Diagnostic Innovation to Combat AMR: Pains & Pearls from an Industry Viewpoint

AMR Insights – Virtual Mission

May 10 – 12, 2021

Mark Miller, MD

Executive VP, Chief Medical Officer, bioMérieux, FRANCE

PIONEERING DIAGNOSTICS

WHY WOULD A COMPANY BE INTERESTED IN ↓ ANTIBIOTIC USE TO COMBAT AMR?

THE WALL STREET JOURNAL.

Doctors Test Tools to Predict Your Odds of a Disease

Program aims to calculate the likelihood that a patient has an illness, enabling doctors to order fewer tests and prescribe fewer antibiotics

By LUCETTE LAGNADO

May 30, 2016 2:46 p.m. ET

"I can either prescribe $4 penicillin" on the chance that a patient has a strep infection, Dr. Beasley says. Or he can order a $51 strep test to make certain the person does. For a patient struggling to make ends meet financially, he says he prefers the $4 penicillin.

COMPANIES PRIMARILY FOCUSED ON DIAGNOSTICS TO REDUCE INAPPROPRIATE ANTIBIOTIC USE (↓AMR)

VIRAL VS. BACTERIAL?

MeMed
MeMed BV™

BIOMÉRIEUX

Inflammatix

CRP
Quantitation of CRP in whole blood, serum or plasma

predigen B/V

FebriDx
an RPS diagnostic solution

RAPID PATHOGEN IDENTIFICATION

BIOFIRE
BY BIOMÉRIEUX

Roche
GenMark Dx

DANAHER
Cepheid

DiaSorin
VERIGENE II
FLEXIBILITY Like Never Before

Luminex

RAPID BACTERIAL AST

Q-LINEA

avails MEDICAL

SPECIFIC

Astrego Diagnostics

NG·BIOTECH LABORATOIRES

FIRST LIGHT DIAGNOSTICS

SeluxDX

mariAST

ePhAST

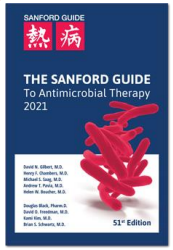
AFFINITY BIOSENSORS

Resistell©

GRADIENTECH

PROGNOSTICS ABX CESSATION

Vidas
B·R·A·H·M·S PCT



Inpatient CDS
1. Cerner
2. First Databank
3. Medispan
4. Truven
5. Zynx Health

VigiLanz
INTELLIGENCE.

LUMED

WHY ARE SO MANY COMPANIES

INTERESTED IN ↓ ANTIBIOTIC USE

TO COMBAT AMR?

O'NEILL "REVIEW ON ANTIMICROBIAL RESISTANCE" (2014)

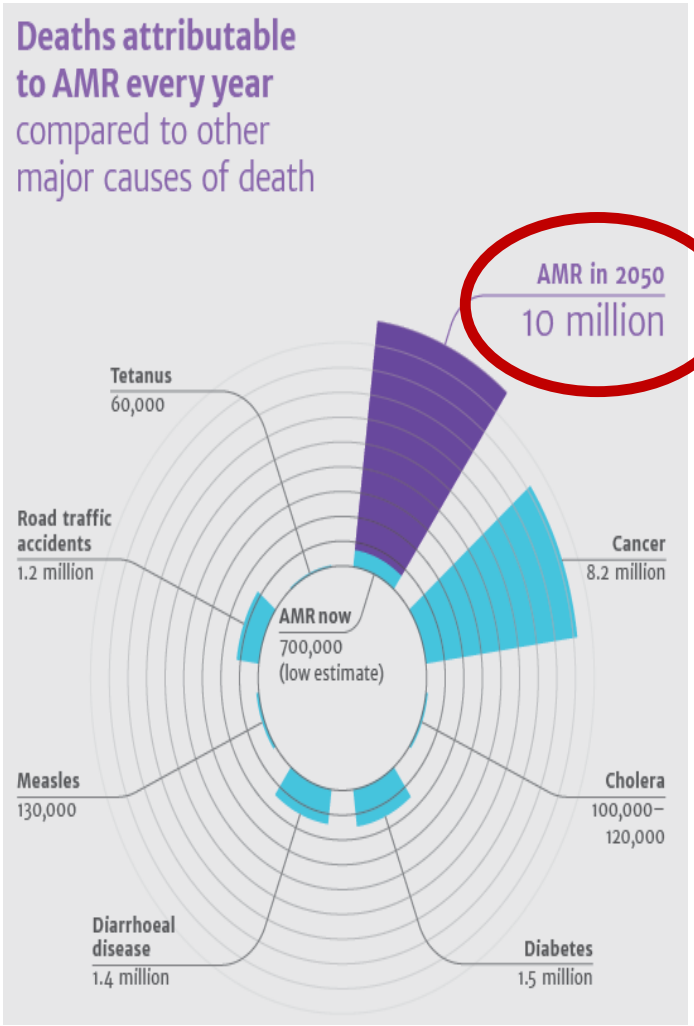
- **Ground-breaking in putting numbers on the nebulous concept of "AMR"**
- **Even though already "scary", it is an under-estimate of the true danger. Why?**
- **#1 - Only some resistant infections counted:**

> First, the studies looked only at a subset of drug-resistant bacteria and public health issues, because of the lack of readily available data for this initial research.

> It is worth noting that the three bacteria were selected from a larger group of seven that the World Health Organization (WHO) has highlighted as being key AMR concerns.

- **#2 – Only GDP effects taken into account:**

> Second, the research was commissioned to understand the economic cost of AMR, interpreted strictly as its impact on global GDP. Other issues, such as social and healthcare costs, were not considered. If AMR continues to grow as a major problem in the world it will have enormous consequences for how we deliver healthcare.



