Diagnostics:
Learning from successful experiences which made it to market

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Diagnostics:
Learning from unsuccessful experiences which almost made it to market

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“Those who cannot remember the past are condemned to repeat it.”

George Santayana (The Life of Reason, 1905)
Diagnostics for biopreparedness, including arboviruses

Lessons learned:
- HIV, hepatitis, TB
- Ebola
- MersCoV
- Zika (ongoing lessons!!)

Obstacles for developing diagnostics and how we can better prepare
With all of the focus on therapeutics and vaccines for emerging pathogens and biopreparedness, are diagnostics really important?
EBOLA

Patients & caregivers were pleading for DIAGNOSTICS

Urgently needed: rapid, sensitive, safe and simple Ebola diagnostic tests

Ebola: Diagnostic capabilities need boosting
Zika testing hard to find if you’re not pregnant, patients say

As Zika Virus Spreads, Gaps In Diagnostic Testing
What I am NOT talking about...........

- I am not talking about VIRAL pathogens

Diagnostic biopreparedness means preparing for the next important pathogen(s), whether they are viral, bacterial, parasitic or fungal
What I am NOT talking about..........

- I am not talking about MOLECULAR TESTING (NAAT)

Diagnostic biopreparedness means developing the most relevant diagnostic assay(s) to suit the medical need or emergency.
What I am NOT talking about...........

- I am not talking about EMERGING COUNTRIES

Diagnostic GLOBAL biopreparedness means preparing for the next important pathogen(s), wherever they might be – from highly developed countries to remote areas in emerging countries, and everything in between.
What I am NOT talking about...........

- I am not talking about HOSPITAL LABS or CLINICS

Diagnostic biopreparedness means putting diagnostics where they will have the “maximal clinical impact”
So………

- What kind of diagnostics do we need for emerging pathogens in order to be “bioprepared”?

- What are the major obstacles in developing such diagnostics and what have we learned from the past?
Diagnostics for a new pathogen: how does it work today?

Parallel uncoordinated processes

New disease or syndrome; suspected new pathogen or change in pathogen

Identification of pathogen, virulence factor(s), resistance factor(s), etc.

Unmet medical needs in DIAGNOSTICS

ACADEMIA & CDC & EVA & ……etc.

Quick development of diagnostic assay(s)

Formal / informal supply to restricted number of academic & reference labs

Market analysis, NPV, ROI, etc.

R&D projects for diagnostic test(s)

Industrialization & distribution to global labs

INDUSTRY
Much more complicated for “industry”

Many additional steps prior to global commercialization

Validation of test(s)
- In vitro
- In vivo
- Clinical study

Emergency registration procedures (FDA [EUA], WHO [PQ], country-specific requirements)

Regular registration with FDA, CE marking, CFDA, individual countries, etc.

Industrialization & distribution to global labs

Manufacture of all primary materials, kits, packaging, labeling, distribution, dealing with distributors, etc.

Reimbursement issues: who will pay for test?
Trust issues: governments and countries “distrust” products which are not WHO or CDC endorsed and/or FDA/CE marked
What kind of diagnostics do we need?

It all depends............................
Some lessons on the TYPE of diagnostics needed

- **Tuberculosis**
  - POC easy inexpensive “screening” test

- **Dengue**
  - POC easy inexpensive sensitive assay
  - Same-day biomarkers to predict who will progress to severe Dengue

- **Ebola**
  - Highly sensitive molecular assay (blood, urine, saliva)
  - POC easy inexpensive sensitive assay

- **Zika** (we are still learning…………)
  - Highly sensitive molecular assay for acute disease (blood)
  - Specific serology for screening and following pregnant women
  - Sensitive molecular test on semen to assess male infectivity during sexual activity to achieve pregnancy in partner
LESSONS LEARNED
Lessons from HIV, hepatitis, TB
The double-edged sword of “3rd-party payors”

ADVANTAGES

- Access to diagnostics which are otherwise not affordable in affected countries
- Reduced prices for tests
- Prices and conditions negotiated “centrally” by 3rd-party payor without discussions with each country or region
- Winning a “central” tender assures access to a large market (but no guarantees)

