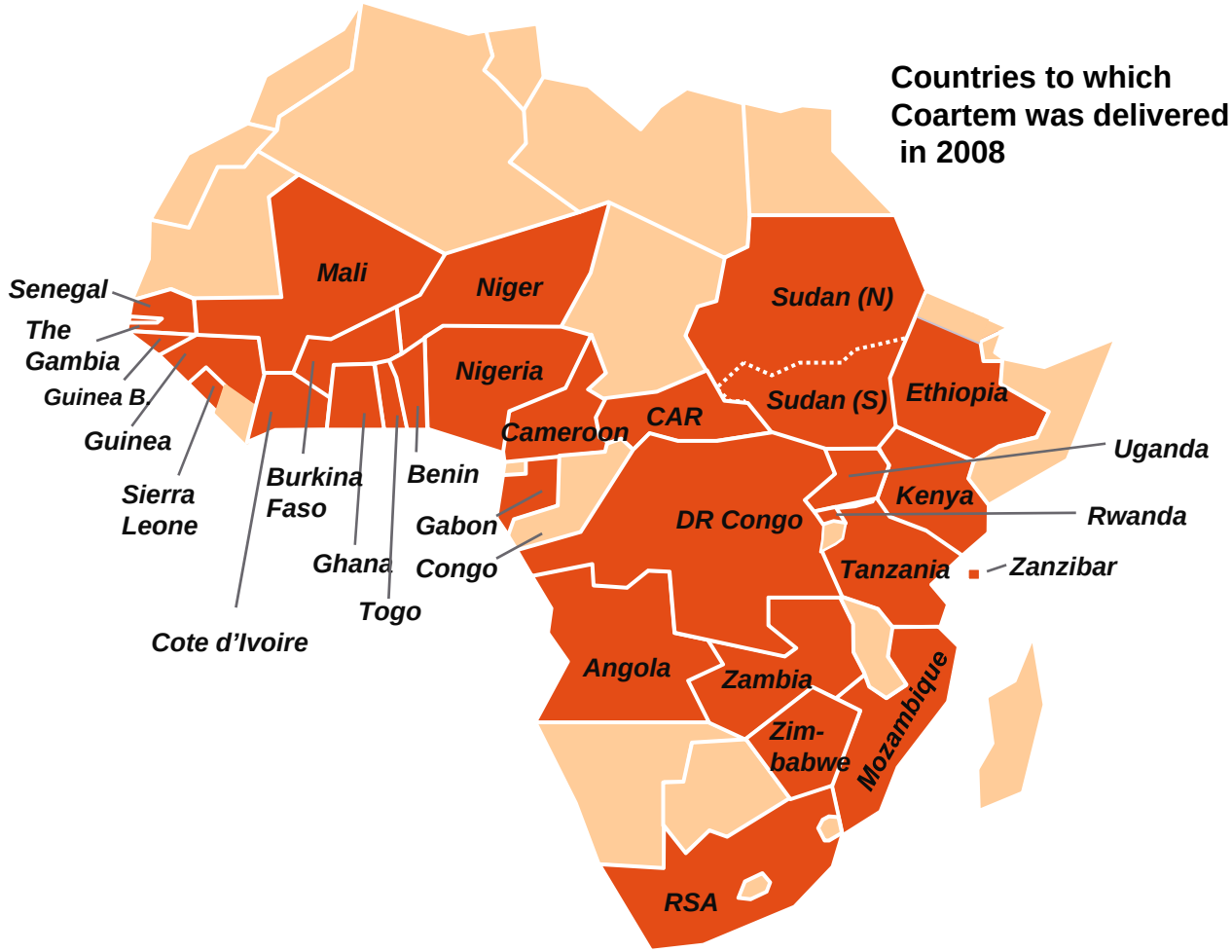
Deliveries to African countries in 2008: worldwide 54 countries deploying ACTs, 45 of which are using Coartem

Top 10 Coartem country deliveries[25] (Mio Tx; total 74 in 2008)

Tanzania: 15.9
Uganda: 11.4
Kenya: 6.9
Mozambique: 6.3
Nigeria: 4.7
Malawi: 4.5
Ethiopia: 4.1
Angola: 3.0
Benin: 2.8
Others: 14.1



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Production of artemisinin combination therapies: longer and more complex than most drugs

Minimum 14 months lead time, *if capacities are established*

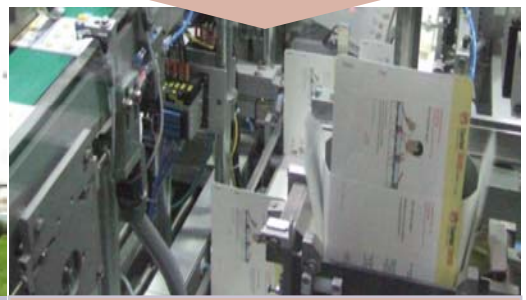
***Artemisia annua* plantation and harvesting (7 months)**

Expanded *Artemisia* production in China and Africa

Artemisinin extraction and chemical modification (3 months)

Transferred chemical production from Switzerland to China

Drug product manufacture and shipment (4 months)