O'Neill Report:
a large under-estimate

Globally, hospital discharge **codes** and **death certificates do not take AMR into account.**

For example: septic death or pneumonia from a MDR Klebsiella is not recorded as such; only ***"septic death"*** or ***"pneumonia"*** are recorded.

More importantly: only a **small subset of MDROs** were included in the O'Neill Report because of **lack of economic data for others**.

THE PATHOGENS / DISEASES

PATHOGENS & DISEASES INCLUDED IN O'NEILL REPORT

- **Staph aureus**
- **Klebsiella pneumoniae**
- **E coli**
- **HIV**
- **Tuberculosis**
- **Malaria**

PATHOGENS & DISEASES NOT INCLUDED IN O'NEILL REPORT

- **All other bacteria:**
  - Strep pneumoniae (PRSP)
  - Enterococcus (VRE)
  - C. difficile
  - Acinetobacter sp.
  - Pseudomonas aeruginosa
  - Non-Klebsiella CRE
  - H. pylori
  - Salmonella sp.
  - Shigella sp.
  - Gonorrhea
  - …….
- **Emerging resistance in fungi, viruses and parasites**
  - Candida auris
  - Neuraminidase-R influenza
  - Parasite resistance due to MDA

USA MDRO DEATHS ARE BEING GREATLY UNDER-ESTIMATED

Infection Control & Hospital Epidemiology (2018), **0**, 1–2
doi:10.1017/ice.2018.304

SHEA
The Society for Healthcare Epidemiology of America

Letter to the Editor

Re-estimating annual deaths due to multidrug-resistant organism infections

Jason P. Burnham MD[1], Margaret A. Olsen PhD, MPH[1] and Marin H. Kollef MD[2]

[1]Division of Infectious Diseases, Washington University School of Medicine, St Louis, Missouri and [2]Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, Missouri

- **"Classic" stats (CDC): 23,000 deaths per year from MDRO**
- **True burden of deaths from MDRO uncertain because:**
  - **Insufficient national reporting rates in USA**
  - **Absence of ICD-10 code for MDRO infections**
- **Realistic modeling: 153,100 to 162,000 MDRO deaths/year in USA**

Burnham JP et al. ICHE 2018; published online Nov. 22, 2018

ECONOMIC BURDEN OF AMR (RAND & KPMG)

RAND report*

- **Focus on S. aureus, E. coli, K. pneumoniae, HIV, malaria, TB, bloodstream infections [BSI], UTI, lower RTI, skin & soft tissue infections [SSTI]**
- **Consequences/costs:**
  - **Disruption to labour supply by increased morbidity & mortality**
  - **Cost calculated as reduction in GDP:**
    - **$5.8 Trillion current cost**
    - **$2.1-124.5 Trillion over 40 years**

KPMG report**

- **Focus on S. aureus, E. coli, K. pneumoniae, HIV, malaria, TB, bloodstream infections [BSI], UTI, lower RTI, skin & soft tissue infections [SSTI]**
- **Consequences/costs:**
  - **4 million excess bed-days (2012)**
  - **Cost calculated as reduction in GDP:**
    - **€1.6 Billion global GDP loss (2050)**
    - **If resistance rate 40%: 1.66% of GDP loss per year**
    - **If resistance rate 100%: 3.4% of GDP loss per year**

*Taylor J et al. Estimating the economic costs of antimicrobial resistance: model and results. Santa Monica: RAND Corporation; 2014. https://www.rand.org/pubs/research_reports/RR911.html

**The global economic impact of anti-microbial resistance. United Kingdom KPMG LLP; 2014. https://home.kpmg/content/dam/kpmg/pdf/2014/12/amr-report-final.pdf

"I am frequently asked by people "what is the ***single most important*** *of the ten points to tackle resistance?"*

"*If I had to pick one that was more important than the others, and why I say* ***"diagnostics"****, is because thinking about it as an economist and as a finance person, in my judgement, the* ***demand-reducing*** *ones are probably more important than the supply-boosting ones."*

Source: Lord Jim O'Neill, bioMérieux AMR Forum 2018
The Review on Antimicrobial resistance 2015

