

Febrile Illness Modeling

Compendium of model results

May 20, 2013

BILL & MELINDA
GATES *foundation*

Agenda

Background and approach

Baseline analysis

Key drivers of fatalities

Intervention scenarios

Poor management of childhood fever drives ~2-4M deaths

More than 350M¹ fevers in under fives every year...



Not all are life-threatening
Parents often unaware of danger signs

Providers often lack tools to adequately manage

...from multiple and diverse causes...



...with significant gaps in their management

Estimates suggest ~2-4M² childhood deaths driven by fever

Malaria causes >500K² deaths in under fives

- >90% in Africa

Pneumonia causes >1.1M² deaths in under fives

- ~50% in Africa

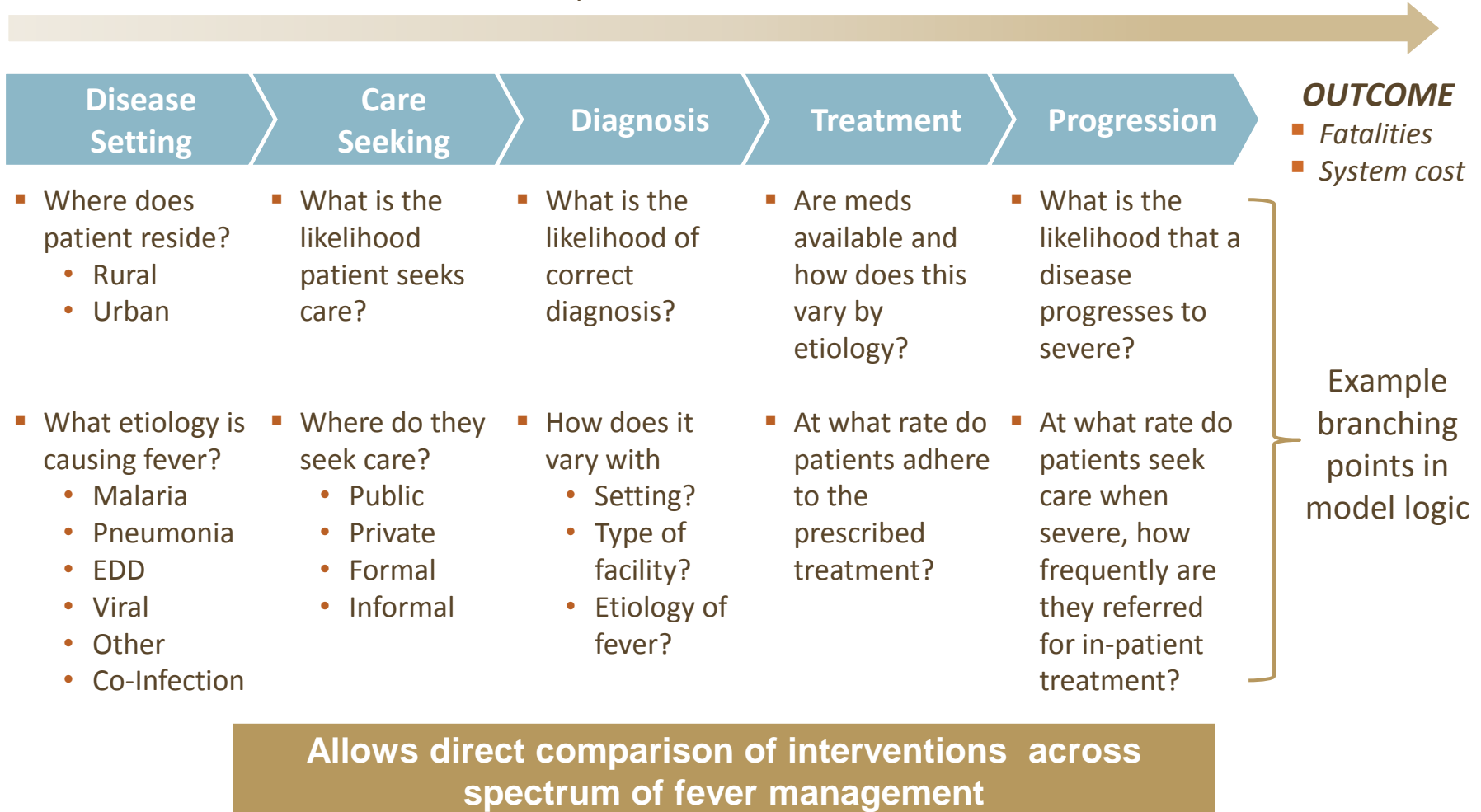
Diarrhea causes >700K² deaths in under fives

- ~50% in Africa

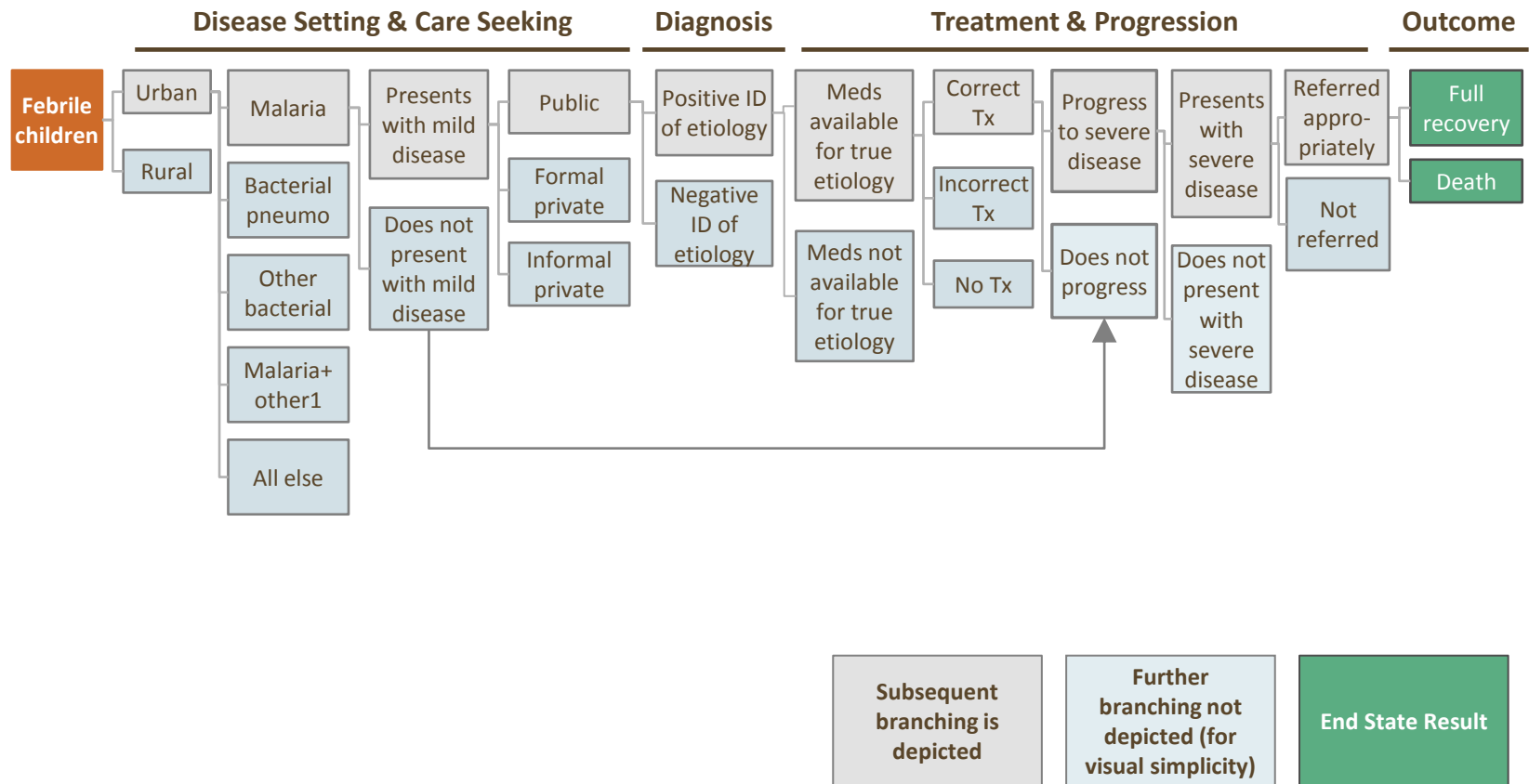
Model designed to test interventions across entire spectrum

Recapitulates end-to-end flow of febrile population in any given context

End-to-end linear flow of patients from incidence of fever to outcomes



Detailed model logic



1. Indicates co-infection of malaria and any other illness;

By design, first-order model has some limitations

First-order prioritization to be followed by deeper analysis

Description

- Model is fully linear

-
- Model does not capture interdependencies between variables

-
- Model provides broad system view, but necessarily simplifies key points of complexity

Considerations

- Model intended for baseline characterization and first order prioritization – look later at temporal dynamics and feedback loops

-
- Captured exogenously through manual adjustment where key interdependencies are known and informed assumptions can be made

-
- Deep dive analyses can be conducted external to model for points of simplification identified as priority (e.g. steps involved in correct diagnosis and treatment selection)

Countries chosen based on geographic and epidemiological diversification



Limited set of parameters, primarily linked to natural progression of disease, were considered country-agnostic

| | Model parameter | Principal source used for Tanzania | Country-specific |
|--------------------------------|-----------------------------|---|------------------|
| Epidemiology | Etiology of fever | Tanzania-specific literature | ✓ |
| | Disease progression | Estimated based on interviews | ✗ |
| Care-seeking | Rate of presentation | DHS report | ✓ |
| | Type of facility | DHS report | ✓ |
| Diagnosis and Treatment | Correct Dx | Triangulated from literature | ✓ |
| | Drug availability | Triangulated from literature | ✓ |
| | Correct Tx given Dx, avail. | Estimated based on interviews | ✗ |
| Outcomes | Referral rates | Triangulated from literature | ✓ |
| | Recovery rates | Estimated based on interviews | ✗ |
| Costs | Drug costs | Medicine Price Monitor (country-specific) | ✓ |
| | Cost of facility visit | Economic model from WHO | ✓ |
| | Inpatient costs | Pan-Africa estimates | ✗ |

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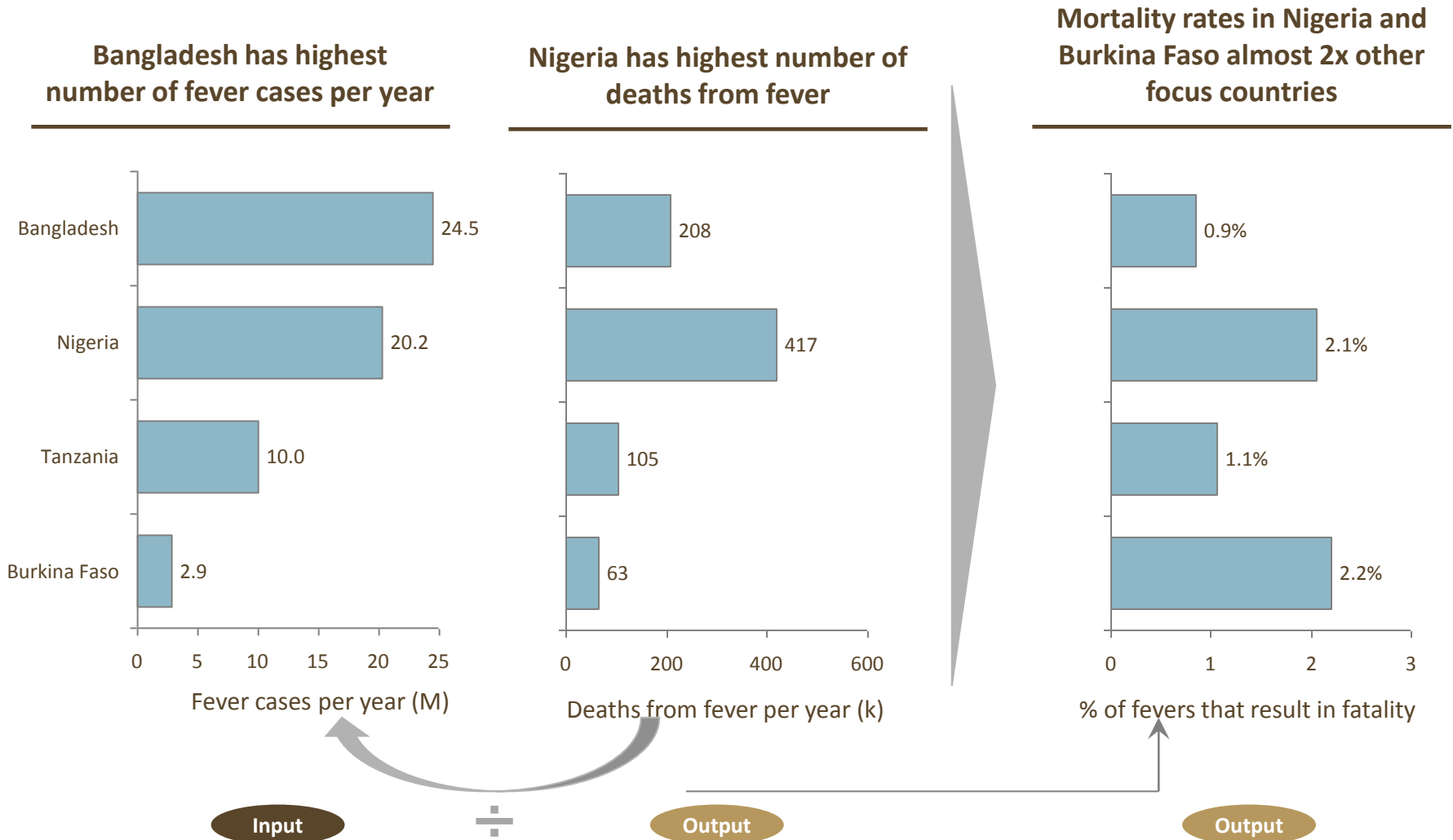
Background and approach

