Development of Diagnostics for Drug Resistant Infections

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Diagnostics Landscape in the Developing World

• **Lack of investment in diagnostics R&D**
  - Little industry interest in diagnostics R&D on diseases prevalent in the developing world, due to a perceived lack of return for investment

• **Lack of Access to diagnostic services**
  - diagnostics under-valued by governments
  - clinics suffer from frequent stock-outs
  - high staff turnover and critical shortage of staff

• **Lack of regulatory transparency and control**
  - Regulatory approval processes are lengthy and not quality based:
    Tests are sold and used without evidence of effectiveness

• **Lack of quality standards for test evaluations**
  - Claimed accuracy on product inserts often misleading
  - Control programmes often misled into buying low quality products
In the US, while diagnostics comprise
- less than 5% of hospital costs
- about 1.6% of all Medicare costs,

their findings influence as much as
60-70% of health care decision-making

The Value of Diagnostics, Lewin Report, 2005
The 2004 Health Development Report cited the lack of access and unaffordability as two major reasons why services fail.

### Inequity of Access to Diagnostics

Distance to Nearest Medical Facility for the Poorest 5th of the population:

<table>
<thead>
<tr>
<th>Country</th>
<th>Distance (km)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benin</td>
<td>7.5</td>
</tr>
<tr>
<td>Bolivia</td>
<td>11.8</td>
</tr>
<tr>
<td>Chad</td>
<td>22.9</td>
</tr>
<tr>
<td>Haiti</td>
<td>8.0</td>
</tr>
<tr>
<td>Madagascar</td>
<td>15.5</td>
</tr>
<tr>
<td>Niger</td>
<td>26.9</td>
</tr>
<tr>
<td>Tanzania</td>
<td>4.7</td>
</tr>
<tr>
<td>Uganda</td>
<td>4.7</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Selected from the 2004 World Health Report, p.22

- Patients often self-medicated or purchase drugs from vendors
- May purchase or be given wrong drugs
- Drugs are often sub-standard
- Clinics may not have diagnostics
- Patients required to return for results
- Stock out of drugs
Lack of Regulatory Oversight for Diagnostics

In Vitro Diagnostic Devices
Regulated

No 52%
Yes 48%

In Vitro Diagnostic Devices Regulation By Region

<table>
<thead>
<tr>
<th>Region</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFRO</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>AMRO</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>EMRO</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>EURO</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>SEARO</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>WPRO</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

TDR survey 2002
# How Good are Dengue Rapid Tests?

<table>
<thead>
<tr>
<th>Test</th>
<th>Claimed Accuracy (%)</th>
<th>WHO Evaluation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sens</td>
<td>Spec</td>
</tr>
<tr>
<td>Core</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Diazyme</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>GlobaleMed</td>
<td>80</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Minerva</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PanBio</td>
<td>70</td>
<td>100</td>
</tr>
<tr>
<td>Standard</td>
<td>93</td>
<td>100</td>
</tr>
<tr>
<td>Tulip</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Blacksell et al 2004
Antimalarial Prescriptions for Febrile Patients

- Patients presenting to outpatient departments in northeast Tanzania with varying level of malaria transmission
- 2,425 Patients for whom a malaria test was requested were randomised to microscopy or rapid tests
- Outcome: proportion of malaria negative patients prescribed antimalarial drugs

**Microscopy**
- N=1204
  - Antimalarials Prescribed: 174 + (14%) 1,030 - (86%)
  - Antimalarials Prescribed: 98% 51%

**Rapid Test**
- N=1193
  - Antimalarials Prescribed: 188 + (16%) 1,005 - (84%)
  - Antimalarials Prescribed: 99% 54%

Reyburn et al BMJ 2007
Most Lives Saved from Reducing Disease Burden Accrue to Africa, While Other Regions Benefit from Reducing Overtreatment

Benefits of New Test for Bacterial Pneumonia

Benefits of New Test by Region

Developing World

Africa

Asia

Latin America

Nature S1, 2006
Culture-based Methods for Antimicrobial Susceptibility Testing
Rapid Tests for MRSA

Limitation: targets a single protein associated with resistance
A Microfluidics Multiplex POC Test

Sorger P. Nature Biotech 2008; 26: 1345-6
Automated Extraction and Real-time Amplification

All reagents and consumables required for lysis, nucleic acid extraction and PCR (optional) are loaded into a Unitized Reagent Strip (URS).

Planned new BD MAX system: MRSA, C. difficile and VRE onto HandyLab platform

Microfluidic based real time PCR
1,730 patients with suspected drug-sensitive or multi drug-resistant pulmonary TB at centers in Peru, Azerbaijan, South Africa, and India: detected 98% of smear +, 90% of smear –; 98% of RIF resist. and 98% of RIF sens. TB, in under 2 hrs.

Boehme et al. NJEM Sept 6 2010
Looking for Hot Spots

- Antibiotics exert strong selective pressure on pathogens and leave signatures of selection in the pathogen genome.

- Screening for genes under selection may suggest potential drug or immune targets, and markers for early detection of treatment failure.

- Genome-wide association studies (GWAS) of bacterial pathogens can now yield genome-wide maps of population recombination events, variation in recombination rate, signatures of recent positive selection due to drug pressure.
Genome Wide Scans

- Custom microarrays, based on molecular inversion probe (MIP) technology, can be developed to interrogate thousands of known single nucleotide polymorphisms (SNPs).

- GWAS of multiple drug-resistant phenotypes can be detected using a custom SNP-typing microarray.

- Pathogen half-MICs for different antibiotics can be used in GWAS to identify genes associated with antibiotic responses.

* Limitation of molecular methods: may yield false positives as resistance genotypes may not always result in a resistant phenotype.
Diagnostics for Detecting Antibiotic Resistance

• For patient management:
  – POCT to distinguish between viral/bacterial/fungal
  – Detection of pathogens within syndrome followed by antimicrobial susceptibility pattern
  – Detection of pathogen + susceptibility testing

• For surveillance
  – Standardised and systematic collection of specimens
  – Highly sensitive and specific test in high throughput format, low technical complexity

• For screening at hospitals
  – POC test for admissions
  – Highly sensitive and specific assay for local outbreak investigations and epidemiology studies
ASSURED Point-of-Care Tests to Improve Global Health

A = affordable
S = sensitive
S = specific
U = user-friendly
R = rapid and robust
E = equipment-free
D = deliverable
Surveillance of Antibiotic Resistance

• Many excellent networks for antimicrobial resistance surveillance have been created

• Networks may not cover locations where antibiotic resistance may emerge

• Many are under-funded: limited capacity

• Action on results need to be timely

• Need for highly sensitive and specific test in high throughput format, low technical complexity and for use with non-invasive specimens
SUMMARY

• Many high quality diagnostics for infectious diseases are available but they are neither affordable nor accessible to most patients in the developing world where disease burden is the greatest

• Urgent need to increase diagnostic capacity at all levels of health care system to provide accurate, evidence-based management for major syndromes such as fever, LRI

• Major technological advances have been made for detection of antimicrobial resistance (integrated specimen prep, amplification, and detection, in <2hrs) and more are anticipated

• Need to establish surveillance networks to cover hot spots where antibiotic resistance will likely emerge

• Need to look for novel biomarkers for early detection of treatment failure

• Need innovative mechanisms to accelerate product development, clinical trials and regulatory approval of new diagnostics