APPROPRIATE DIAGNOSTICS REDUCE DEMAND FOR ANTIBIOTICS

Sore throat
Chills
Urine symptoms
Cough
Fever


Healthcare Provider

No use of diagnostics

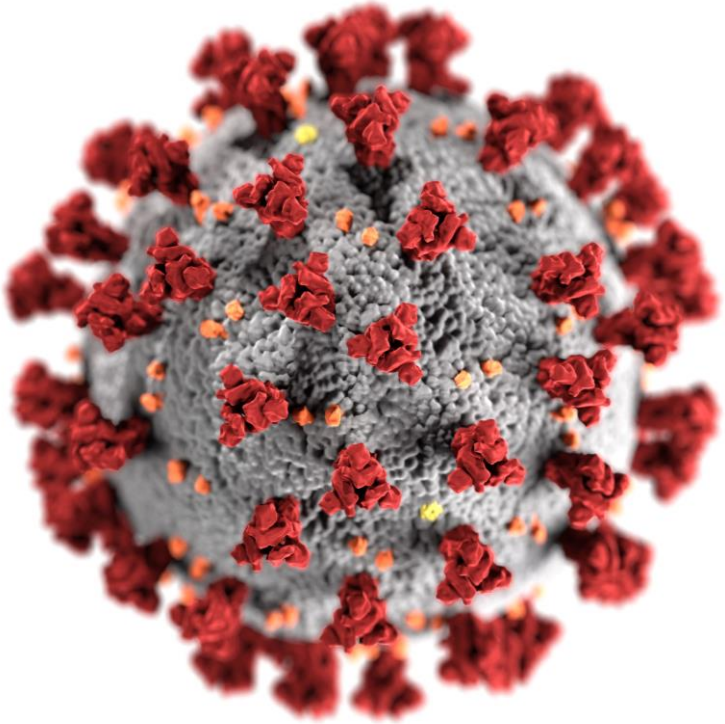
↑AMR

Sore throat
Chills
Urine symptoms
Cough
Fever


Healthcare Provider

Appropriate use of diagnostics

↓AMR



KEY CHANGES POST-COVID IN …

…. DIAGNOSTICS

CHANGES TO THE DIAGNOSTIC ENVIRONMENT

- Perception of “diagnostics”
- Reliability on “diagnostics”
- The location for performing “diagnostics”
- Who will perform the diagnostic test?
- Time To Results (TTR)
- “Molecularization” of Infectious Diseases diagnostics (“PCR”)
- Increased installed base of diagnostic platforms post-COVID
- Still to come: improvements in the “pre-test” and “post-test” aspects

KEY CHANGES POST-COVID IN …

… ANTIMICROBIAL RESISTANCE (AMR)

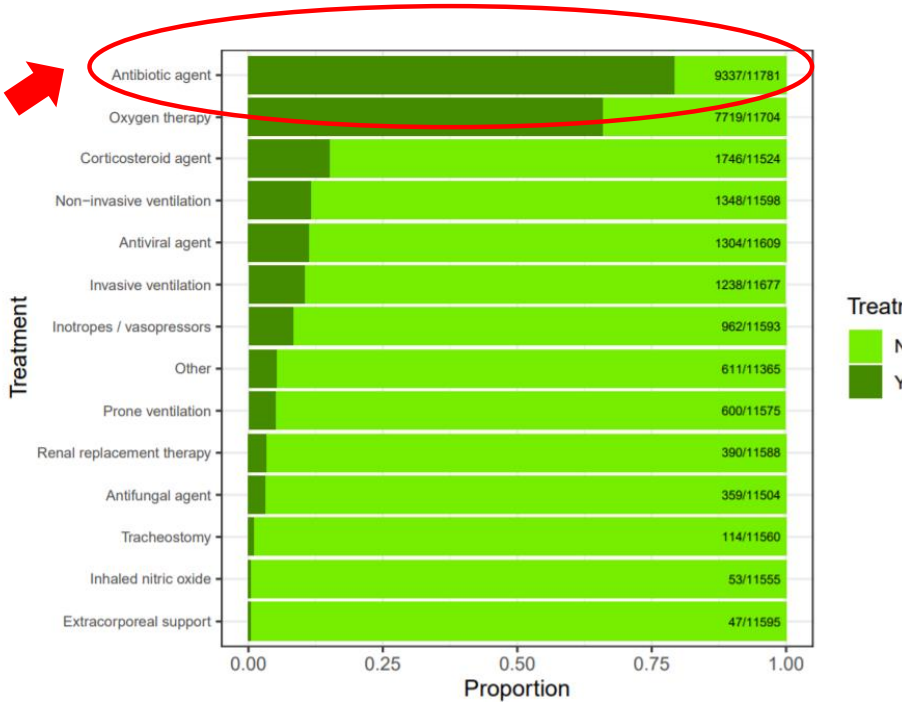
A VERY HIGH PROPORTION OF PATIENTS HOSPITALIZED WITH PRESUMED COVID-19 ARE RECEIVING ANTIBIOTICS

- **72% of total hospitalized* patients (# 1 450 / 2 010) of 17 studies received antimicrobial therapy[1] – usually broad-spectrum "empiric"**
- **73% of the ISARIC cohort[2]**

"Antibiotics" is the #1 treatment category

received by 11 407 documented COVID-19 patients from 30 countries & 278 sites

A patient group highly likely to develop antibiotic-resistant infections



1. Rawson 2020 2. ISARIC data platform April 27, 2020

SECONDARY INFECTIONS (HAIs) & AMR IN COVID-19

- **Meta-analysis: 2ary bacterial pneumonia in 14.3% hospitalized COVID-19 patients[1]**
- **China: 13.9% of COVID-19 patients in ICU developed secondary bacterial pneumonia[2]**
- **India: 13% of COVID-19 patients in ICU developed HAIs, most being MDR[3]**
- **China: 2ary bacterial pneumonia rates in hospitalized COVID-19 varied with severity[4]:**
  - **3.9%** of **moderately** ill patients; **8.3%** of **severely** ill patients; **34.5%** of **critically** ill patients
  - **despite the widespread use of antibiotics in all 3 group**
- **HAI rates higher in COVID-19 patients, likely multifactorial:**
  - Prolonged use of invasive devices in COVID-19 patients, compared to other patients[5]
  - Emergency & rapid upscaling of ICU capacity
  - Reduced staff-to-patient ratios; replacement staff unfamiliar with usual IPC precautions for ICU patients
  - Increased length of stay of COVID-19 patients
  - Inadequacy of PPEs in the pandemic setting

1. BJ Langford et al. Clin Micro Infect https://doi.org/10.1016/j.cmi.2020.07.016
2. Y Fu et al. Open Forum Inf Dis 2020;7(6)
3. Khurana S et al. Indian J Med Micro (in press)
4. Y Feng et al. Am J Resp Crit Care Med 2020;201:1380–1388
5. Baiou A et al. J Hosp Infect 2021;110:165-71