Dedicated pharmaceuticals production / packaging in Suffern, US

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Coartem: leading the fight in malaria
Key Milestones and Achievements

ACCESS
250 million Coartem treatments
- Estimated 630,000 lives saved*

REGULATORY
FDA Approval
- Achieved April 2009: the first ACT to receive approval in the US

INNOVATION
Launch of Coartem Dispersible
- Swissmedic approval granted
- Meets need for child-sized medicine

*Estimate based on: 250 million malaria infections per year result in 1 million deaths per year, therefore, it can be estimated that the distribution of 250 Coartem® treatments (one treatment per patient) may have helped to save one life. It is assumed that 168 million Coartem® treatments have reached patients since 2001. Therefore, using an average efficacy of 95% (PCR-corrected cure rate in the evaluable population), it can be assumed that Coartem® may have helped save an estimated 630,000 lives.

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Novartis patient-centric approach

Fast and reliable delivery of original quality drugs, not-for-profit

Training of Healthcare Professionals (several languages, e.g. Swahili)

Best Practice Sharing Workshops with National Malaria Control Program Managers

Patient education through Coartem packaging and patient information

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Training of healthworkers

- Materials consisting of:
  - Healthworkers workbook
  - Healthworkers job aid
  - Train-the-trainer slide kit
- Translated into several African languages
- Distributed free of charge

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Patient information/education

- Coartem Packaging
  - Novel design
  - User-friendly dispensing packs, color-coded for 4 dosage levels
  - Designed to be used in areas with poor literacy
  - Strong message of compliance – the packaging reinforces the importance of completing the full treatment course and provides the rationale for it
  - Field-tested for user-friendliness in Africa

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Employing a strategy of prevention (bed nets) plus treatment with ACTs yields real patient impact

- Rwanda: 67% reduction in mortality in children <5 years old[26]
- Ethiopia: 62% reduction in mortality in children <5 years old[26]
- Zambia: 66% reduction in malaria deaths[27]

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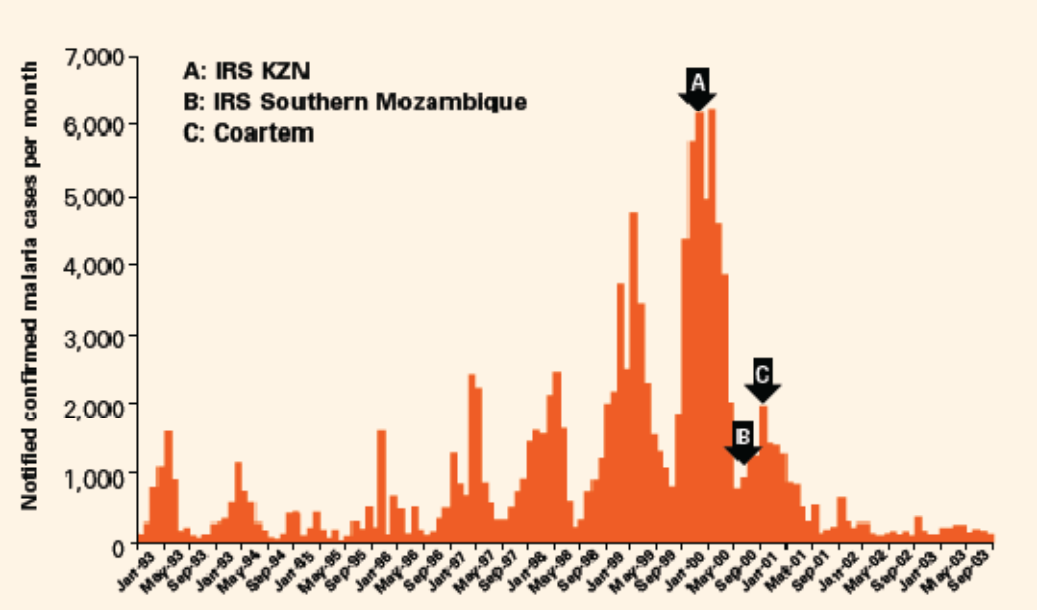
KwaZulu Natal, South Africa: malaria deaths fell by over 95%[1]

South Africa: KwaZulu Natal district

- Malaria outpatient cases reduced by 85% in 2001 and 99% in 2003[1]
- Hospital admissions for malaria reduced by 99% by 2003[1]



NNumber of notified cases of malaria in KwaZulu-Natal by month.
A indicates indoor residual spraying in KwaZulu-Natal
B indicates introduction of indoor residual spraying in neighboring Southern Mozambique
C indicates the implementation of Coartem® as first-line therapy in KwaZulu-Natal

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Funds and donors

- The Global Fund provides money for countries to purchase antimalarial medicine
  - Funds are primarily provided by G8 countries and Bill and Melinda Gates Foundation
- US President's Malaria Initiative
- The World Bank Malaria Booster Program
- New funds have become available through UNITAID using airline taxes as a sustainable funding source for HIV/AIDS, malaria & tuberculosis