Baseline analysis

Key drivers of fatalities

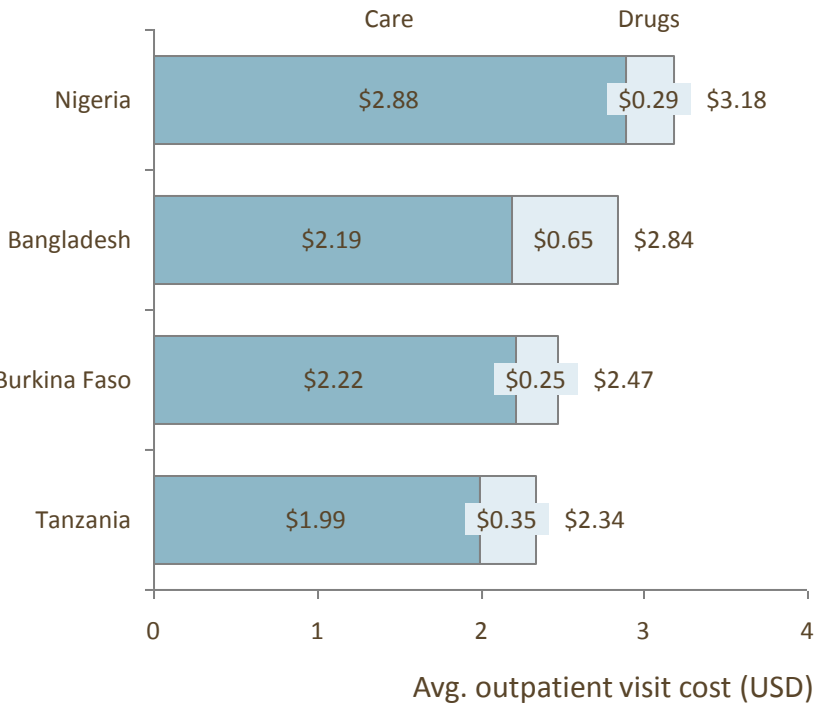
Intervention scenarios

Nigeria and Burkina Faso have highest under-5 fever mortality rates while Bangladesh has lowest



Nigeria has highest facility costs, while Bangladesh has most expensive drugs

Outpatient visit costs primarily from cost of care rather than medications



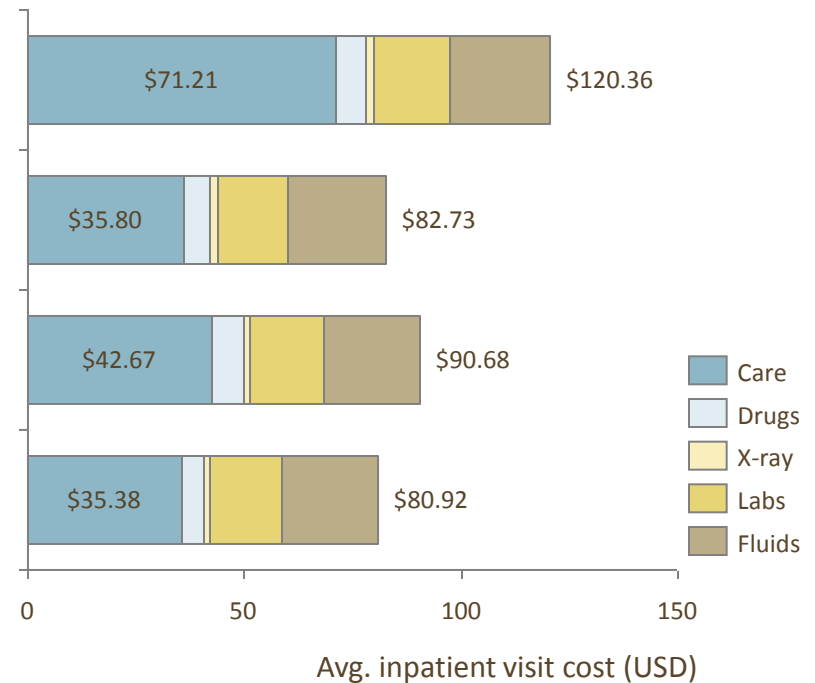
Inpatient visit costs significantly higher because of expensive procedures and high daily costs

x 38 →

x 27 →

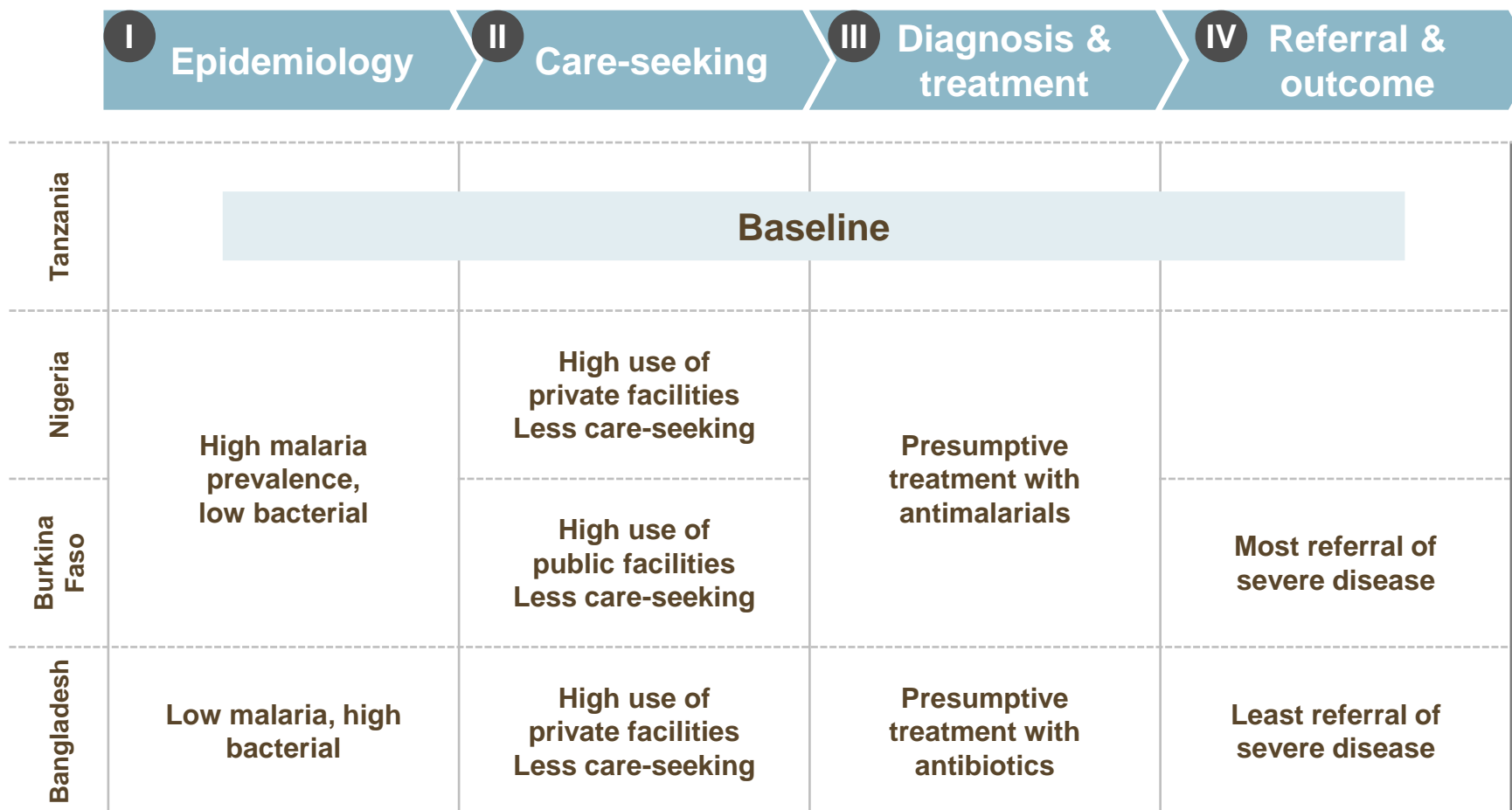
x 37 →

x 34 →



Source: BCG Analysis; Medicine Price Monitor; Disease Control Priorities Project, Acute Respiratory Infections in Children; Taghreed et al, Analysis Report on the Costs of IMCI in Tanzania, 2004; WHO Choice Program, Adam T, Evans D, Murray CJ. "Econometric estimation of country-specific hospital costs; Lubell et al, "Cost-effectiveness of parenteral artesunate for treating children with severe malaria in sub-Saharan Africa"

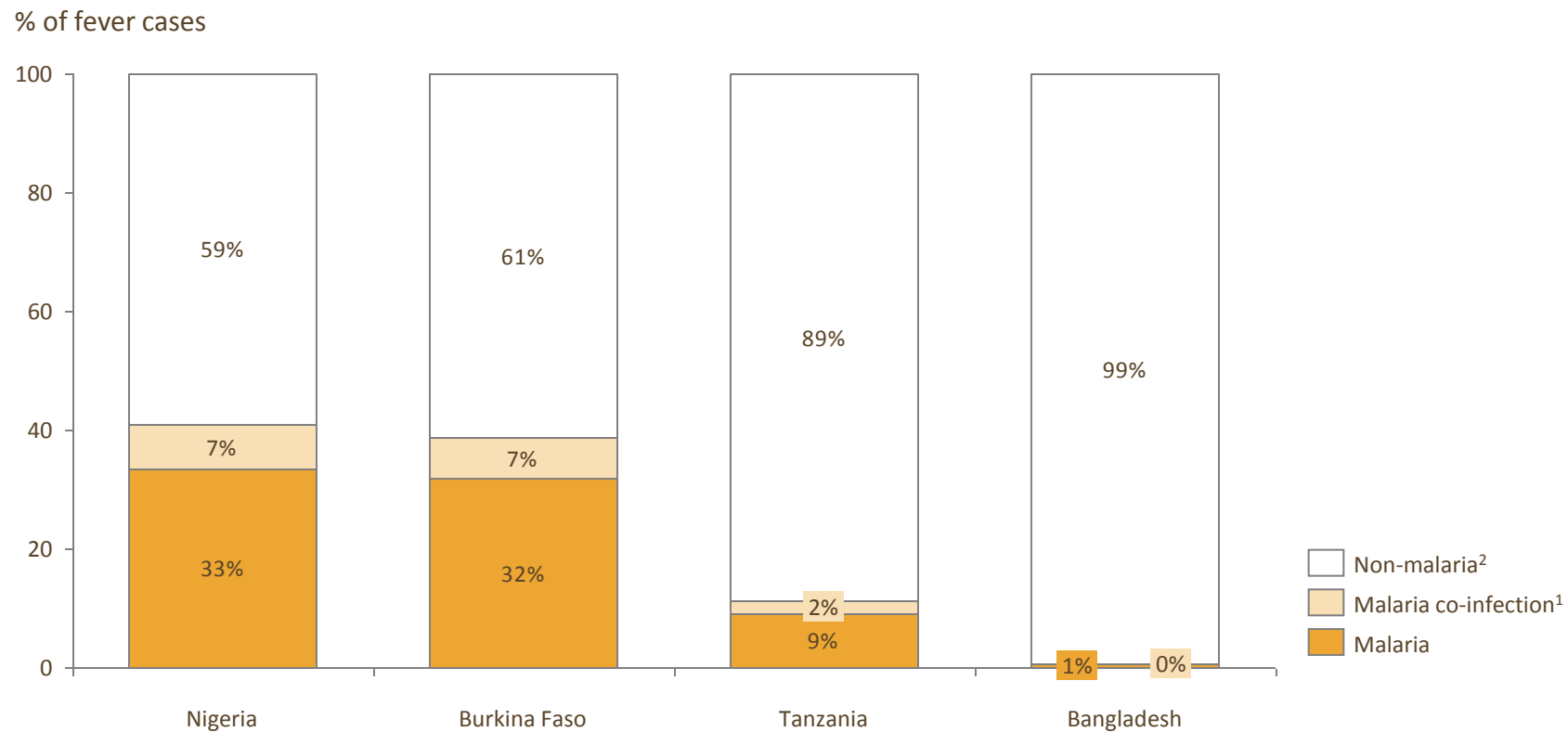
Baseline differences emerge across the patient flow