MDR-GN OUTBREAKS DURING COVID-19

Morbidity and Mortality Weekly Report

Increase in Hospital-Acquired Carbapenem-Resistant *Acinetobacter baumannii* Infection and Colonization in an Acute Care Hospital During a Surge in COVID-19 Admissions — New Jersey, February–July 2020

Stephen Perez, PhD[1,2]; Gabriel K. Innes, VMD, PhD[2]; Maroya Spalding Walters, PhD[3]; Jason Mehr, MPH[2]; Jessica Arias[2]; Rebecca Greeley, MPH[2]; Debra Chew, MD[4]

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Perspective

Antibiotics and antimicrobial resistance in the COVID-19 era: Perspective from resource-limited settings

Mentor Ali Ber Lucien[a,*], Michael F. Canarie[b], Paul E. Kilgore[c], Gladzdin Jean-Denis[d], Natael Fénélon[d], Manise Pierre[d], Mauricio Cerpa[d], Gerard A. Joseph[a], Gina Maki[e], Marcus J. Zervos[e], Patrick Dely[f], Jacques Boncy[a], Hatim Sati[g], Ana del Rio[g], Pilar Ramon-Pardo[g]

World Health Organization Europe

18-11-2020

Preventing the COVID-19 pandemic from causing an antibiotic resistance catastrophe

Available online at www.sciencedirect.com

Journal of Hospital Infecti

journal homepage: www.elsevier.com/lo

Clinical characteristics and risk fact of multi-drug-resistant Gram-negative bacteria from critically ill patients with COVID-19

A. Baiou[a], A.A. Elbuzidi[a], D. Bakdach[b], A. Zaqout[c,d], K.M. Alarbi[e], A.A. Bintaher[a], M.M.B. Ali[c,d], A.M. Elarabi[f], G.A.M. Ali[c,d], J. Daghfal[d], M.A. Almaslamani[c,d], A.S.S. Ibrahim[a], A. Alkhal[c,d], A.S. Omrani[c,d,*]

Available online at www.sciencedirect.com

Infection Prevention in Practice

journal homepage: www.elsevier.com/locate/ipip

Short Report

An outbreak of carbapenem-resistant *Acinetobacter baumannii* in a COVID-19 dedicated hospital

Tamar Gottesman[a,b], Rina Fedorowsky[a], Rebecca Yerushalmi[c], Jonathan Lellouche[d], Amir Nutman[b,d,*]

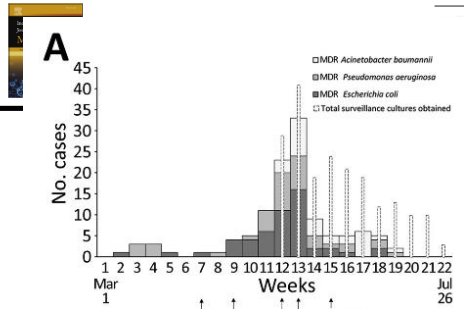
Contents lists available at ScienceDirect

Indian Journal of Medical Microbiology

journal homepage: www.journals.elsevier.com/indian-journal-of-medical-microbiology

Profile of co-infections & secondary infections in COVID-19 patients at a dedicated COVID-19 facility of a tertiary care Indian hospital: Implication on antimicrobial resistance

Surbhi Khurana[a], Parul Singh[a], Neha Sharad[a], Vandana V. Kiro[a], Neha Rastogi[b], Amit Lathwal[c], Rajesh Malhotra[d], Anjan Trikha[e], Purva Mathur[a,*]



Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

-bapenem-resistant *Klebsiella pneumoniae* in ICU-admitted VID-19 patients: Keep an eye on the ball

Montrucchio[a,e,1,*], S. Corcione[b,c,1], G. Sales[a], A. Curtoni[d], F.G. De Rosa[b], L. Brazzi[a,e]

OTHER COVID CONSEQUENCES NEGATIVELY IMPACTING AMR

- Inability to conduct AMR surveillance
- Inability to oversee and modify antibiotic-prescribing habits
- Inability to continue Antibiotic Stewardship Programs as per normal
- Inability for labs to perform routine cultures and conduct AST tests when overwhelmed with COVID testing

WHO: OVERUSE OF ANTIBIOTICS FOR COVID-19 WILL ULTIMATELY CAUSE MORE DEATHS

“The Covid-19 pandemic has led to an increased use of antibiotics, which ultimately will lead to higher bacterial resistance rates that will impact the burden of disease and deaths during the pandemic and beyond”

WHO Director General

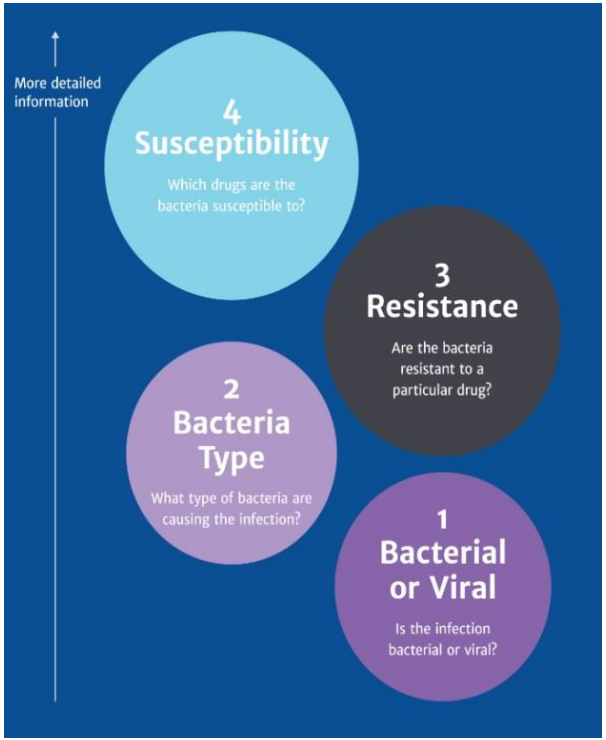
June 1 2020

World Health Organization

DIAGNOSTICS IN THE BATTLE AGAINST AMR

How can diagnostics be used to battle AMR?

