



Role of **DIAGNOSTICS** in **BIOPREPAREDNESS**

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A distant history lesson

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

George Santayana (The Life of Reason, 1905)

““When the situation was manageable it was neglected, and now that it is thoroughly out of hand we apply too late the remedies which then might have effected a cure.”

Sir Winston Churchill (House of Commons, May 2, 1935)

EBOLA

Patients & caregivers were pleading for **DIAGNOSTICS**



WHO

- Media centre
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Media centre

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

Ebola situation assessment
18 November 2014



The inside story on emergencies

Ebola: Diagnostic capabilities need boosting

ZIKA

Patients & caregivers are pleading for **DIAGNOSTICS**



HEALTH CARE SEPTEMBER 1, 2016 3:43 PM

Zika testing hard to find if you're not pregnant, patients say

EL ESPAÑOL | DIAGNOSIS



International Business Times

WORLD

As Zika Virus Spreads, Gaps In Diagnostic Testing

BY ELIZABETH WHITMAN

ON 02/03/16 AT 2:11 PM

Additional recent history lessons

- Influenza H1N1

- MERS-CoV

- XDR-TB

- To come:

 - ? Yellow Fever

 - ? TDR Acinetobacter

 - ? C. auris

 - ? Artemisinin-resistant P. falciparum

What I am NOT talking about.....

- I am not talking about VIRAL pathogens

**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

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

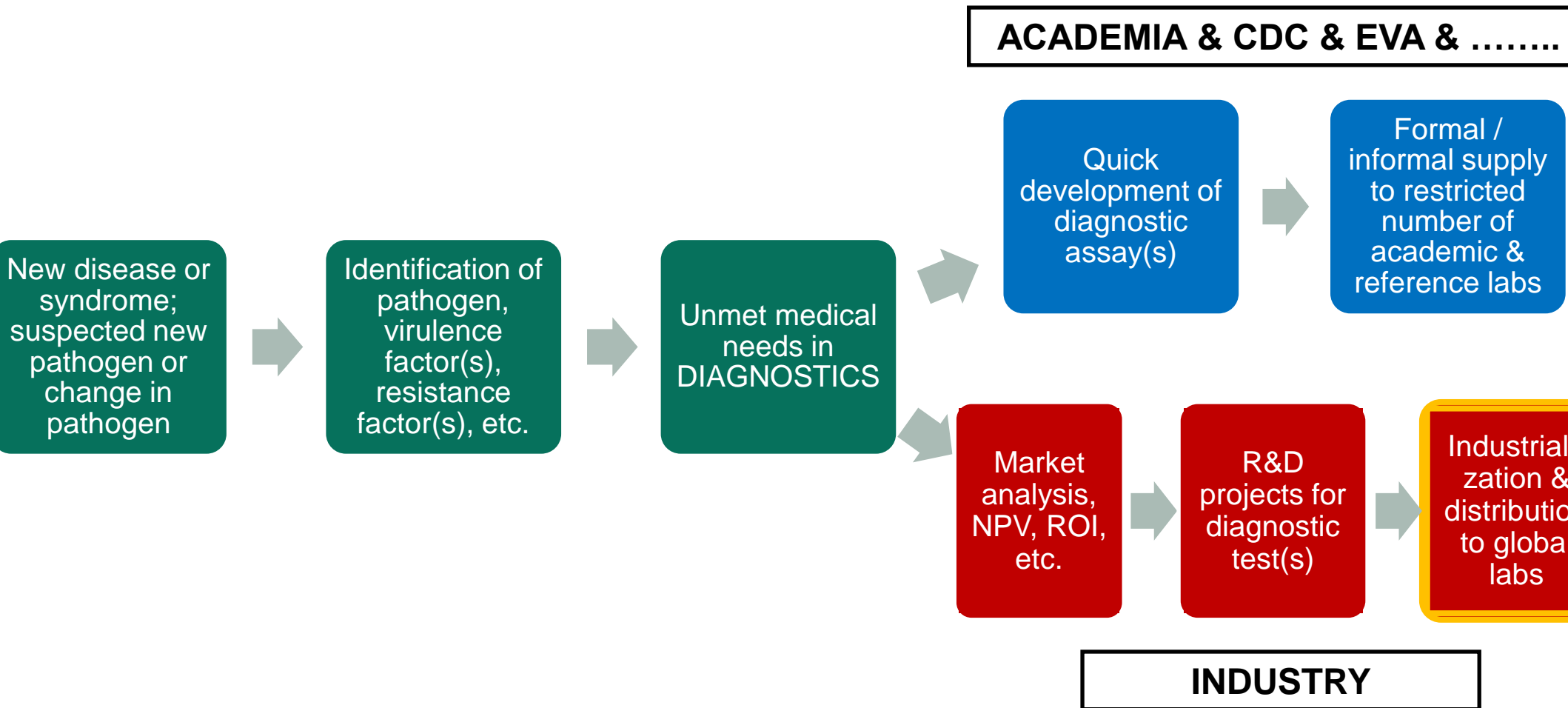
Biopreparedness means putting diagnostics where they will have the “maximal clinical impact”

What I WILL be talking about.....