Malaria prevalence highest in Burkina Faso and Nigeria

Malaria is very small share of fevers in Bangladesh

Over 35% of febrile cases in Burkina Faso and Nigeria are caused by malaria

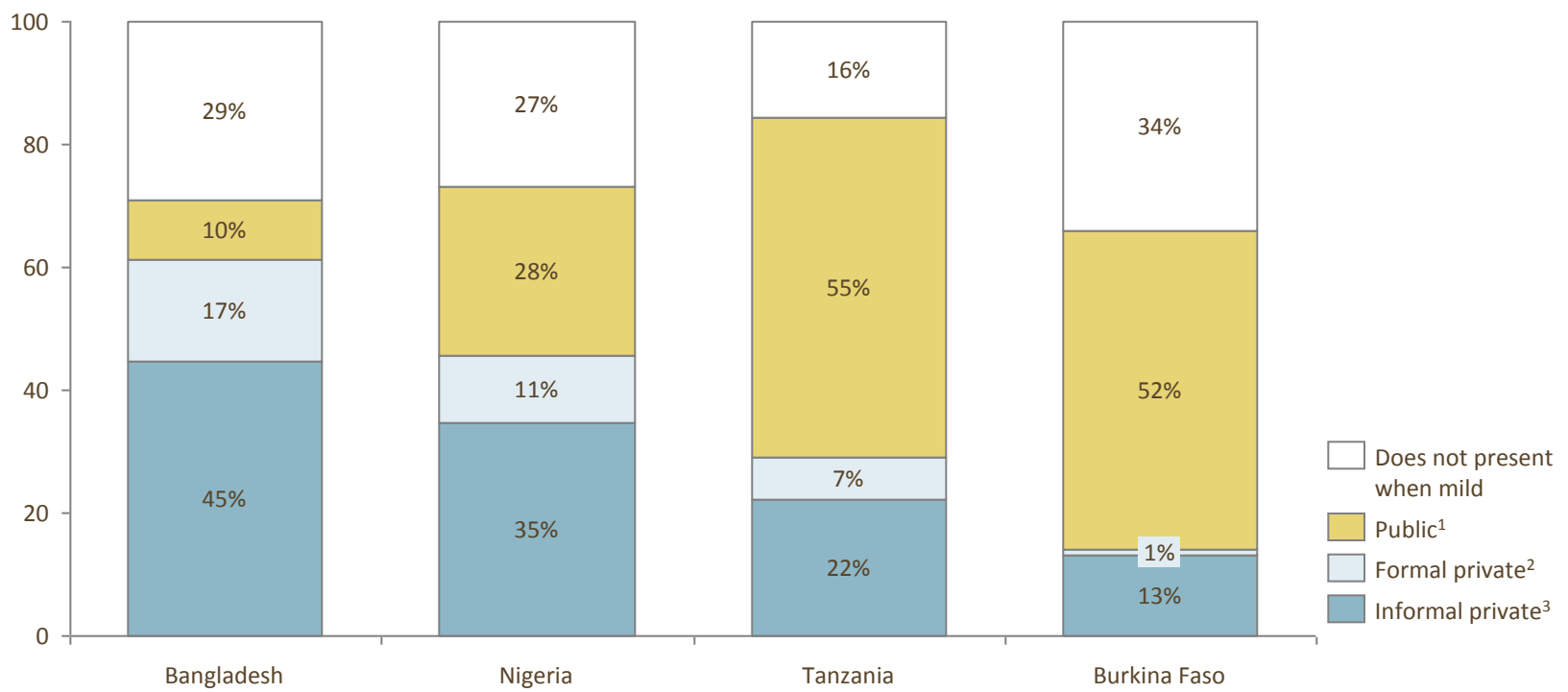


Majority of care-seeking in Bangladesh and Nigeria is private

Public facilities play much larger role in Tanzania and Burkina Faso

Tanzania has >10% higher rates of care-seeking than other focus countries

% of febrile cases



1. Comprised of all government-run facilities, including hospitals, clinics, health centers, mobile clinics, public fieldworker, etc. 2. Includes private hospitals, private health centers / clinics, private fieldworkers, mission hospitals, NGOs, etc. 3. Includes shops, traditional practitioners, private pharmacies, private chemists.

Source: BCG Analysis, DHS surveys

Widespread presumptive treatment across all 4 focus countries

Providers in Tanzania / Nigeria / Burkina presume malaria, those in Bangladesh presume bacteria

Provider behavior based on historical prevalence of disease

- Despite increasing availability of malaria RDTs, low adherence to result
- Respiratory rate rarely checked for pneumonia
- Viruses typically treated unnecessarily with antimalarials or antibiotics

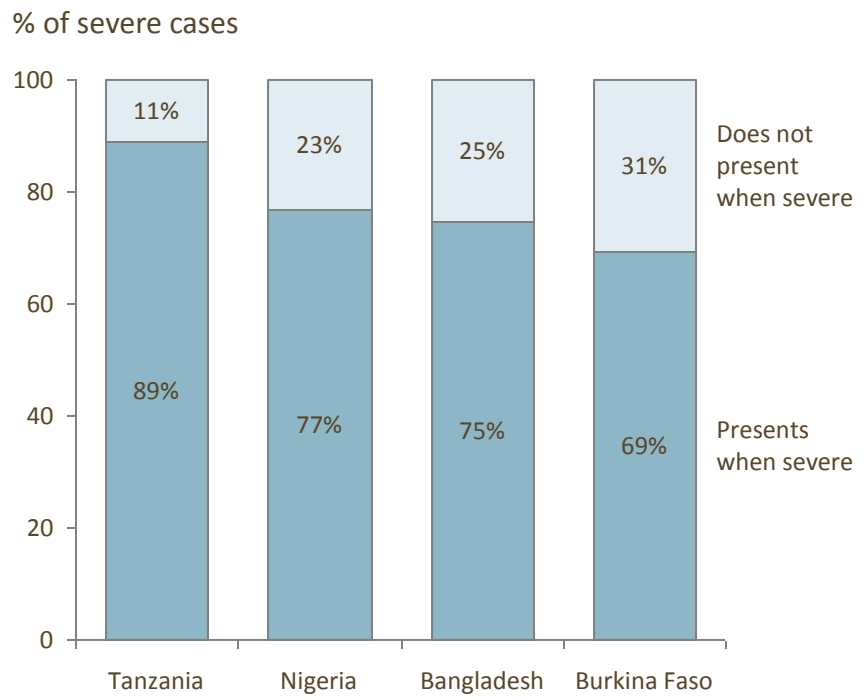
Care seeking behavior also drives overtreatment

- In Tanzania, Nigeria, and Burkina Faso, antimalarials generally available without a prescription
- In Bangladesh, providers give some kind of antibiotic to most patients, but now many *S. typhi* strains are resistant

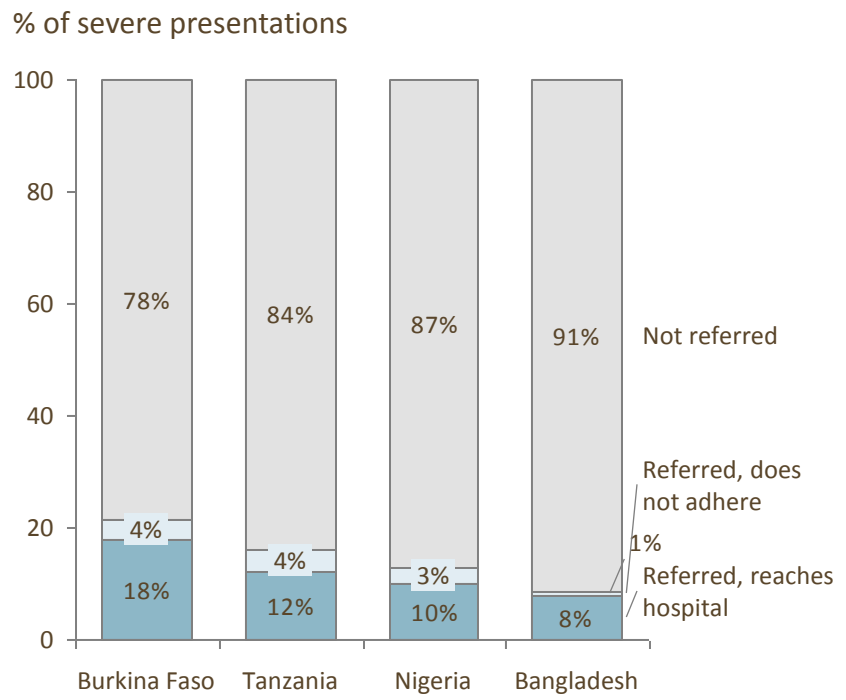
No more than ~18% of severe cases treated on in-patient basis

Lowest rates in Bangladesh and highest in Burkina Faso

Severe febrile patients in Tanzania more likely to present than in other countries



Only ~18% of severe patients who present in Burkina Faso reach appropriate referral facility



| | | | | |
|----------------------|-----|-----|-----|-----|
| Malaria: | 9% | 25% | 2% | 30% |
| Bacterial pneumonia: | 13% | 19% | 17% | 17% |

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Overview of gaps in care of febrile illness

Top-level finding

- a** Priority drivers are **similar across sub-Saharan Africa**, differ for Bangladesh

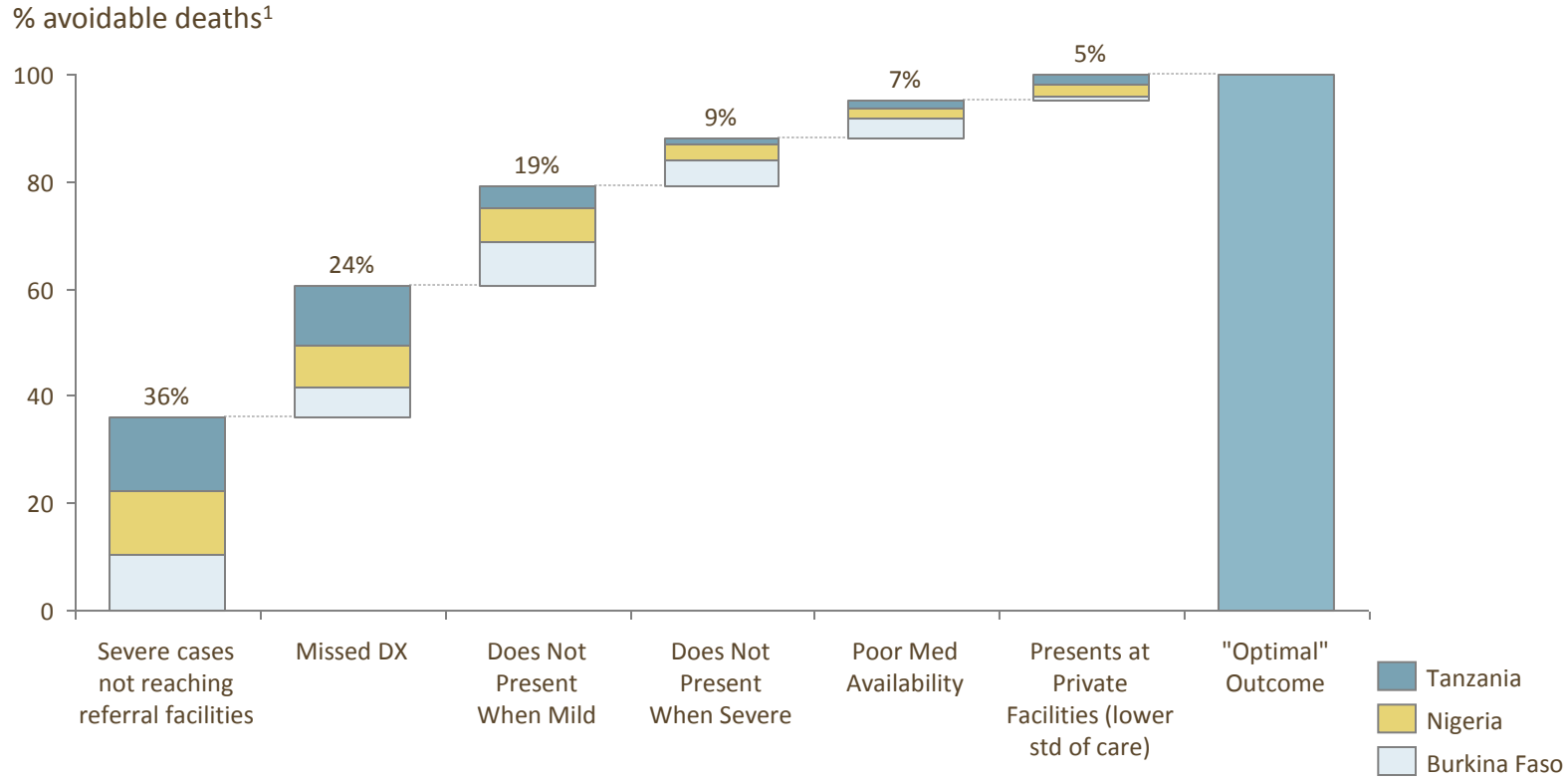
Geography-independent drivers of fatalities