- **Bacterial or viral infection?**
- **Which exact etiologic pathogen?**
- **Resistance** (*which antibiotics **must I not** use?)*
- **Susceptibility** (*which antibiotics **can I** use?)*
- **Epidemiology & Surveillance** *(status & trends)*
- **Host response:**
  - colonized or infected?
  - susceptible or immune?
  - is the infection under control?



Adapted from O'Neill http://amr-review.org/

THE 2 MAJOR GOALS OF DIAGNOSTICS IN THE BATTLE AGAINST AMR

- Bacterial or viral infection?
- Bacterial type?
- Resistance profile
- Susceptibility profile
- Epidemiology & Surveillance
- Host response

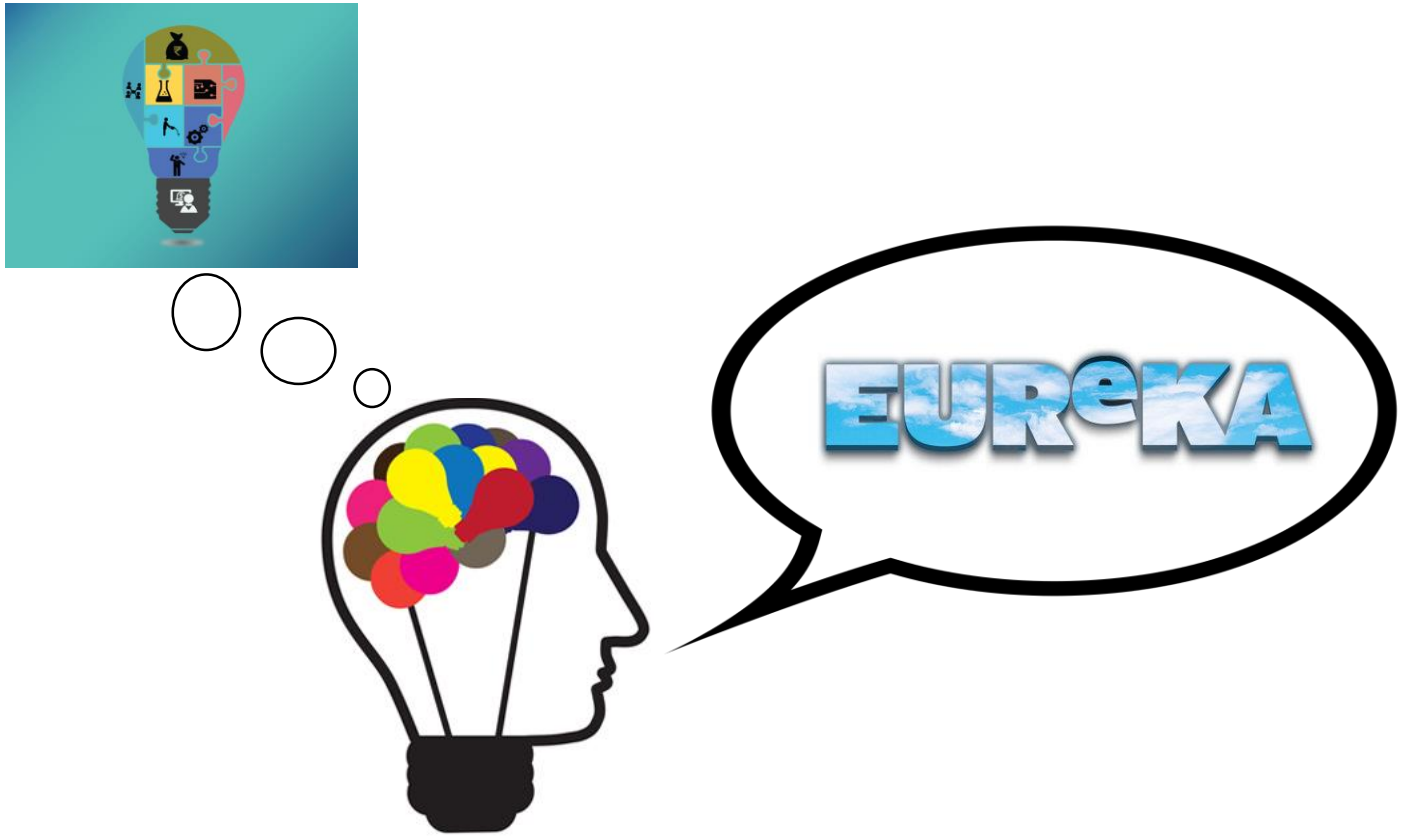
Faster

More actionable information

HOW TO

A DIAGNOSTIC TEST TO BATTLE AMR

A BRILLIANT IDEA



“MY IDEA WILL BECOME A DIAGNOSTIC PRODUCT”

INCREASINGLY DIFFICULT TO BRING DISCOVERIES TO THE BEDSIDE

The NEW ENGLAND JOURNAL of MEDICINE

2005

SOUNDING BOARD

Translational and Clinical Science — Time for a New Vision

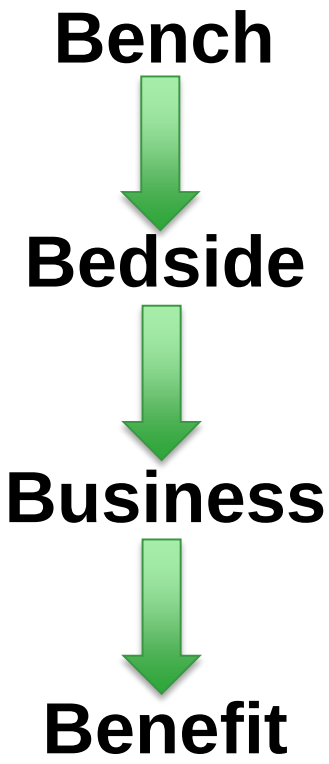
Elias A. Zerhouni, M.D.

