Digital tools for diagnosis of infections in low-income settings

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Each year, 3.3 million children die from an acute febrile episode.
Children in LMICs are heavily affected by antibiotic over-prescription

Children 0-5 years
8 Low-Middle Income Countries

68%
(41-83%)
Prescribed antibiotics

24.5x
(7-59)
Estimated number of antibiotic prescriptions per child up to 5 years old

Fink et al., Lancet ID, 2019
Children in LMICs are heavily affected by incorrect antibiotic prescriptions

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>% of 282 febrile patients prescribed amoxicillin</th>
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</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>69.5% (196)</td>
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<tr>
<td>Urinary tract infection</td>
<td>11.0% (31)</td>
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<tr>
<td>Gastroenteritis</td>
<td>8.9% (25)</td>
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<tr>
<td><strong>Pneumonia</strong></td>
<td><strong>3.6% (10)</strong></td>
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<tr>
<td>Fever without source</td>
<td>2.5% (7)</td>
</tr>
<tr>
<td>Skin infection, other than abscess</td>
<td>2.0% (6)</td>
</tr>
<tr>
<td>Oral thrush</td>
<td>1.4% (4)</td>
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<tr>
<td><strong>Ear infection</strong></td>
<td><strong>0.4% (1)</strong></td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>0.4% (1)</td>
</tr>
<tr>
<td>Viral illness</td>
<td>0.8% (2)</td>
</tr>
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</table>

95% of febrile children received an antibiotic

**Dosing:**
- 29% within range (25-100mg/kg/d)
- 71% too small

Keitel K et al., PlosMed 2017
Antibiotics are primarily prescribed in the outpatient setting

80 – 90% of antibiotic use occurs in outpatient setting

WHO IS PREScribing?

74%

- General practice

- Hospital inpatients: 11%

- Hospital outpatients: 7%

- Dental practices: 5%

- Other community settings: 3%

Digital health interventions in LMICs

Client

Healthcare providers

Health systems management

Data services

Laboratory tests to order/interpretation? Treat? Refer?

eCDSS/eCDSA

WHO, 2016
Diagnostics and Treatment Decisions are inherently linked

Practice guidelines
- Quickly outdated
- Format inappropriate

Diagnostic tests
- Not available

In-service training/supervision
- Insufficient

Inappropriate treatment
Starting Point: Integrated Management of Childhood Illnesses

Assess

Classify

Treat/Refer

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**IF YES:** Decide malaria risk: high or low

**THEN ASK:**
- **For fever?**
- **Fever last 7 days, lasts longer than 3 days a week?**
- **Has the child had measles within the last 3 months?**

**LOOK AND FEEL:**
- **Look for signs of MEASLES**
- **Generalized rash and**
  - One of these: cough, runny nose, or red eyes

**IF the child has a fever now or within the last 3 months:**
- **Look for white spots. Are they deep and separable?**
- **Look for purging away from the eye.**
- **Look for lesions of the mouth.**

**EXPECTED OUTCOMES:**
- **HIGH MALARIA RISK**
  - Malaria is significantly likely
  - **VERY SEVERE FEBRILE DISEASE**
    - Give quinine for severe malaria (first dose)
    - Give twice a day of an appropriate antimalarial
    - Treat the child for pneumonia
    - Give one dose of paracetamol (Ibuprofen for high fever)*
    - Rule disease other than malaria
  - **MALARIA**
    - Enter treatment with chloroquine or other recommended antimalarial
    - Give one dose of pyrimethamine/sulfadoxine for high fever (54°C or above)
    - Arrange for referral to seek immediate care
    - Follow-up in 2 days after hospital admission
  - **FEVER - MALARIA UNLIKELY**
    - Give one dose of paracetamol (Ibuprofen for high fever)*
    - Rule disease other than malaria
  - **FEVER - NO MALARIA**
    - Enter treatment with chloroquine or other recommended antimalarial
    - Give one dose of pyrimethamine/sulfadoxine for high fever (54°C or above)
    - Arrange for referral to seek immediate care
    - Follow up in 2 days after hospital admission
    - Rule disease other than malaria

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* These temperatures are based on axillary temperature. Rectal temperature readings are approximately 0.5°C higher.
** Other important complications of measles - pneumonia, otitis media, diarrhea, encephalitis, and enanthema - are classified in other boxes.

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Electronic decision support algorithms

- Cough?
- Malaria rapid test
  - CRP
- Cold
  - Paracetamol
IMCI 2014 – section on fever

Does the child have fever?
(by history or feels hot or temperature 37.5°C* or above)

Look and feel:
- Look or feel for stiff neck.
- Look for runny nose.
- Look for any bacterial cause of fever**.
- Look for signs of MEASLES.
  - Generalized rash and
  - One of these: cough, runny nose, or red eyes.