- b** Patients who do not **present when mild** are almost twice as likely to become severe
- c** **Severe cases not reaching referral facility** is biggest driver of avoidable deaths

Geography-specific drivers of fatalities

- d** **Bacterial disease** is major driver in countries where malaria is less prevalent
- e** In sub-Saharan Africa, more **missed diagnoses** for bacterial disease than for malaria
- f** In Bangladesh, **low medicine availability** limits ability to treat correctly

Individual drivers of avoidable deaths similar across SSA, some differences in Bangladesh



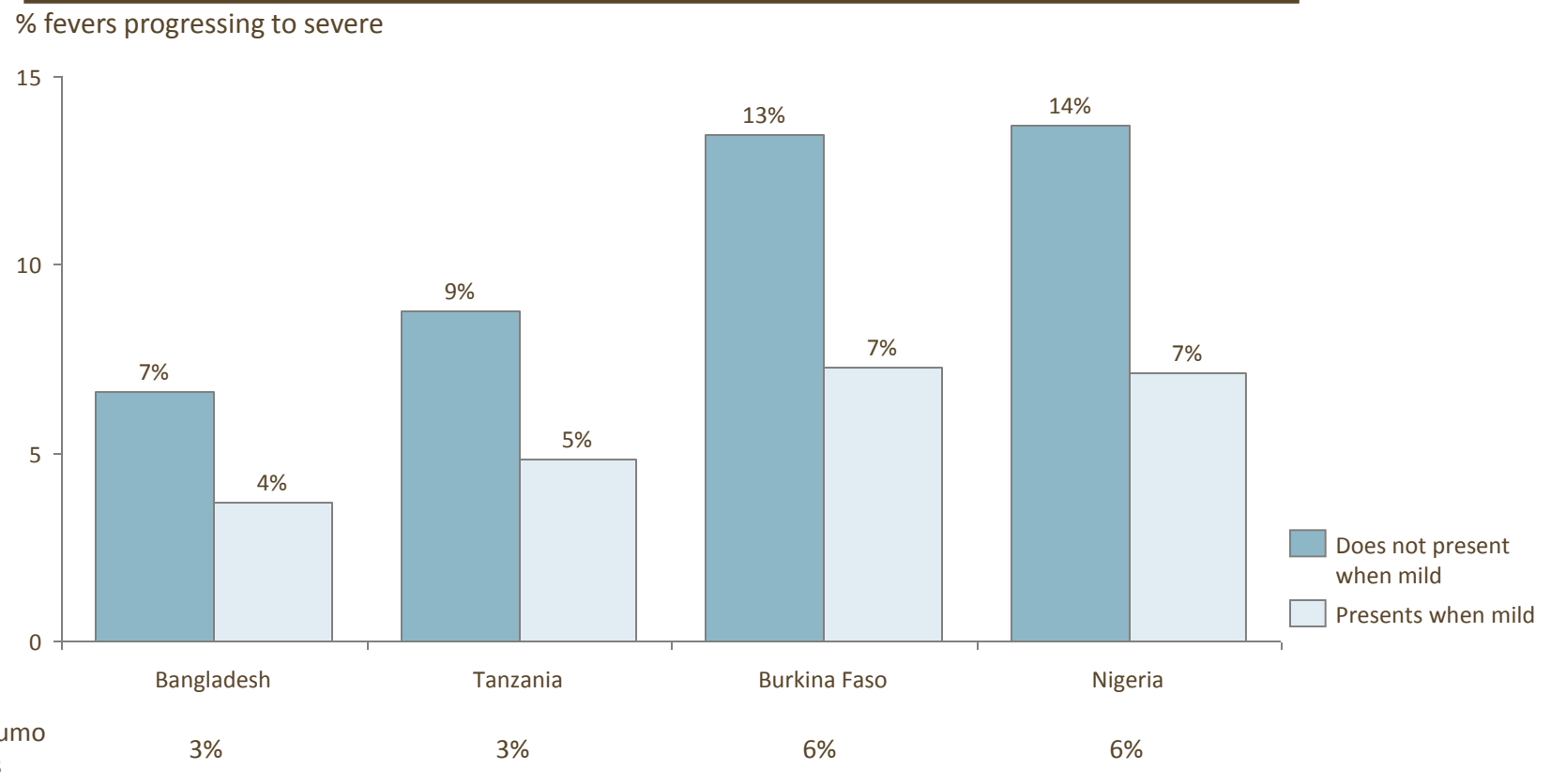
Bangladesh

| | | | | | | |
|--------------------|-----|----|-----|----|-----|----|
| % avoidable deaths | 38% | 7% | 23% | 9% | 18% | 6% |
| Driver rank | 1 | 5 | 2 | 4 | 3 | 6 |

1. Calculated as sum of % of avoidable deaths for each country divided by 3. Source: BCG Analysis

Across all focus countries, fevers are almost twice as likely to become severe if patient does not seek treatment when mild

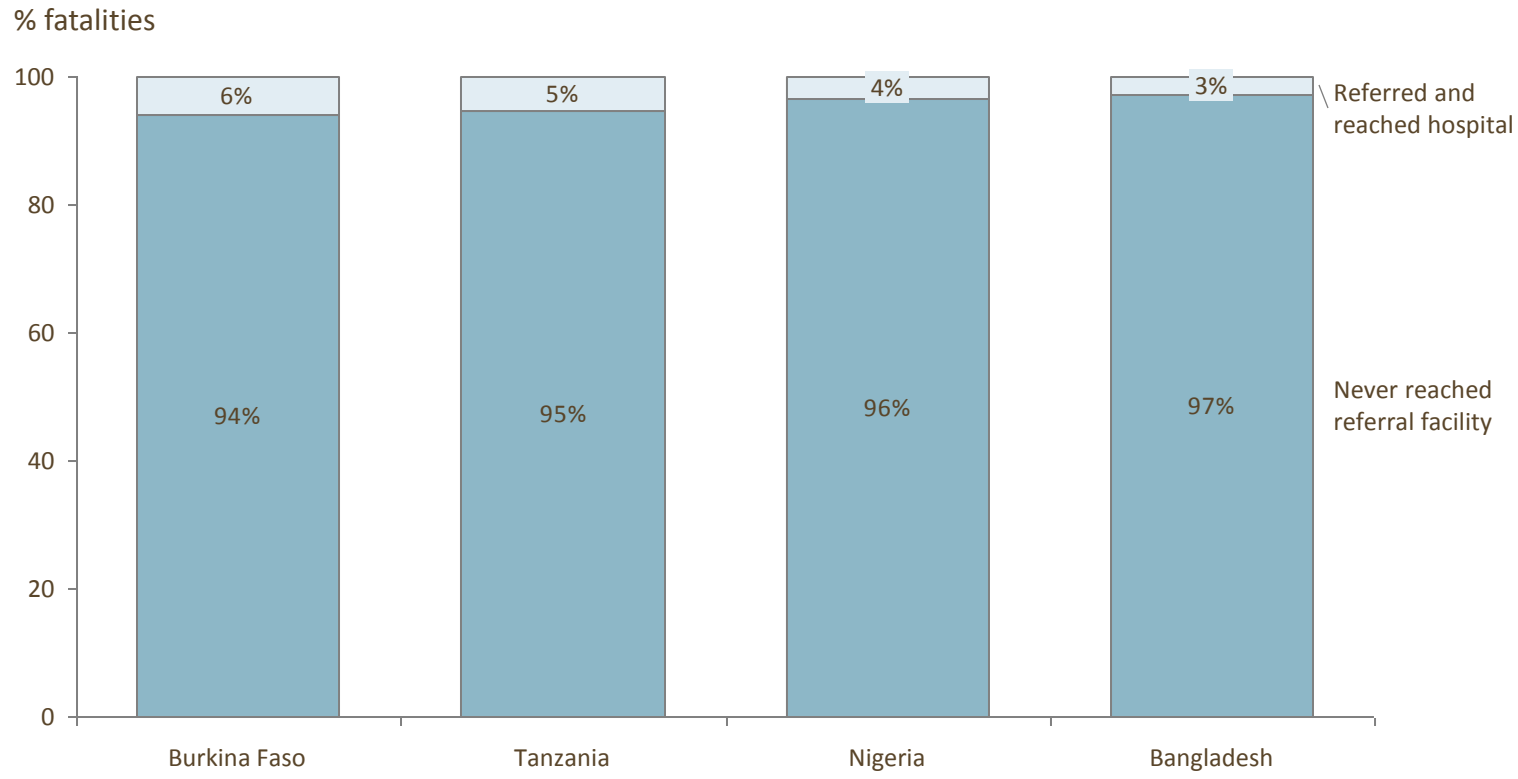
In Nigeria and Burkina Faso, over 10% of fevers that are not presented when mild progress to severe



Bacterial Pneumo as % of fevers

Across all focus countries, most fatalities occur in cases that never reach the hospital

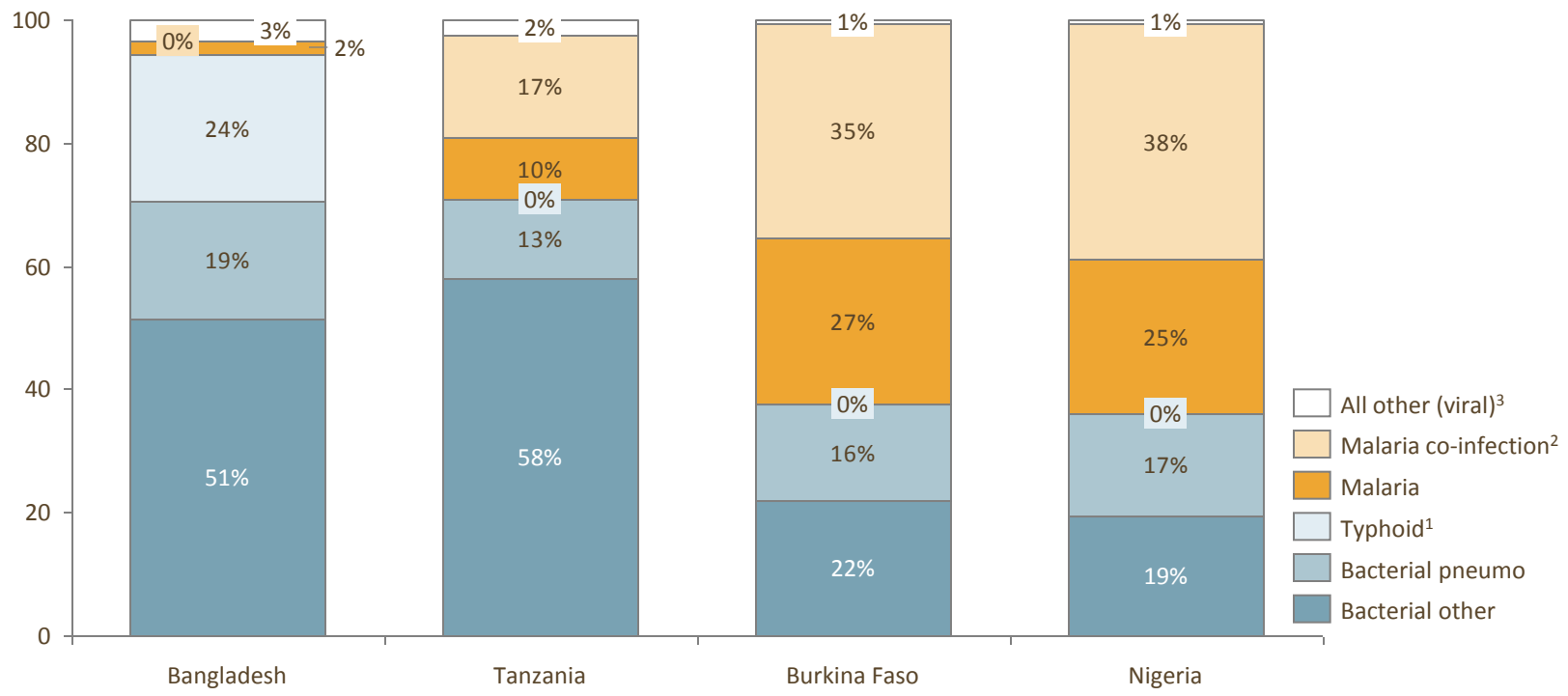
> 90% of deaths do not occur in the hospital