It is the responsibility of those of us involved in today's biomedical research enterprise to translate the remarkable scientific innovations we are witnessing into health gains for the nation. In order to

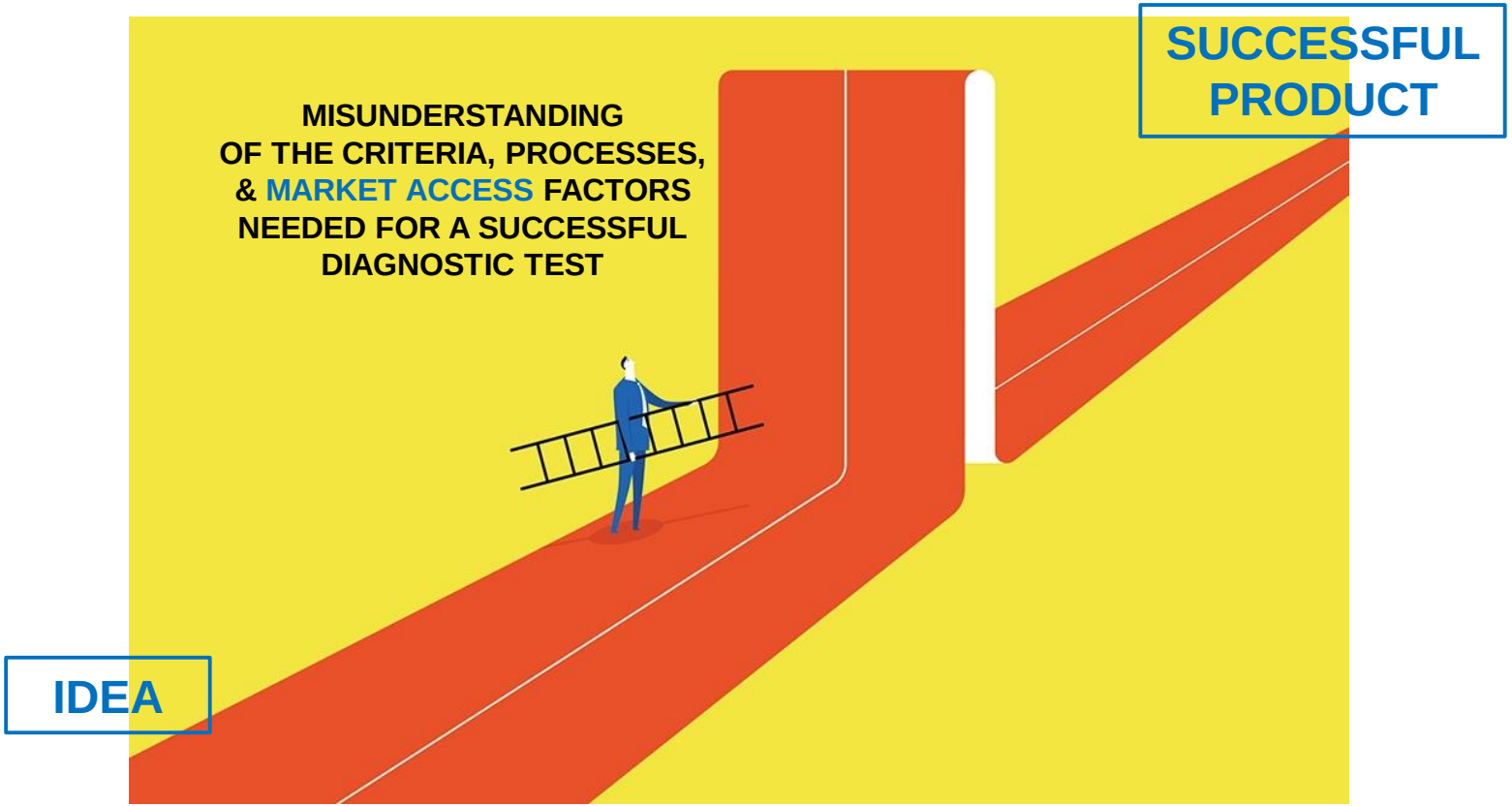
paramount among the NIH's immediate responsibilities. This led us to formulate the third Roadmap theme, "Re-engineering the Clinical Research Enterprise."