- What kind of diagnostics do we need for emerging pathogens?
- What are the major obstacles in developing such diagnostics?
- What can we do in advance, in order to be better prepared?

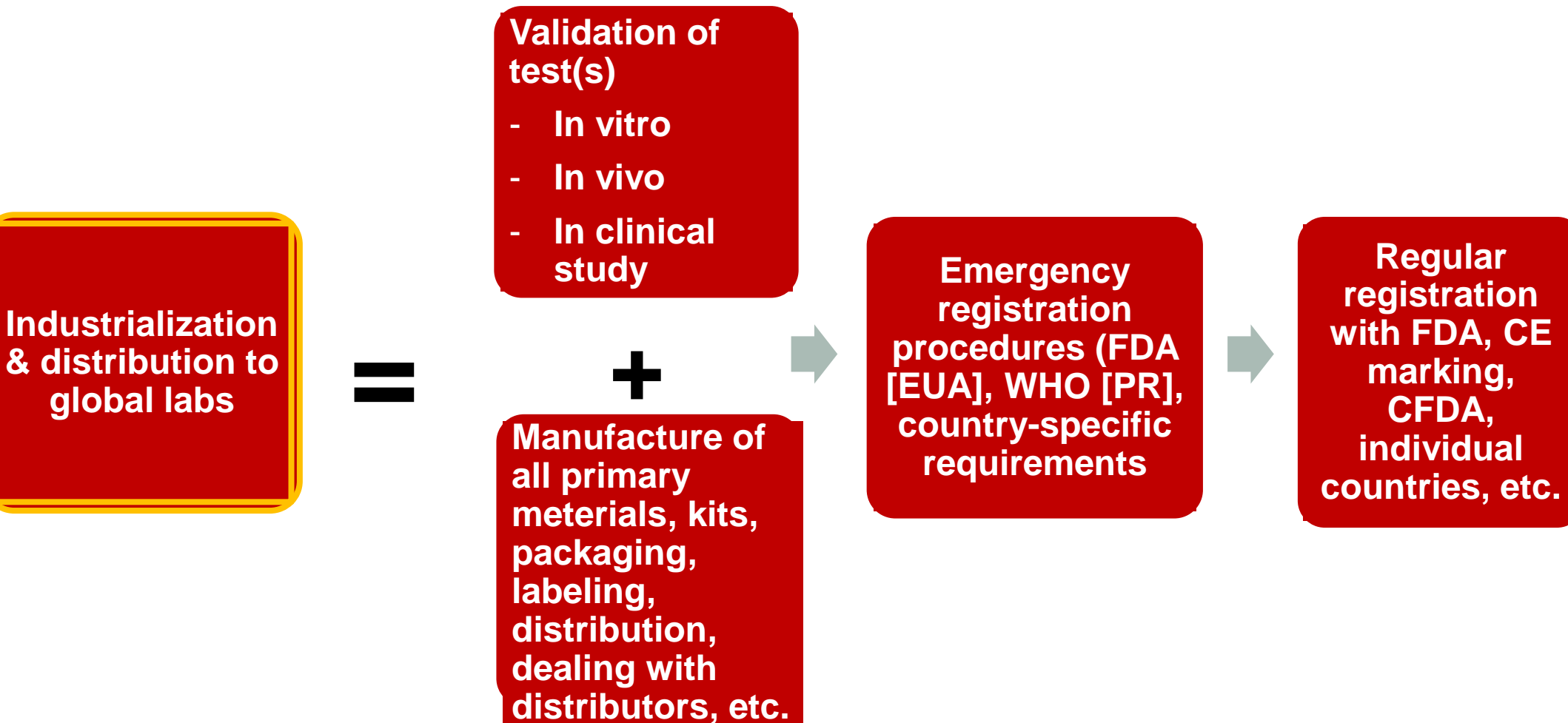
How does it work today?

Parallel uncoordinated processes.....



Much more complicated for “industry”

Many additional steps prior to global commercialisation



What kind of diagnostics do we need?

It all depends.....

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 had limited usefulness because of their 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

Matthew K. O'Shea,^{1,2} Kate A. Clay,^{1,3} Darren G. Craig,^{1,4} Steven W. Matthews,⁵ Raymond L. C. Kao,^{6,7} Thomas E. Fletcher,^{1,8} Mark S. Bailey,^{1,3} and Emma Hutley^{5,9}

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.

Example #2

. 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 which is able to differentiate “susceptible” from “non-susceptible” women (pre-, intra- and post-partum); able to detect asymptomatic infection; highly specific with no cross-reaction with Dengue and Chikungunya and 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)

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

What are the major obstacles to deployment of diagnostics for emerging 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
- 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 LFIAAs)

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 (region-specific; variable; complex; costly)

Supply chain issues (cold chain, shipping, storage, etc.)

Connectivity for rapid, efficient, reliable result communication and traceability

Education, Quality Control of users & labs

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 LFIA)
- 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 emerging pathogens 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

Thank you

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