Bacterial disease is key driver of fatalities in Bangladesh and Tanzania, less significant when malaria rate is higher

Bacterial diseases drive >70% of deaths in Bangladesh and Tanzania but <40% in Nigeria and Burkina Faso

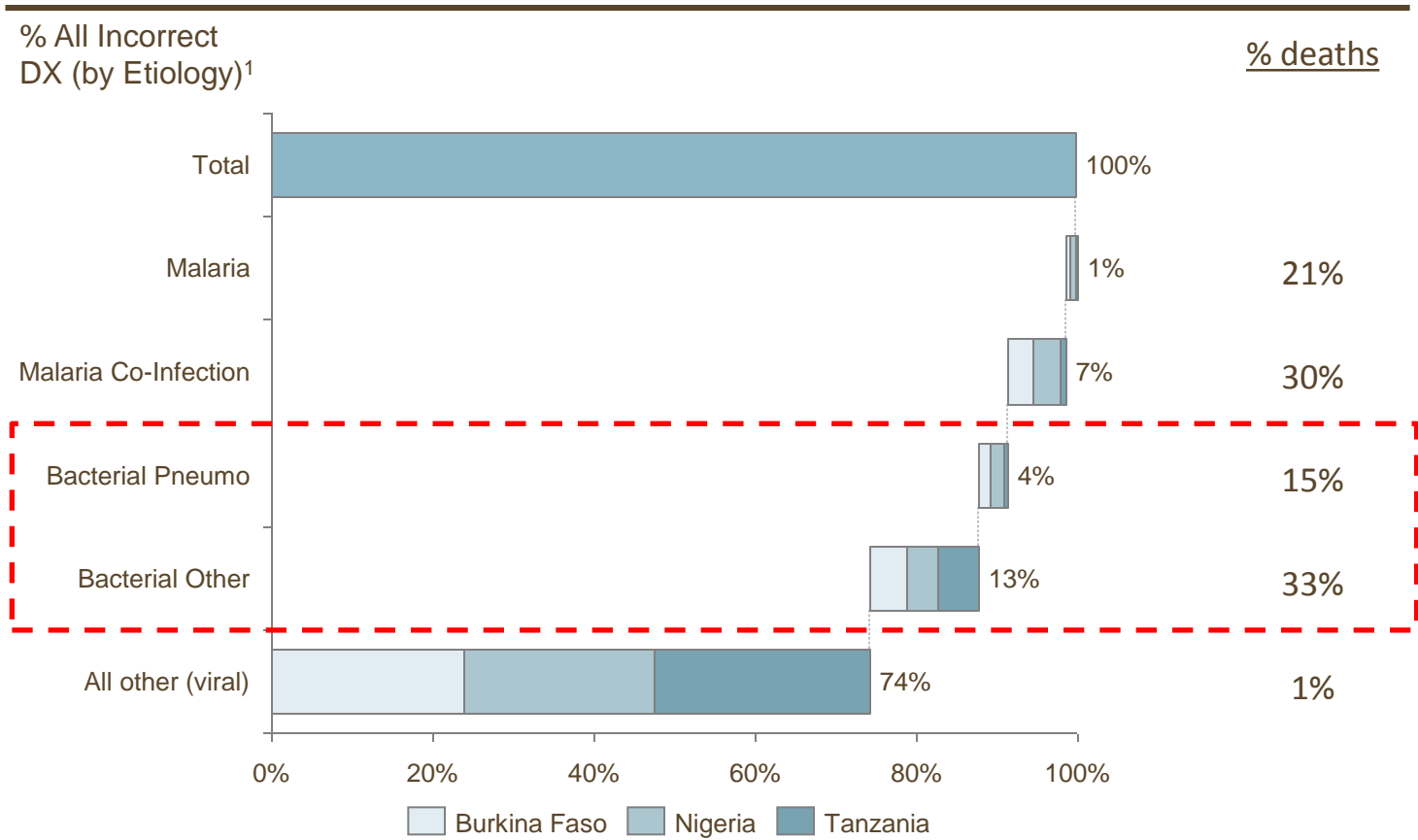
% of fever fatalities



1. Included in "Bacterial other" for Tanzania, Nigeria, and Burkina Faso. 2. Represents co-infection with a bacterial disease. 3. Viral cases represent a broad spectrum of etiologies but deaths are attributed primarily to pneumonia resulting from influenza and RSV
Source: BCG Analysis

In focus countries in sub-Saharan Africa, most missed diagnoses among non-viral are bacterial infections

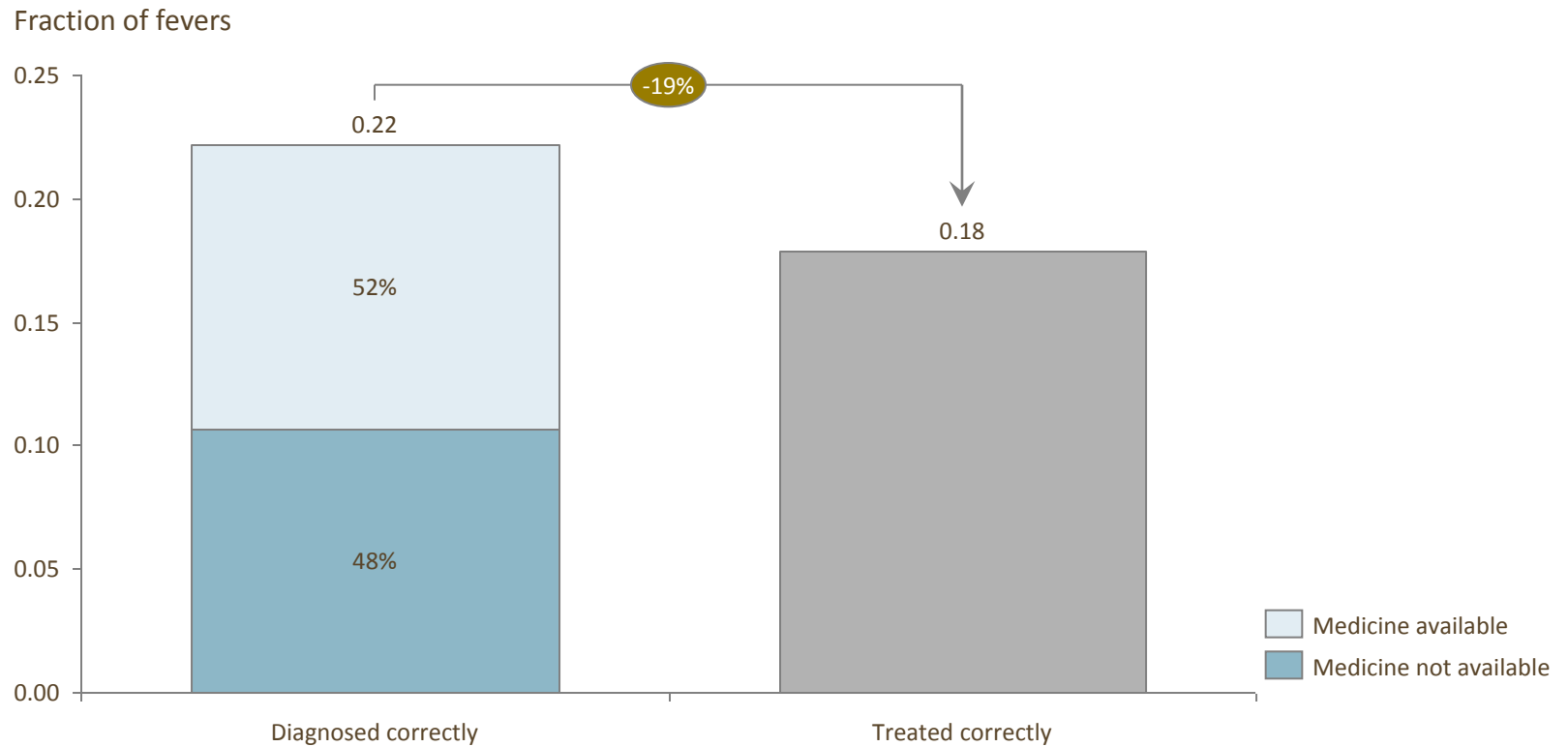
Bacterial infections comprise 18% of missed diagnoses



1. Calculated as sum of % of incorrect diagnoses for each country divided by 3. Source: BCG Analysis

In Bangladesh correct medication is often unavailable at primary site of care, so fevers diagnosed correctly are treated incorrectly

Of the 48% of correctly diagnosed fevers for which medication is not available, model assumes that half are able to buy at secondary facility



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Baseline analysis

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Intervention scenarios

Overview of interventions and high-level findings

| | Intervention | Comments |
|------------------------------------|---|---|
| 1 Diagnosis | 1a Universal access to malaria RDTs | <ul style="list-style-type: none"> Impact in malaria-endemic settings¹ is improved bact. dx Gains offset if RDT+ not assessed for co-infection |
| | 1b PoC diagnostic for bacterial vs. viral illness | <ul style="list-style-type: none"> Technology to be developed Expected to be implemented together with malaria RDT |
| | 1c Presumptive abx mgmt of all febrile cases | <ul style="list-style-type: none"> May effectively address bacterial disease in immediate term, but may drive abx resistance in long long run |
| 2 Other aspects of patient flow | Improved care-seeking | <ul style="list-style-type: none"> Very high impact due to poor outcomes for children who never receive treatment |
| | Improved medicine availability | <ul style="list-style-type: none"> Incorporates both antimalarial and abx availability Cost-savings of tx when mild due to severe disease averted |
| | Improved referral | <ul style="list-style-type: none"> Addresses biggest gap in system High cost intervention because of inpatient costs |
| 3 Integrated approach | Multi-pronged interventions | <ul style="list-style-type: none"> Incorporates combinations of promising interventions |

1. Settings in which there is presumptive treatment of malaria
Source: BCG Analysis

No single intervention averts more than 26% of fatalities

Ranges reflect differences across countries

| | Intervention | Impact (% fatalities averted) | Cost-effectiveness (\$/ fatality averted) |
|------------------------------------|--|-------------------------------|---|
| 1 Diagnosis | 1a Universal access to malaria RDTs | 4-22% ¹ | \$106-\$296 ¹ |
| | 1b PoC diagnostic for bacterial vs. viral illness | 4-20% ² | \$115-\$523 ² |
| | 1c Presumptive abx management of all febrile cases | 5-19% ¹ | \$(36)-\$423 ¹ |
| 2 Other aspects of patient flow | Improved care-seeking | 14-16% ² | \$136-\$351 ² |
| | Improved medicine availability | 2-7% ² | \$(40)-\$(11) ² |
| | Improved referral | 3-6% ² | \$693-\$920 ² |
| 3 Integrated approach | Multi-pronged interventions | 3-34% ² | \$(135)-652 ² |

1. Range represents output values for Tanzania, Nigeria, and Burkina Faso. 2. Range represents output values for Tanzania, Nigeria, Burkina Faso, and Bangladesh.
Source: BCG Analysis