- Increased **costs** of research (basic & clinical)
- Increased **complexity** of research (basic & clinical)
- Increased **clinical demands**
- Increased **regulatory burden** (extent, complexity)
- Decreased **risk-taking of companies**
- Increased requirement for **health economic justification (HEOR) = "value"**

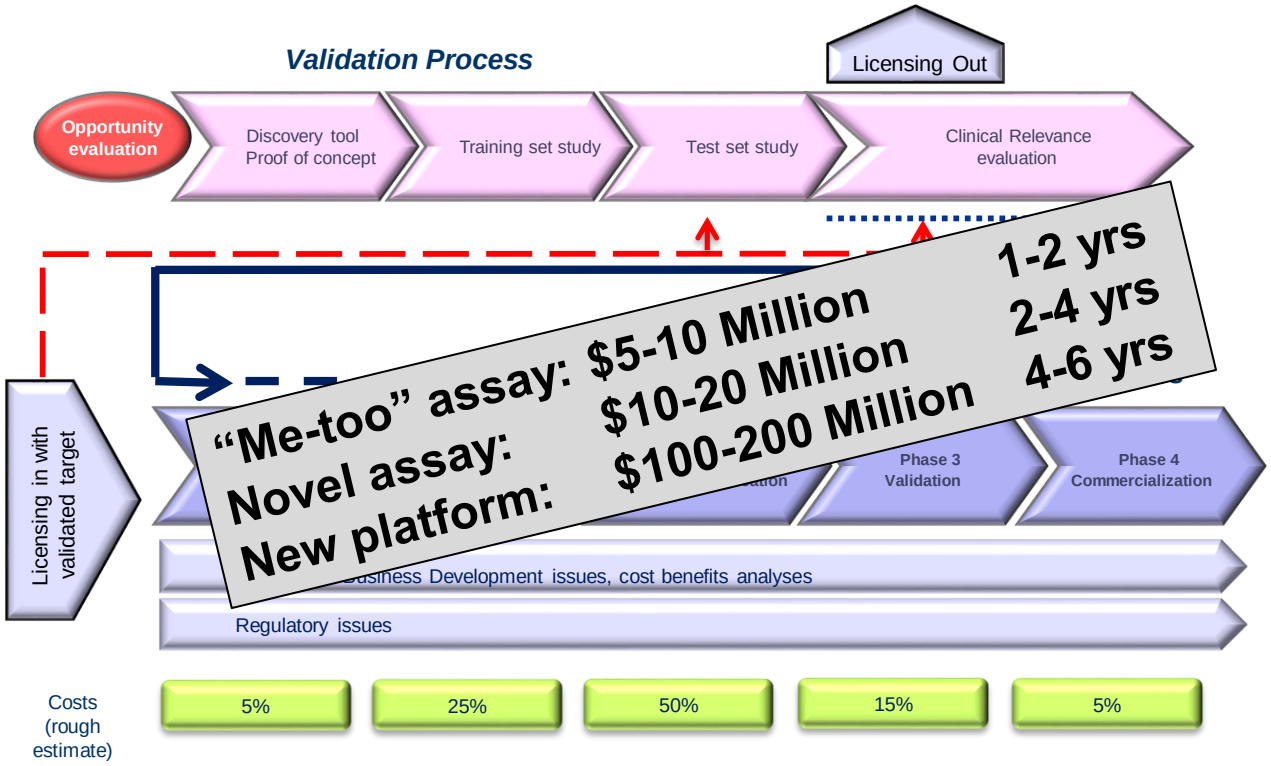
THE “B” PATH FROM DISCOVERY TO MEDICAL VALUE



THE BIGGEST BARRIER……

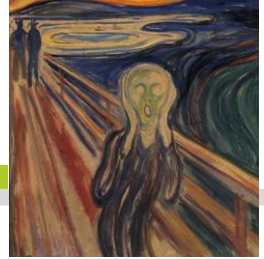


DISCOVERY TO DEVELOPMENT PROCESS



THE CRITERIA USED FOR INDUSTRIAL DECISION-MAKING OF “ACCEPTABILITY”

- Medical impact: clinical utility, medical & economic value
- Strategic fit within the company
- Cannibalize or compete with other products within the company
  OR
- Synergize or complement other products within the company
- Additional applications or medical uses possible
- Supportive data (studies, publications, collaborations)
- Freedom to operate (FTO): patents, material knowledge, secret formulations, access to people/knowledge, etc.



THE CRITERIA USED FOR INDUSTRIAL DECISION-MAKING OF “ACCEPTABILITY”

- Technical risks: new vs. old technology; “me too” vs “innovative”
- Access to patients and clinical samples for validation
- Competition (similar or identical products)
- Business evaluation: NPV, time to return of investment, product margin
- Sales capacity: access to clients; size of sales force; direct or via distributors
- R&D capacity
- “Market Access” issues

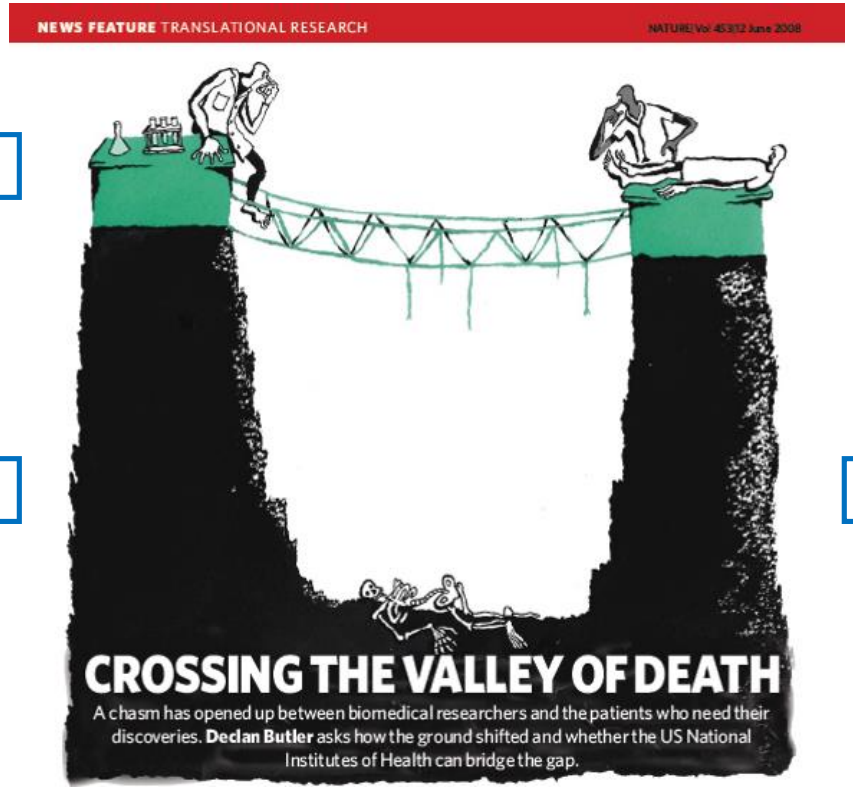
VALLEY OF DEATH FROM IDEA TO SUCCESSFUL ROLL-OUT & USE