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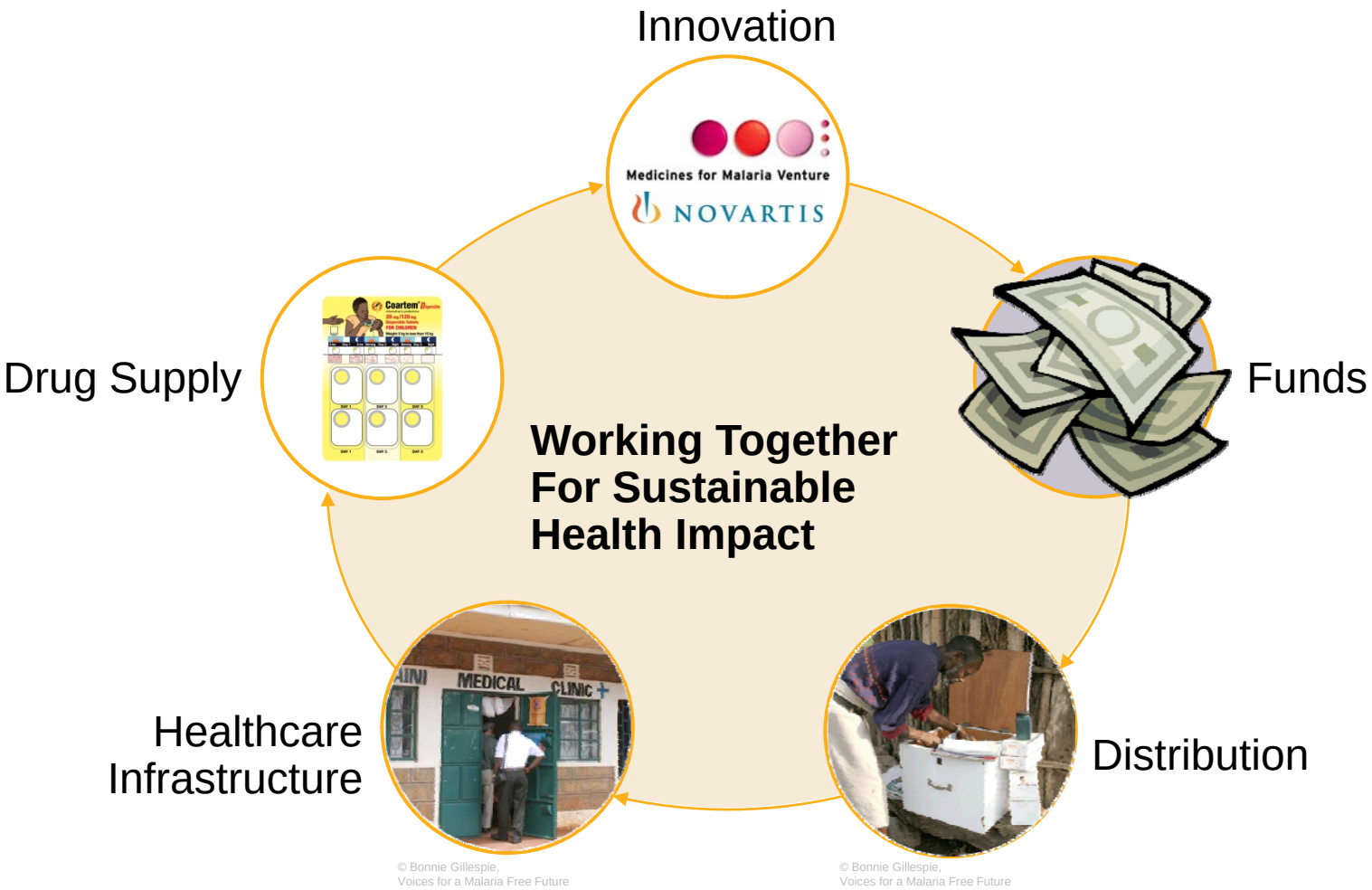
Collaboration is key
Novartis and MMV pioneering the fight against malaria



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Malaria Initiatives

- Supply Coartem without profit to public sector: 9 million Tx in 2005, 74 million Tx in 2008
- Reduced average price to USD 0.80 to help expand access to medicine
- Estimated contribution to saved lives since 2001: approximately 630,000*
- R&D – vulnerable patient populations
  - Coartem Dispersible for children and infants recently approved by Swissmedic and many African countries

*Estimate based on: 250 million malaria infections per year result in 1 million deaths per year, therefore, it can be estimated that the distribution of 250 Coartem® treatments (one treatment per patient) may have helped save one life. It is assumed that 168 million Coartem® treatments have reached patients since 2001. Therefore, using an average efficacy of 95% (PCR-corrected cure rate in the evaluable population), it can be assumed that Coartem® may have helped save an estimated 630,000 lives.

Novartis Foundation for Sustainable Developmer

- Donation of Leprosy medication: more than 4.8 million patients cured since 2000
- Donations of fixed-dose TB combination Tx: aiming at 0.5 million patients over 5 years

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scount program for the
insured

In 2008, Novartis co
access to medicines

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1. Barnes KI, Durrheim DN, Little F. Effect of artemether-lumefantrine policy and improved vector control on malaria burden in KwaZulu-Natal, South Africa. PLoS Med 2005; 2: e330.
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