DISADVANTAGES

- Complex “central” contract and negotiation process (Global Fund, CHAI, etc.)
- Complicated process not suitable for small companies
- Low prices are a disincentive (i.e. low margins)
- Does not solve the “supply chain” issues, which can be significant
- Each country still has to sign a separate contract, using the “master contract” prices and conditions

Lessons from HIV, hepatitis, TB
The double-edged sword of “3rd-party payors”
Lessons learned: specific example #1

1. Ebola virus disease
   - Disease similar to other febrile illnesses; almost all cases symptomatic, so want diagnostic for *acute disease*
   - High mortality rate; high transmission rate
     - Therefore, don’t want to mix EVD+ and EVD- patients
   - Want to minimize invasive sampling (protect HCWs)
   - Many patients died prior to medical care; need a test validated with easy-to-obtain post-mortem specimens (saliva)
   - Lab facilities in afflicted countries are “basic”

Medical needs:
1. Rapid, easy-to-use, easy-to-read test on urine, saliva or blood with a high sensitivity (i.e. don’t miss cases) and high specificity (i.e. don’t over-diagnose and place with EVD+ patients)

NAAT assays were clearly best option, but needed easy POC types

LFIA tests: limited usefulness because of less-than-optimal sens & spec

2. Easy, rapid diagnostic tests for “other” similar diseases in order to help manage ill HCWs in these emerging settings
Why did we need diagnostics for “other” diseases?

CASE HISTORY

- EVD Treatment Unit of the British Defence Medical Services in Sierra Leone (2014-15)
- As EVD incidence declined, difficult to determine who had EVD and who had other febrile infections; cohorting non-EVD & EVD patients would expose them all to EVD
- HCWs were getting ill; confusion++ whether they had EVD or local infections
- Diagnostic testing was done as per history and physical exam:
  - RT PCR for Ebola for all
  - LFIA for malaria
  - Dengue (Bioline) & HIV (Alere)
  - BioFire FA GI panel if diarrhea
  - BioFire FA RP panel if resp symptoms

Diagnosis of Febrile Illnesses Other Than Ebola Virus Disease at an Ebola Treatment Unit in Sierra Leone

Patients with febrile illnesses presenting to an Ebola treatment unit in Sierra Leone had a wide range of diagnoses other than Ebola virus disease. Rapid diagnostic tests were useful in confirming these diagnoses, reducing the length of patient stay with valuable consequences. These alternative diagnoses should assist in future planning.
Evaluating novel diagnostics in an outbreak setting: lessons learned from Ebola

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Lessons learned: specific example #2

1. Zika virus
   ▪ Disease similar to Dengue, Chikungunya (endemic in same countries); most cases **asymptomatic**, and most patients don’t come to medical care
   ▪ Low mortality rate; high complication rate in pregnant women (fetuses)
   ▪ Sample type is not an issue, but blood and urine seem suitable
   ▪ Few patients die of Zika; don’t need a post-mortem test
   ▪ Zika transmitted by transfusion of blood products from asymptomatics
   ▪ Lab facilities in afflicted countries are variable

**Medical needs:**

1. Assay able to differentiate “susceptible” from “non-susceptible” women (pre-, intra- and post-partum); able to detect asymptomatic infection; highly specific & no X-reaction with Dengue and Chikungunya & other (arbo)viruses
   - Immunoassays (IgG and IgM) are clearly best option, with POC or “mobile” types of the most use
2. High sensitivity, high-throughput assay for screening blood donors
   - Highly-automated NAAT
3. Sensitive screening test for diagnosing symptomatic pregnant women
   - High-sensitivity LFIA or NAAT (spec. not essential)
Lessons learned: specific example #3

1. MERS-CoV
   - Distribution of asymptomatic, mildly symptomatic and severely symptomatic patients
   - Most concern for severely ill; need for diagnostics in ICU
   - Need to differentiate from other coronaviruses, which are common
   - Sample type is almost always an invasive pulmonary specimen (BAL)
   - Concern also for “zoonotic source”: camels; how many colonized or infected?
   - Lab facilities in afflicted countries are sophisticated

Medical needs:

1. Assay which is able to diagnose acute disease from BAL in hospital or central labs
   - NAAT assays are clearly best option but need validation on BAL
2. Immunoassay for seroprevalence studies of camels; serologic surveys of affected human populations
   - Immunoassay (IgG) validated on both humans and camels
Lessons learned:
Major obstacles in development of diagnostics for new pathogens

- **Difficult-to-find** standardized and well-characterized biobanks of clinical specimens, organisms, “interfering substances” (other pathogens; other analytes)
- Lack of “raw materials” to create reliable immunoassays:
  - monoclonal antibodies of sufficient specificity
  - purified immuno-reactive antigens
- Dearth of BSL3 labs
- Lack of true POC platforms for NAAT tests and immunoassays (all of our true immunoassay POC platforms are for relatively insensitive LFIAs; true POC molecular platforms are limited to a few companies with other priorities)
- Regulatory approval (region-specific; variable; complex; costly)
- Supply chain issues (cold chain, shipping, storage, etc.)
- Education, Quality Control of users & labs
- Reimbursement: who is going to pay for the tests?
Additional major obstacles to deployment of diagnostics for emerging/rare pathogens

- **Lack** of standardized and well-characterized biobanks of clinical specimens, organisms, “interfering substances” (other pathogens; other analytes)
- Lack of “raw materials” to create reliable immunoassays:
  - monoclonal antibodies of sufficient specificity
  - purified immuno-reactive antigens
- Dearth of BSL3 labs and **extreme dearth of BLS4 labs** in which to work
- Difficulty in conducting clinical trials with “real” patients in order to validate true “in the field” clinical performance [same problem as for vaccines & therapeutics]
- Regulatory approval for “emergency” use (region-specific; variable; complex)
- Connectivity issues in LMIC (for rapid, efficient, reliable result communication and traceability)
- Education, Quality Control of users & labs
- **Reimbursement**: who is going to pay for the tests?
What preparations can be made in advance?

- Lack of standardized and well-characterized biobanks of clinical specimens, organisms, “interfering substances”
- Lack of “raw materials” to create reliable immunoassays:
  - monoclonal antibodies of sufficient specificity
  - purified immuno-reactive antigens
  - primers/probes for NAAT
- Dearth of BSL3 and extreme dearth of BLS4 labs in which to work
- Lack of true POC platforms for NAAT tests and immunoassays (all of our true POC platforms are for relatively insensitive LFIAs)
- Difficulty in conducting clinical trials with “real” patients in order to validate true “in the field” clinical performance [same problem as for vaccines and therapeutics]
- Regulatory approval (region-specific; variable; complex; costly)
- Supply chain issues (manufacturing, distribution, cold chain,, storage, etc.)
- Connectivity for rapid, efficient, reliable result communication and traceability
- Education, Quality Control of users & labs
Conclusions

• The diagnostics for addressing new pathogens and arboviruses will depend on the respective medical needs

• Biopreparedness for diagnostics can be done for many of the known obstacles, but will require **international cooperation** and **academic/private collaborations or consortia**

• Deployment of diagnostics requires more than just developing a test; it requires:
  • - regulatory approval in the countries in need
  • - manufacturing capacity
  • - supply chain issues to be understood and resolved in advance, including the use of distributors in LMIC
  • - education, training, QC and support of labs and lab personnel
  • - resolution of reimbursement and payment issues
The FilmArray integrates sample preparation, amplification, detection, and analysis all into one complete process that delivers results in about an hour.
How the FilmArray Works

The FilmArray pouch stores all the necessary reagents for sample preparation, reverse transcription-PCR, PCR, and detection in a freeze-dried format. Just inject hydration solution and an unprocessed sample. The FilmArray takes care of the rest.
The Panels
A Syndromic Approach

FilmArray Panels

- Respiratory Panel
  - FDA Cleared 2011

- BCID Panel
  - FDA Cleared 2014

- GI Panel
  - FDA cleared 2014

- Meningitis Panel
  - FDA cleared 2015

- Biothreat-E Ebola assay
  - FDA EUA 2014

FilmArray Platform

After all panels are FDA-cleared, FilmArray will have assays covering >120 of the most common pathogens that cause death and disease.
Thank you