Multiple First-line (MFT) for malaria: concept and updates

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History of Malaria Treatment

- The treatment drugs were initially adopted on what is available
- A drug was used until lose of therapeutic efficacy
- Elimination in certain geographic regions dampened drug discvery drive till the threat of re-emergence
- The adoption of commniation therapy was adopted in a coarsive manner
- Development of new molecules has been more reactive driven by threat of failure

Genome size and proposensiti of Drug Resistance

Viruses

HIV - genome is 9750 nucleotides

Measles – genome 15,894 bp

Mpox – genome is 197,209 bp

Bacteria

Streptococcus – genome is 2,160,267 bp

- Parasites
  - Malaria – genome 23-Mb
  - Leishmania - 20- 33 Mb
- Trematodes
  - Schistosoma – 363 Mb

Drug Resistance development in Malaria

- Mechanisms of action of most potent antimalarials is poorly undertood
- Enzymatic pathways inhibitors more susceptible to resistance
- Resistant mutants parasites likey to be less fit
- The more drug pressure exerted previously conserved genetic regions become fragile
- With the relatively large genome multiple genome mutations likely to be detrimental to the parasite fitness survival
- The double combination with umatched PK parameters model has proven useful but not good enough if the anchor molecule fails

Mechanism or resistance propagation

- Denovo emergence or spread
- Does rare importation resistant mutants more likely to lead to establishment during a high-transmission season or constant importation

The Next Options for Malaria Treatment for the END GAME

- Redesigned integrated mutipronged approach
  - Appropriate and relavant treatment
  - Vector control
  - Vaccinantion and **Vaccination plus**

- What has to be new
  - Target the transmissin resrviour
    - Context specific and targeted Mass Screening and Treatment or Variants of MDA
  - Deploy Multiple treatment modalities
    - Multiple First line Treatment modalities

MFT and Drug Resistance

- Slow the Spread or Expansion of Resistance
- Delay Emergence of Resistance
- Prevent Emergence of Resistance

MFT Contextual Issues

- MFT must be a deliberate and managed intervention at all levels of the public health system and the private sector.

- MFT requires that all antimalarial drugs deployed are efficacious, so treatment policies need to be changed before drug resistance undermines clinical efficacy
- The more diverse is your drug deployment – in time, in space, and locally? The more diverse the better
- Manage drug resistance early, don't wait

Country-level calibration – guided by four major data streams

1. P. falciparum prevalence
2. Drug coverage and drug choice
3. Reported falciparum incidence
4. Genotype frequencies of pfkelch13 variants

Definitions and implementations – what does it mean to deploy multiple first-line therapies?

1. Randomization (e.g. as in a clinical trial, by day of week) difficult to implement	4. Distribution by type of health facility needs dialogue and detail	7. Different drugs given during different time periods (rotation or cycling) works well only if rotation is rapid
2. Free-market procurement and distribution, with subsidies; prescribing done by doctor/patient choice may result in high AL use	5. Different drugs in public and private markets challenging – many opinions here	8. Stepwise introduction of new therapies
3. Geographic distribution (by province, district) need to rotate as well	6. Different drugs assigned to different age groups analysis in Summer 2024	9. Expanding second-line treatment guidelines (e.g. longer post-treatment window, broader inclusion criteria)

Emerging Issues on MFT

- Appropriate knowledge about malaria and positive community care-seeking behaviour at health facilities for fever/malaria episodes is critical in the implementation of a MFT

The Reality

- Implementation of a pragmatic policy response to currently circulating artemisinin-resistant genotypes in Africa is urgently needed to prevent a population-wide rise in treatment failures
- Local ownership of the policy response is critical
- A regional approach is paramount
- The policy response must have a pragmatic robust pharmaco-vaccinovigilance component
- The policy must have framework for seamless integration of new antimalarials into the treatment paradigm until the point of saturation