WHO, 2014
**Look for local tenderness; oral sores; refusal to use a limb; hot tender swelling; red tender skin or boils; lower abdominal pain or pain on passing urine in older children.**
- Malaria test NEGATIVE
- Other cause of fever PRESENT.

Green:
FEVER:
NO MALARIA

- Give one dose of paracetamol in clinic for high fever (38.5°C or above)
- **Give appropriate antibiotic treatment** for an identified bacterial cause of fever
- Advise mother when to return immediately
- Follow-up in 3 days if fever persists
- If fever is present every day for more than 7 days, refer for assessment

WHO, 2014
ePOCT: electronic clinical decision algorithm

Disease etiology
- Virus
- Bacteria
- Parasite

Clinical / lab decision tree

Host biomarkers
- Malaria rapid test
- CRP
- Cough
- Paracetamol
- Cold

Swiss TPH
eCDSS medical content development process

Scope

Diagnostic classifications

Identify areas in need/amenable for review, in need for evidence-generation

Perform scoping review, refine

External review

Software programming, internal validation, piloting (MOC cases, supervised consultation)
Global evidence-base- evaluation and management of common childhood infections

analytical
clinical/Outcome-based
epidemiological

? evidence
**IMCI cough branch**

**Clinical screening:**
- demographics
- medical history
- clinical signs

1) Severe disease requiring hospital-based treatment - antibiotics

2) Clinical pneumonia - antibiotics

3) Self-limiting, mild infection
STEP 1: clinical screening:
- demographics
- medical history
- clinical signs

1) Severe disease requiring hospital-based treatment
2) Relevant pre-test probability for bacterial pneumonia
3) Self-limiting, mild infection

STEP 2: test for bacterial pneumonia
A) Antibiotics
B) No antibiotics

Decision support through CDSA
Validation of the ePOCT tool

<table>
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<th>Stage of maturity</th>
<th>1 &amp; 2: Pre-prototype/prototype</th>
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**Monitoring goals**
- Functionality, stability
- Fidelity, quality

**Stages of evaluation**
- Feasibility/Usability
- Efficacy
- Effectiveness
- Implementation science

**Illustrative number of system users**
- 10–100
- 100–1000
- 10,000+
- 100,000+
ePOCT “efficacy” study

Children 2-59 months with fever, 9 OPDs in Dar es Salaam

Follow-up at D3, D7, D30
- Primary outcome: clinical failure by D7, non-inferiority margin: 3%
  - Severe symptom D0-D7
  - Cough+ tachypnea/chest indrawing D3
  - Persistent symptoms D7
- Secondary outcomes: antibiotic prescription, severe adverse events

Keitel et al., PlosMed 2017
Cough branch

3192 randomised

- **ePOCT**: 868 with non-severe respiratory symptoms
  - 3 lost to follow-up
  - 865 completed day seven follow-up (per protocol analysis)

- **eIMCI**: 858 with non-severe respiratory symptoms
  - 4 lost to follow-up
  - 854 completed day seven follow-up (per protocol analysis)
ePOCT subgroup analysis: cough branch

ATB prescription at D0

RD -38%; RR 0.06 (0.04, 0.09)

Clinical outcome

RR 0.60 (0.37, 0.98)  RR 0.30 (0.10, 0.93)

Clinical Failure D7

Severe adverse events (2° hosp, deaths)

Keitel et al., CID, 2019
Algorithm Classifications – Antibiotic Prescription

- URTI
- Viral pneumonia
- Bacterial pneumonia
- Other bacterial infection
- Malaria

e-POCT, n=865
- URTI: 44%
- Viral pneumonia: 1%
- Bacterial pneumonia: 10%
- Other bacterial infection: 1%
- Malaria: 1%

eIMCI, n=854
- URTI: 60%
- Viral pneumonia: 4%
- Bacterial pneumonia: 36%
- Other bacterial infection: 1%
- Malaria: 10%
Outlook/next steps

**Stage of maturity**

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**Stages of evaluation**

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Future steps: adding granularity to the cough branch

**STEP 1:**
- Clinical screening:
  - Demographics
  - Medical history
  - Clinical signs

1) Severe disease requiring hospital-based treatment
2) Relevant pre-test probability for bacterial pneumonia
3) Need of treatment for reactive airway disease
4) Self-limiting, mild infection

**STEP 2:**
- Test for bacterial pneumonia
  - Decision support through CDSA
  - Improvement through machine learning

A) Antibiotics
B) No antibiotics
Next steps: ePOCT content extension

ePOCT+

Neonatal algorithm (G. Levine)

Age 2 month – 14 years (R. Tan, N. Vaezipour)
• Febrile+ non-febrile conditions
• Basic surgical problems

Chronic risk factors (R. Tan)
• Sickle cell disease
• Severe acute malnutrition
Next steps: Triage - Tree

• Electronic triage algorithm based on triage tools for LMICs
• Vetted by Tanzanian target users through a Delphi survey

J. van der Maat
A. Hartley