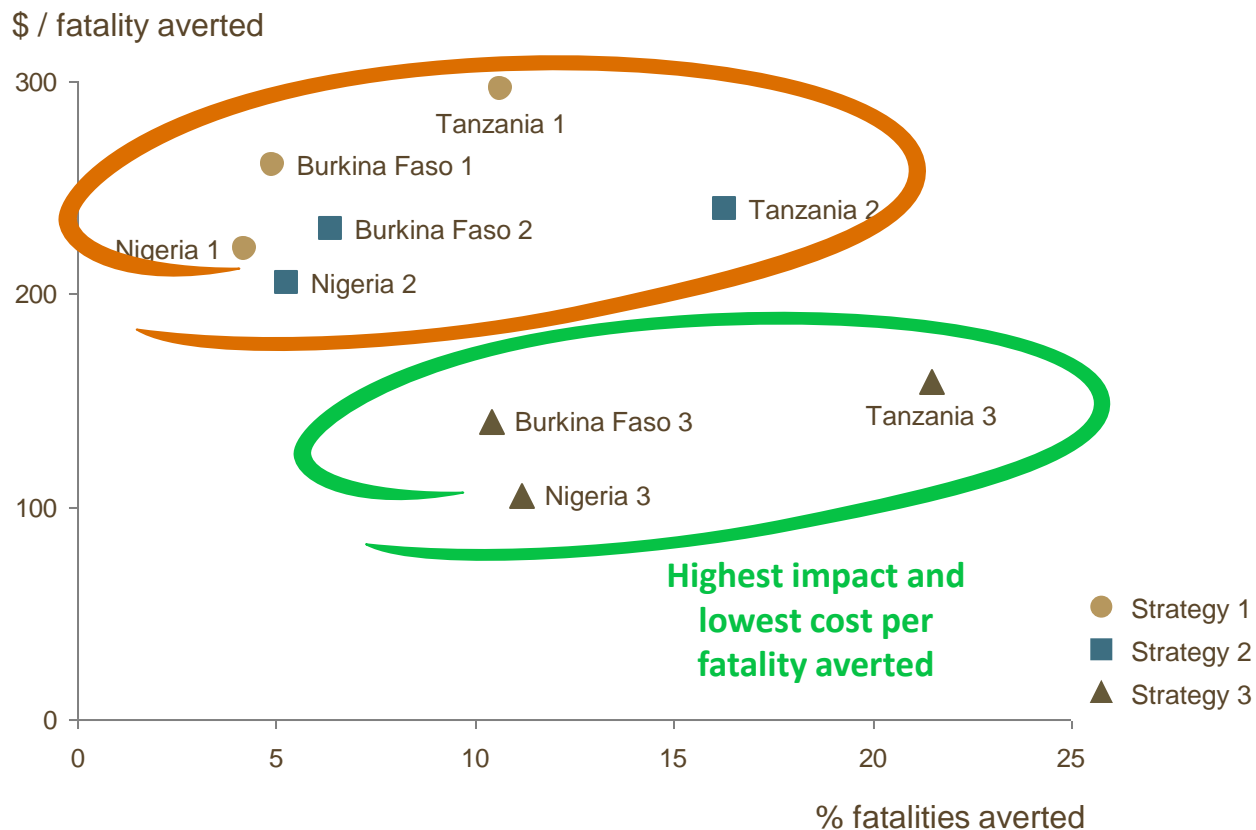
Impact of malaria RDT in context of presumptive malaria mgmt derived from improved identification of bacterial disease

Presumes application of malaria RDT in context of presumptive malaria mgmt

| | RDT (+) | RDT (-) | Expected outcome |
|---|--|---|--|
| Strategy 1 Universal RDT – no other policy change | Antimalarial & further clinical assessment | Further clinical assessment | <ul style="list-style-type: none"> RDT (-) result increases likelihood of identifying bacteria when mild |
| Strategy 2 Abx for RDT (-) | Antimalarial & further clinical assessment | Antibiotic | <ul style="list-style-type: none"> Ensure almost all mild bacteria infections correctly treated Broad unnecessary treatment of viral with abx |
| Strategy 3 Abx for severe fevers | Antimalarial, plus Abx if severe | Further clinical assessment (Abx if severe) | <ul style="list-style-type: none"> Consistent abx when severe drives improved outcomes RDT (-) result increases likelihood of identifying bacteria when mild |

Abx for severe fevers (Strategy 3) has greatest impact and is most cost-effective across Tanzania, Nigeria, and Burkina Faso

For all strategies, impact in Tanzania ~2x impact in Nigeria and Burkina Faso



Scenario parameters

Strategy 1:

- RDT-minus result for non-malaria etiologies increases likelihood of correct diagnosis by 20%

Strategy 2:

- 99% of bacterial etiologies treated correctly with abx; all viral cases treated incorrectly

Strategy 3:

- RDT-minus result for non-malaria etiologies increases likelihood of correct diagnosis when mild by 20%
- RDT also used at severe presentation, consistent abx use when severe

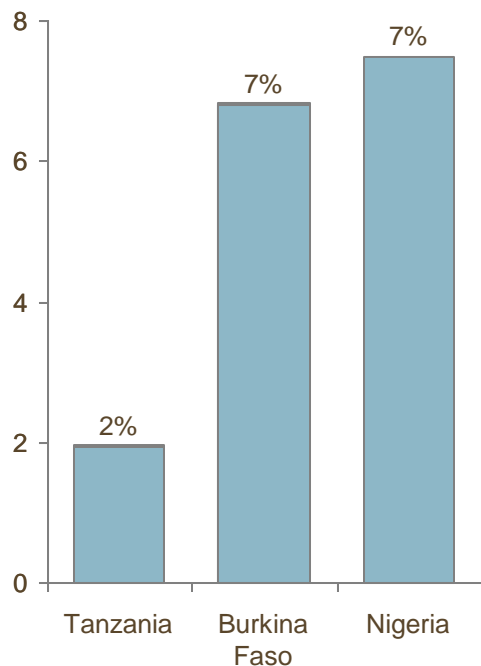
Costs:

- Malaria RDT ~\$0.70 per test
- Training and implementation costs not in scope

If no further assessment for co-infection on RDT+, benefit of RDT outweighed by increased fatalities in Nigeria and Burkina Faso

Nigeria and Burkina Faso have 3-4x co-infection rates of Tanzania

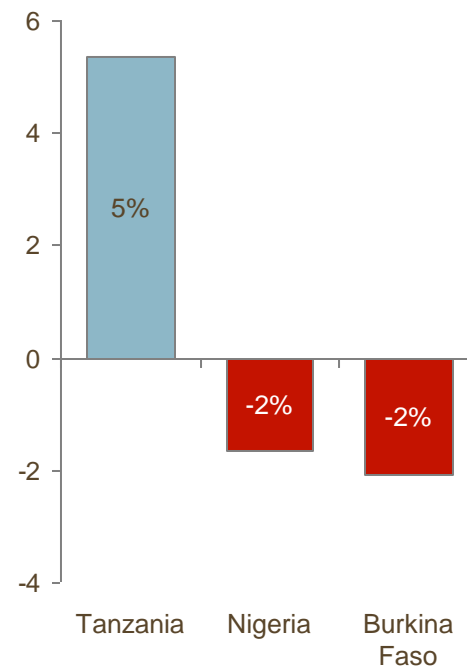
% cases with malaria co-infection



Input

Add'l fatalities from co-infection in Nigeria and Burkina Faso greater than fatalities averted

% decrease in fatalities



Output

Scenario parameters

Probabilities:

- Strategy 1: assumes RDT-minus result for other non-malaria etiologies increases likelihood of correct diagnosis by 20%
- Revision: 50% of co-infections incorrectly diagnosed

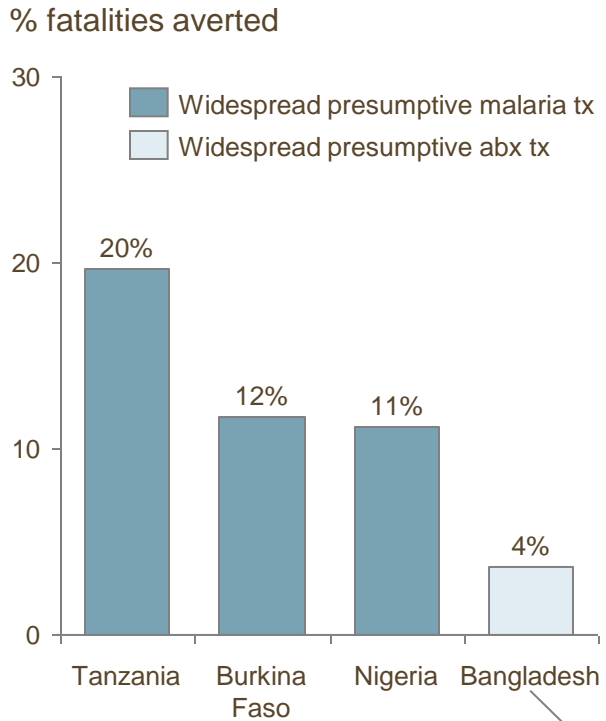
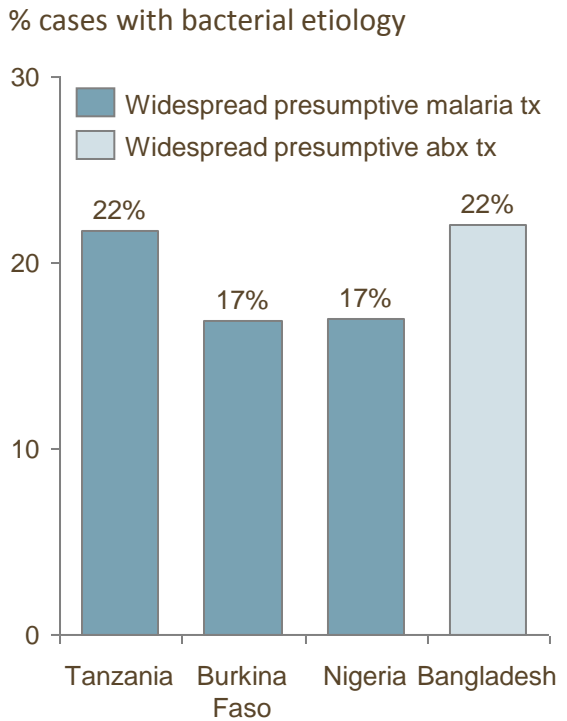
Costs:

- Malaria RDT ~\$0.70 per test
- Training and implementation costs not in scope

Bacterial PoC diagnostic most impactful in Tanzania because of relatively higher rates of bacterial disease

~60% of bacterial cases correctly diagnosed (>97% for malaria)

If malaria presumptively treated but bacterial disease prevalent, intervention has greater impact



\$ / fatality averted

\$185 \$129 \$115 \$523

Input

Output

Impact derives from increased presentation when mild

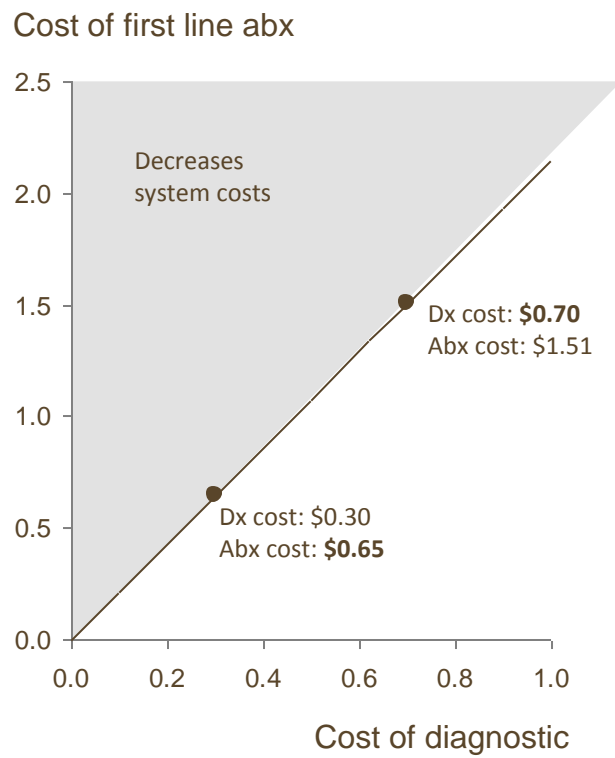
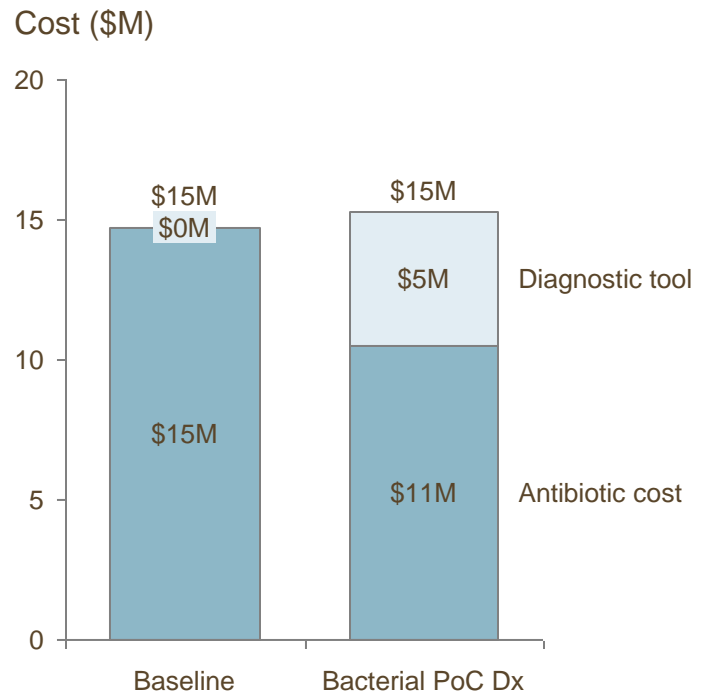
Scenario parameters