Reality

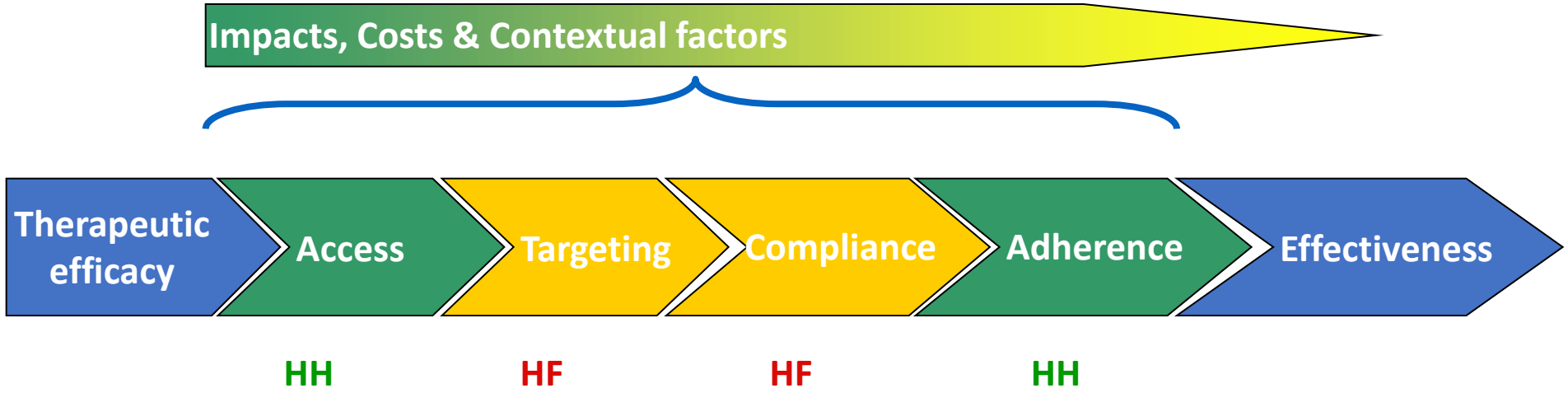
- The framework should have nested genomic surveillance, Efficacy testing, pharmacological profiling (PK/PD) and generate genotype / pharmacologic resistance index for each drug

- The framework will generate data to inform **MFT** optimization

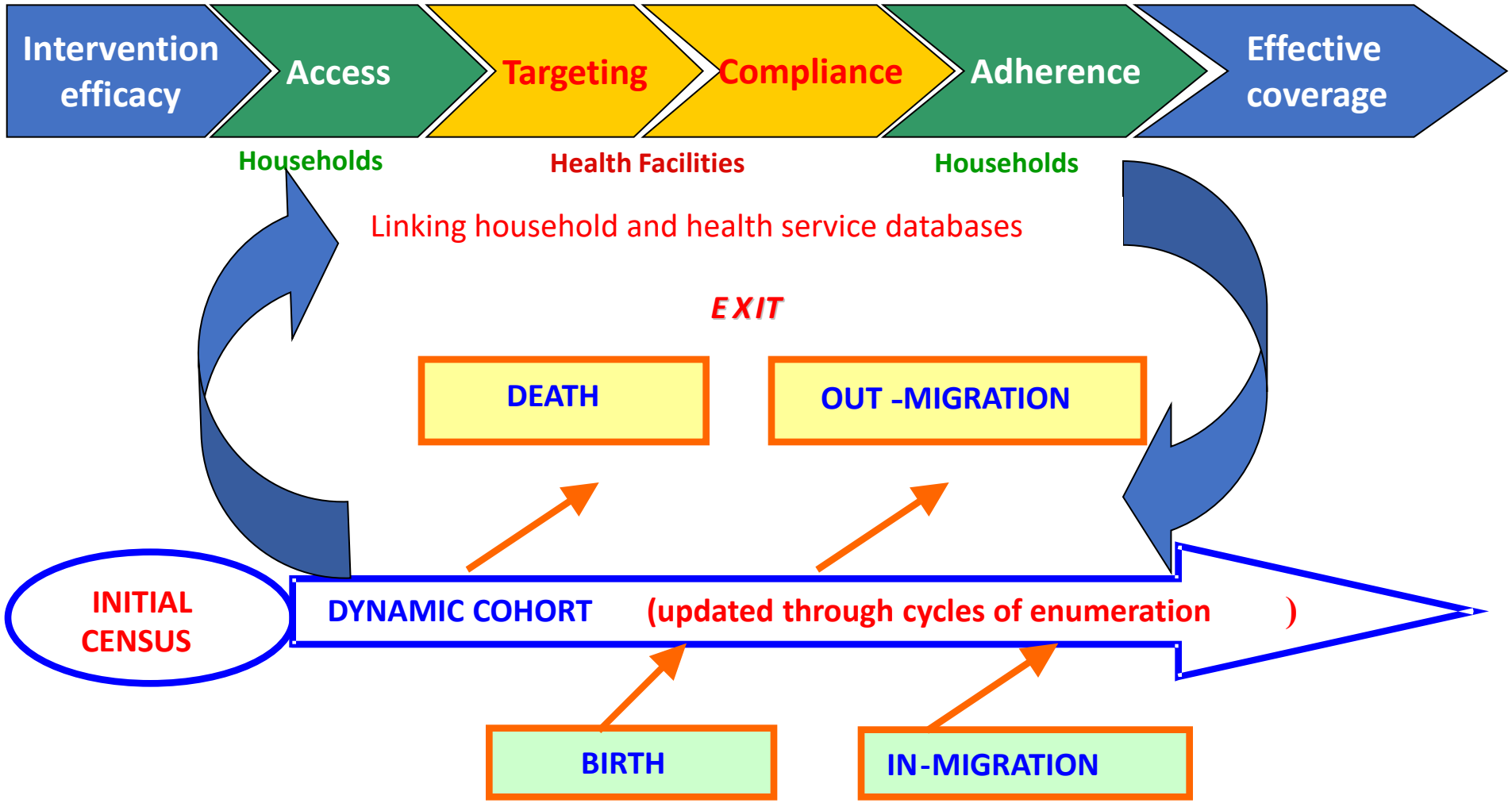
- **It is not if we will implement MFT but When and How much pain to endure before it is DONE**