- Probabilities:**
- Probability of correct diagnosis for bacterial and viral etiologies of 90%
 - Probability of correct diagnosis of malaria of 95% from simultaneous RDT use
 - Caretakers select providers for availability of diagnostics (presentation improves by 5% of baseline value)
- Costs:**
- Assume consumables cost ~\$0.70 / test (benchmarked against current malarial RDT cost)
 - No exogenous cost impact

Bact. diagnostic limits abx overuse for viral cases in Bangladesh

For baseline, cost of diagnostic greater than savings from reducing viral abx use

If cost of diagnostic decreases or cost of abx increases, intervention decreases system costs



Scenario parameters

Probabilities:

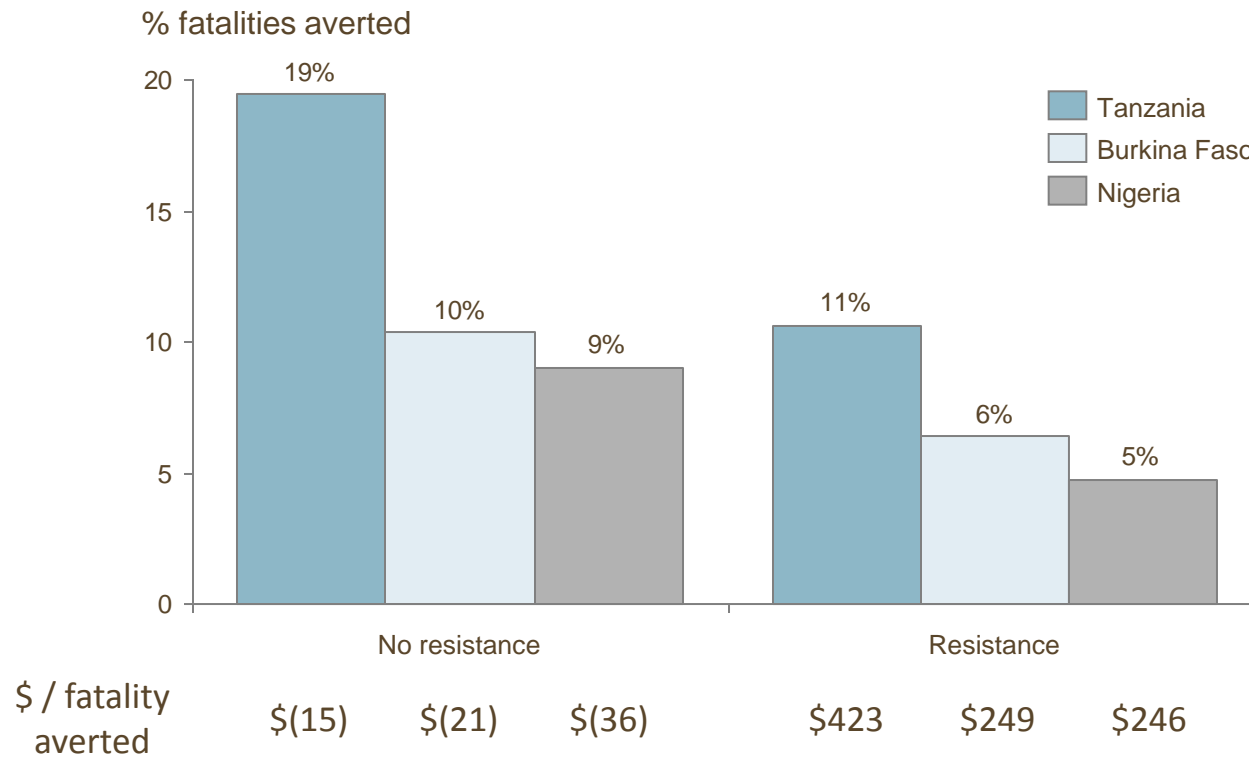
- Probability of correct diagnosis for bacterial and viral etiologies of 90%

Costs:

- Assume consumables cost ~\$0.70 / test (benchmarked against current malarial RDT cost)
- No exogenous cost impact

Presumptive abx mgmt improves treatment of bacterial fevers, but impact may be attenuated in long run by drug resistance

Impact in Tanzania consistently greater because of higher relative rates of bacterial disease



Output

Scenario parameters

No resistance:

- 99% of bacterial etiologies treated correctly with abx; all viral cases treated incorrectly

Resistance:

- 99% of bacterial etiologies treated correctly with abx; all viral cases treated incorrectly
- Use of costlier second-line abx
- 1.5x progression to severe for bacterial disease

Costs:

- Training and implementation costs not in scope

Interventions not focused on diagnosis were also assessed

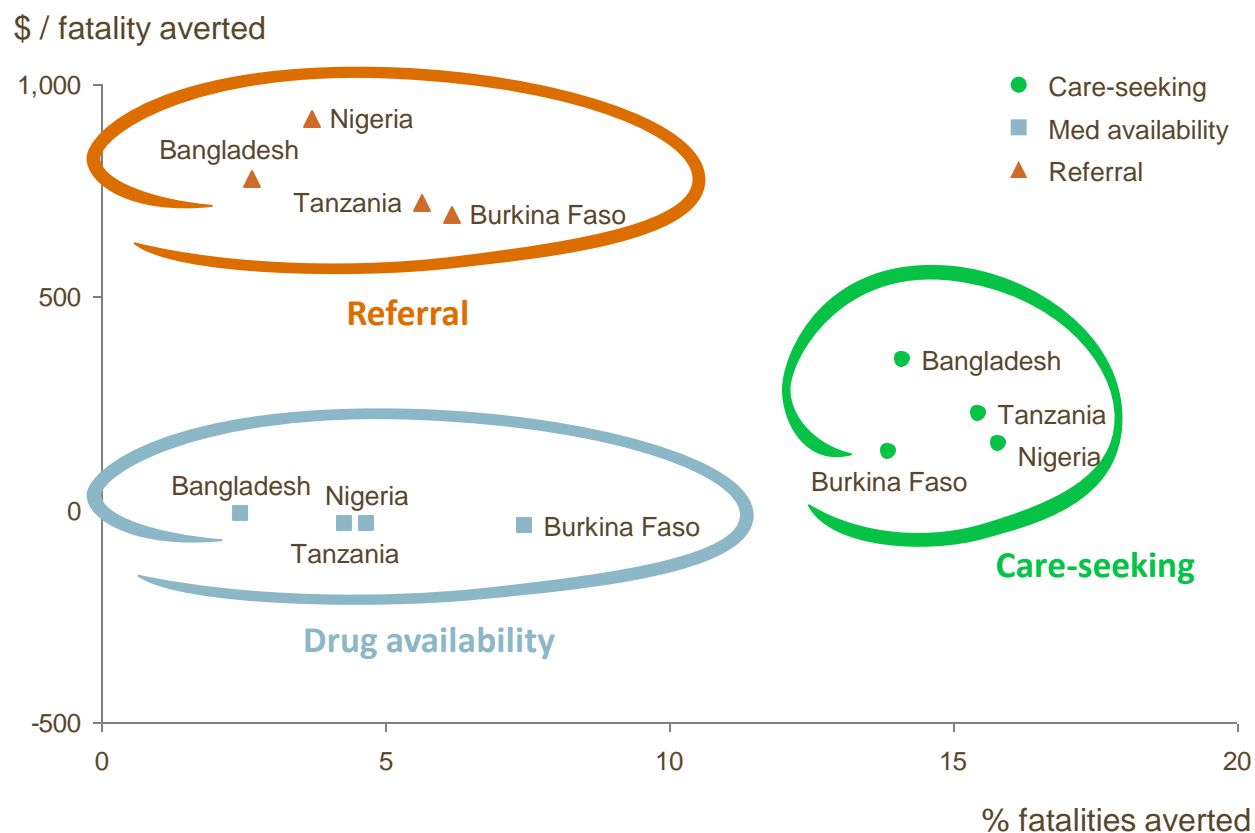
Patient flow from incidence to outcome

| | Care-seeking | Drug availability | Referral |
|--|---|---|--|
| Example programs | <ul style="list-style-type: none"> Mass education campaign | <ul style="list-style-type: none"> Programs to boost supply chain Subsidized medicine | <ul style="list-style-type: none"> Ambulance coverage Subsidized travel Provider training on danger signs |
| <hr/> | | | |
| Baseline values | | | |
| Tanzania | 84% ¹ | 82% ² | 12% ³ |
| Nigeria | 73% ¹ | 72% ² | 10% ³ |
| Burkina Faso | 66% ¹ | 69% ² | 18% ³ |
| Bangladesh | 71% ¹ | 23% ² | 8% ³ |
| Presumed effect of intervention | x1.2 | x1.5 | x2 |

1. % of cases that present with mild disease; average across rural and urban settings. Rate of presentation of severe disease was also increased proportionally. 2. % of non-viral cases for which the correct medication (antimalarial or antibiotic) was available. 3. % of cases presenting with severe disease who are referred and reach referral facility.
Source: BCG Analysis

Improving care-seeking has highest impact among non-Dx-focused interventions evaluated

Treatment when severe costs more than when mild, so referral increases costs while drug availability reduces disease progression and lowers costs



Scenario parameters

Care-seeking:

- Improve rate of care-seeking by 20% of baseline value for mild and severe

Drug availability:

- Medicine availability for malaria and bacterial disease increases by up to 50%

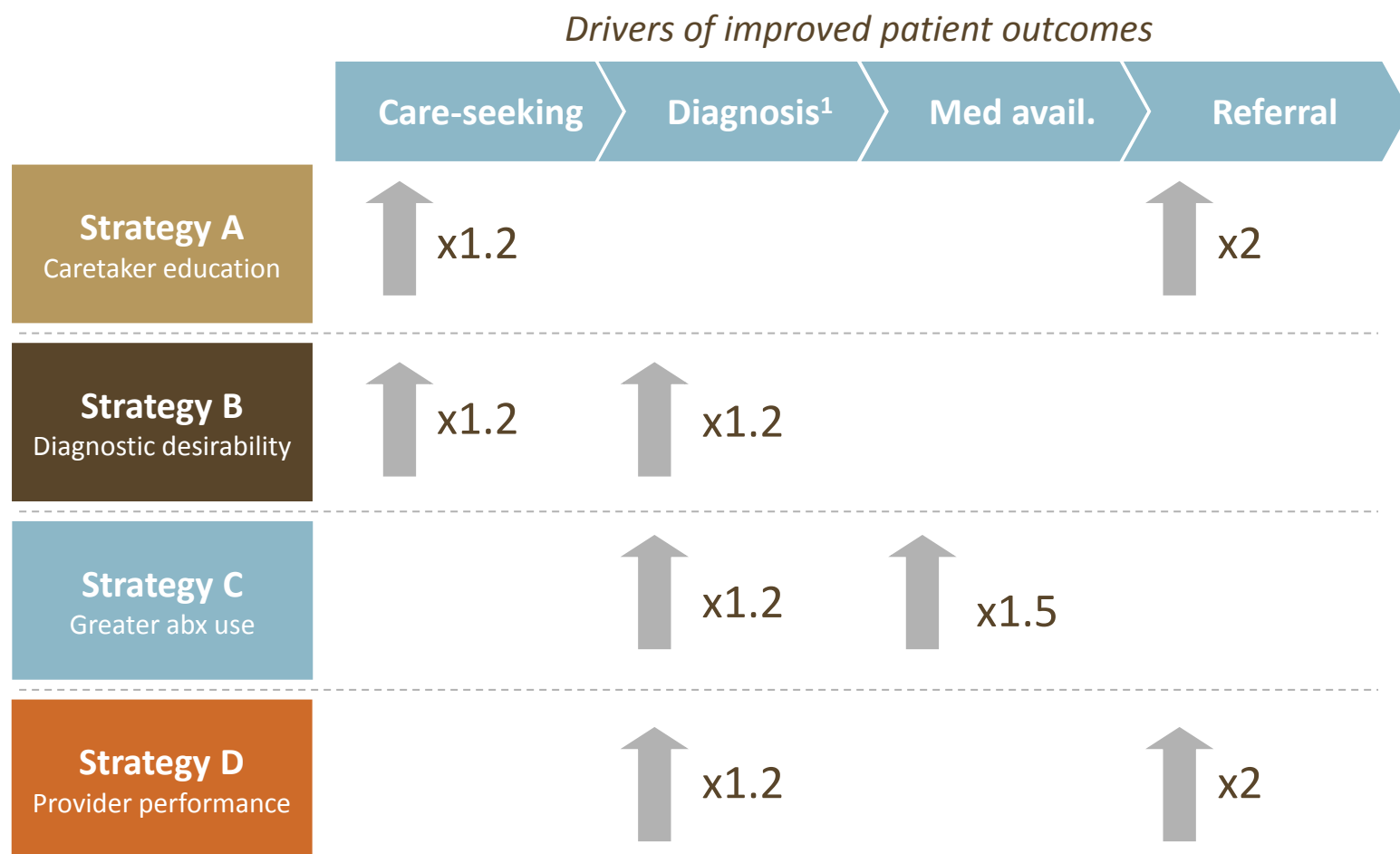
Referral:

- Referral rate doubles

Costs:

- Training and implementation costs not in scope

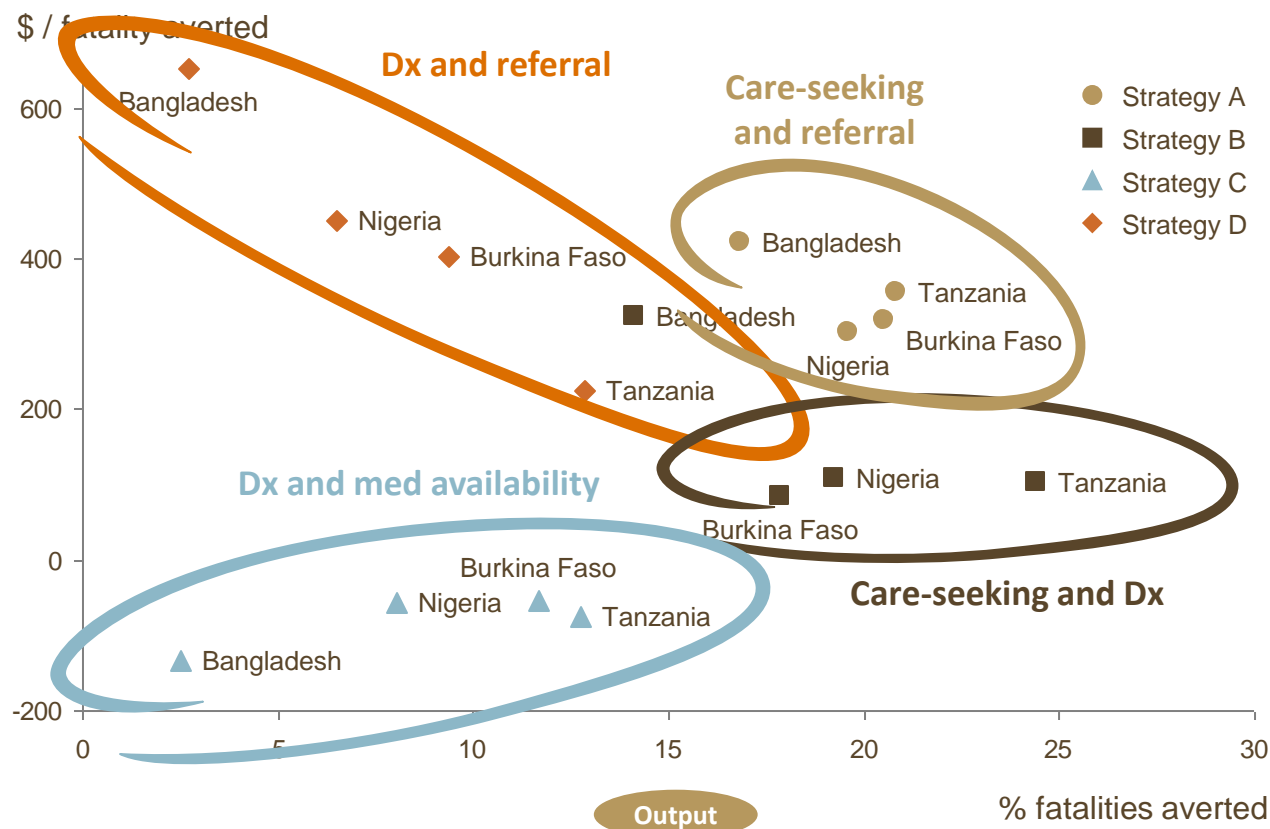
Multi-pronged interventions simultaneously address multiple drivers of improved outcomes



1. Value for correct diagnosis of each disease were consistently incremented by a flat 15%, which represents an average of 20% increase across all disease.
Source: BCG Analysis

Improving care-seeking and diagnosis has highest impact with lowest cost per fatality averted

Tanzania has greatest impact for interventions involving diagnosis



Scenario parameters

Strategy A:

- Rate of care-seeking increases by 20% of baseline value for mild and severe
- Referral rate doubles

Strategy B:

- Rate of care-seeking increases by 20% of baseline value for mild and severe
- Rate of correct Dx increases by 15% for each disease

Strategy C:

- Rate of correct Dx increases by 15% for each disease
- Medicine availability for malaria and bacterial disease increases by up to 50%

Strategy D:

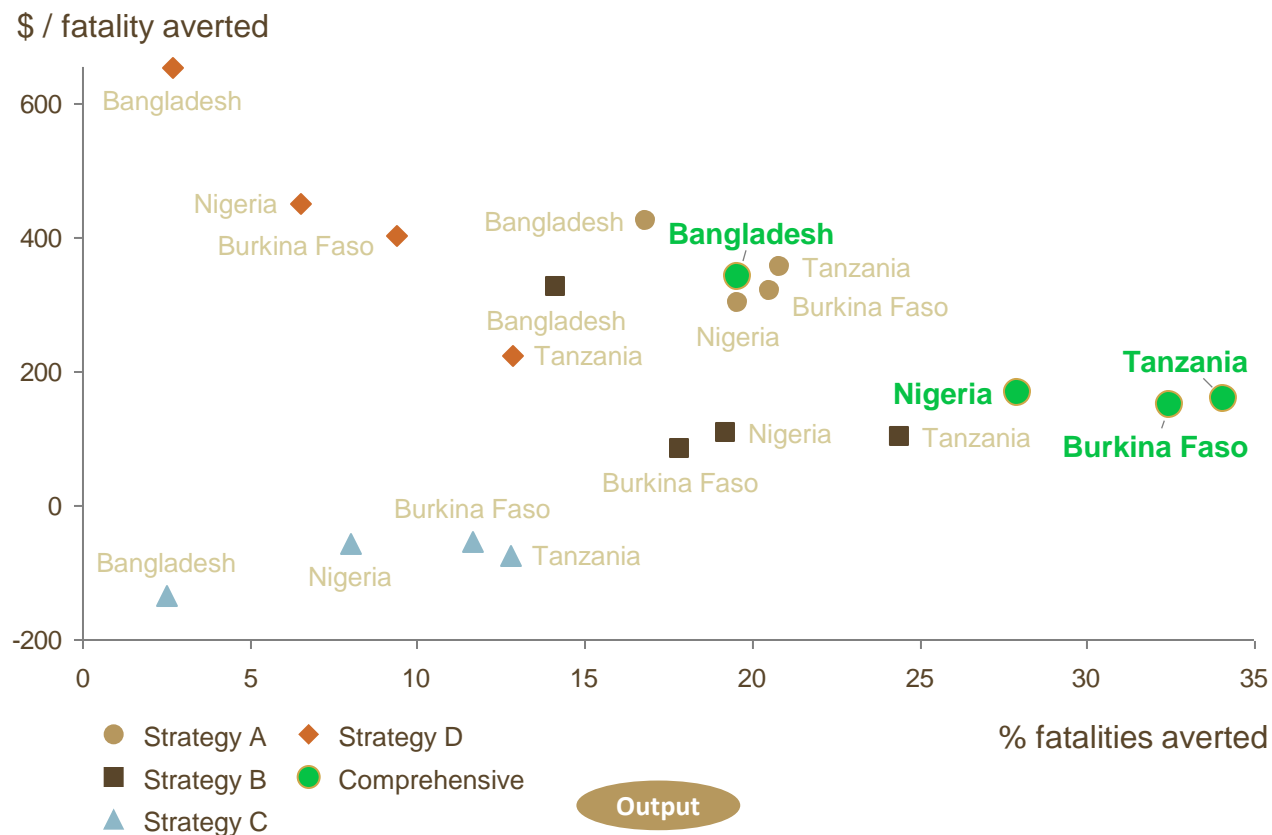
- Rate of correct Dx increases by 15% for each disease
- Referral rate doubles

Costs:

- Training and implementation costs not in scope

Interventions targeting all 4 drivers of improved outcomes have greater impact in Tanzania, Nigeria, and Burkina than Bangladesh

20-35% impact on fatalities when all 4 drivers of improved outcomes applied simultaneously



Scenario parameters

Strategy A:

- Rate of care-seeking increases by 20% of baseline value
- Referral rate doubles

Strategy B:

- Rate of care-seeking increases by 20% of baseline value
- Rate of correct Dx increases by 15% for each disease

Strategy C:

- Rate of correct Dx increases by 15% for each disease
- Medicine availability increases by up to 50%

Strategy D:

- Rate of correct Dx increases by 15% for each disease
- Referral rate doubles

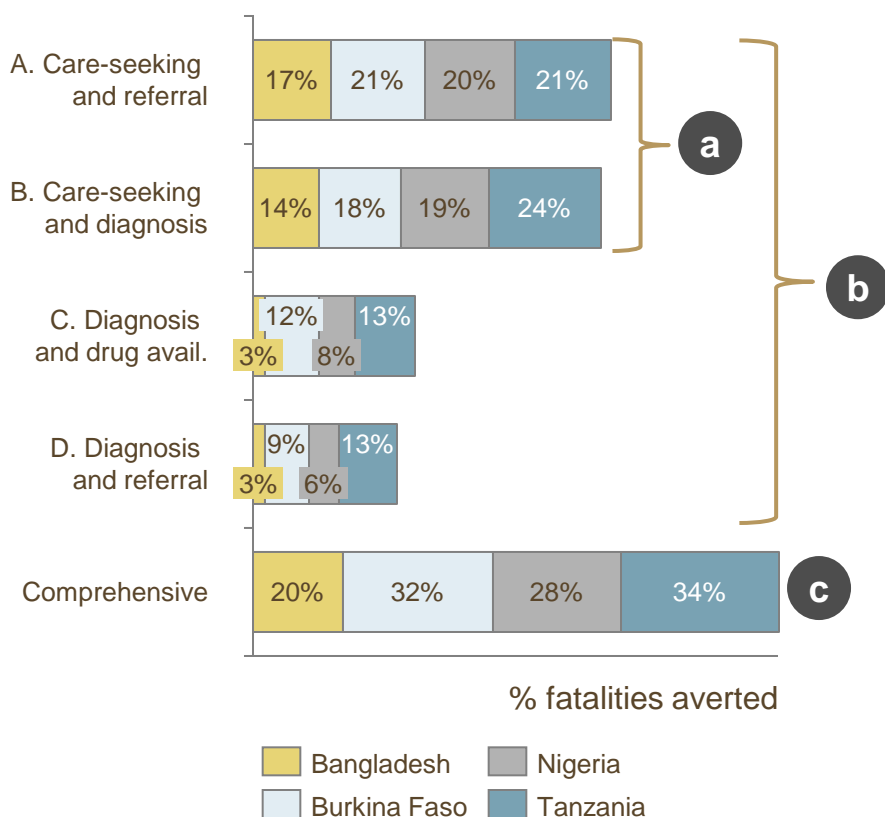
All:

- Rate of care-seeking increases by 20% of baseline value
- Rate of correct Dx increases by 15% for each disease
- Medicine availability increases by up to 50%
- Referral rate doubles

An integrated intervention that targets multiple drivers of patient outcomes is powerful but should prioritize care-seeking

Across all countries, strategies A and B have greatest impact

Comments



- a** Improving care-seeking and either referral or diagnosis achieves >60% of impact of a comprehensive intervention
- b** In SSA countries strategies C and D possess ~50% of impact of strategies A and B, but in Bangladesh impact of C and D is <20% that of A and B
- c** Potential overall impact greatest in Tanzania and Burkina Faso, where use of public and formal private facilities is higher.

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