INESS Systems Effectiveness

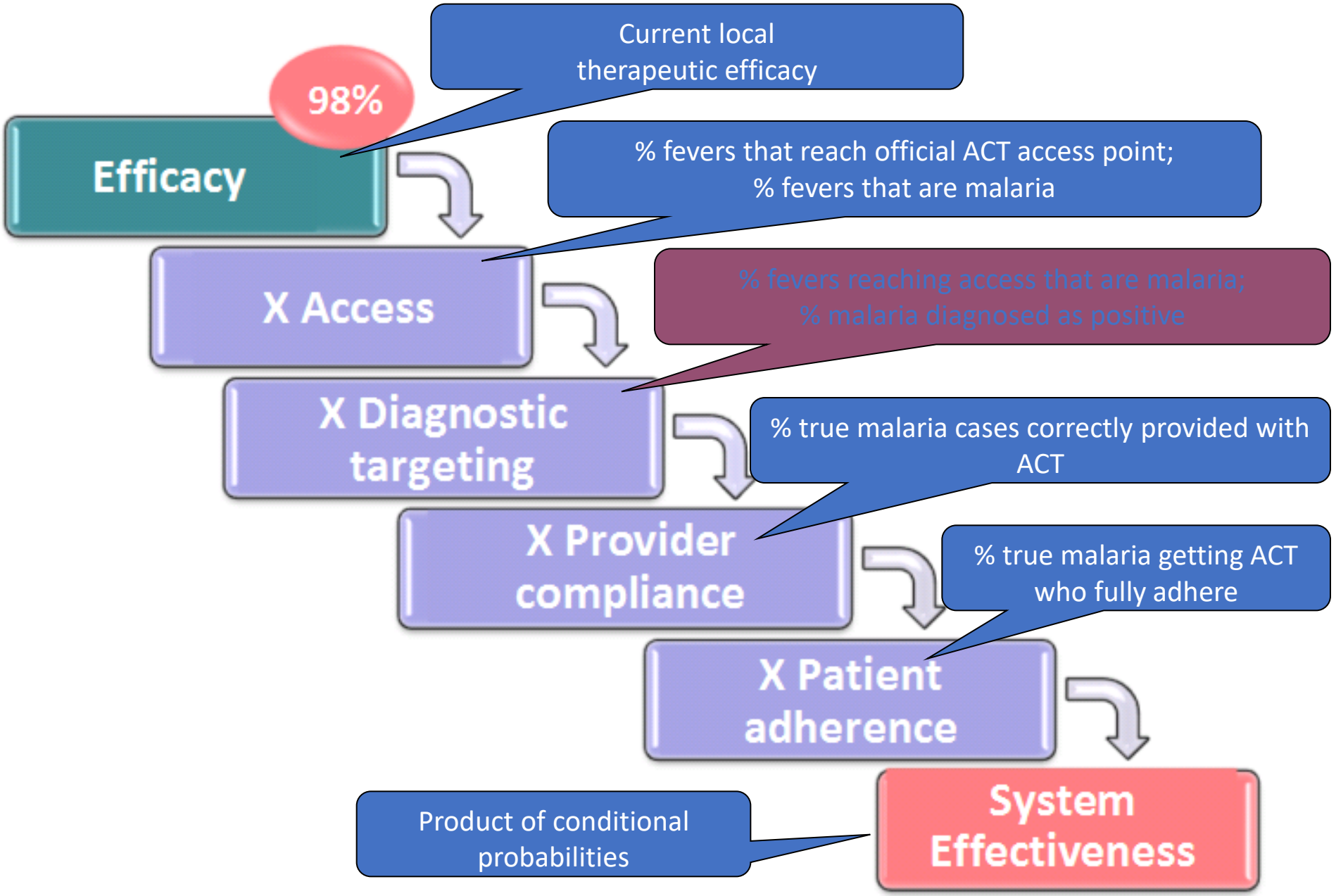
INESS: Understanding barriers to effectiveness



Towards District Health System Observatories



What we need from analyses: Conditional probabilities




Looking at the Horizon with confidence
Thank you