Researchers

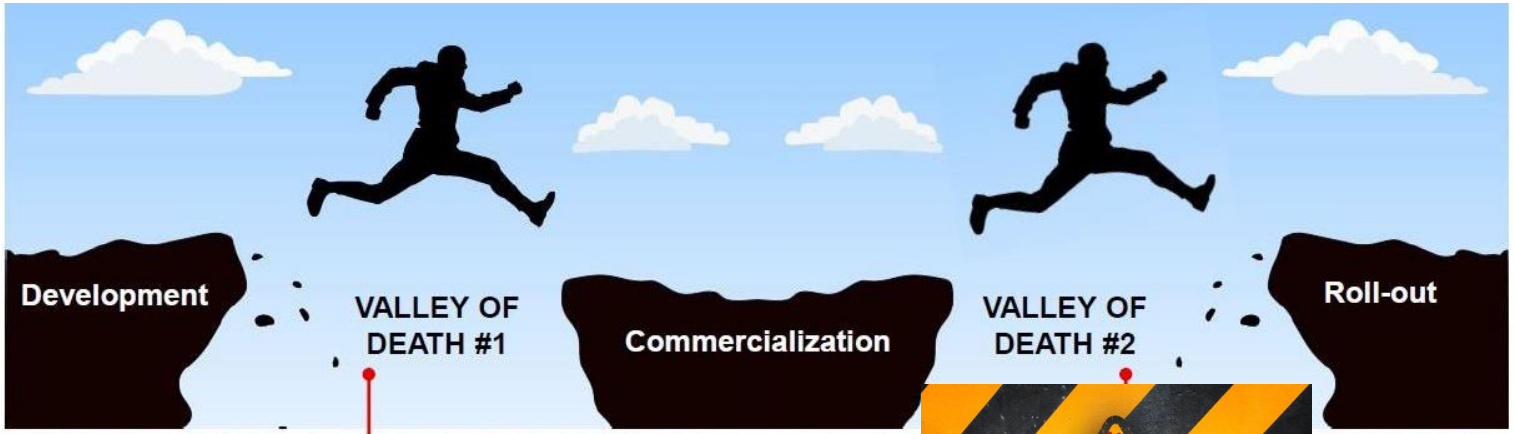
Patients

Discovery

Commercialization



2 VALLEYS OF DEATH FROM IDEA TO SUCCESSFUL ROLL-OUT & USE



DEVELOPMENT => COMMERCIALIZATION

- **Insufficient evaluation** in settings of intended use
- **Weak end-user involvement** in product research and development
- **Mis-alignment** in the product design and manufacturing process

- **Lack of planning and resources** for country adoption

Source: Ditiu L, Boehme C. Crossing the Valleys of Death in TB: From Development to Roll-Out. GBC Health NEWS; May 2017. https://gbchealth.org/crossing-the-valleys-of-death-in-tb-from-development-to-roll-out/#_ftn2

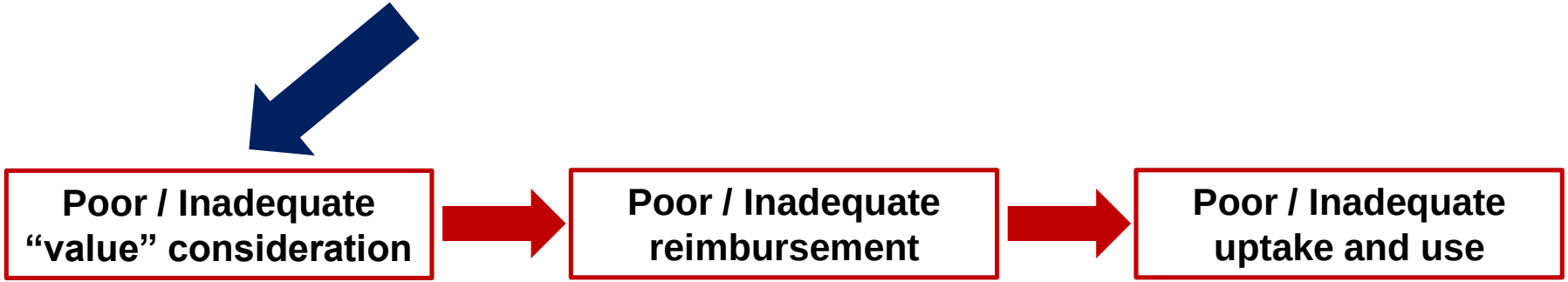
2ND VALLEY OF DEATH: "MARKET ACCESS" COMPONENTS

P = Performance in real world (precision, accuracy, sens, spec, NPV, PPV, etc.)
R = Regulatory issues (registration pathway; multiple countries & processes)
O = Operators - **who** does test? MDs, RNs, techs, pts) - **where**? lab, POC, at home
G = Guidelines (included in local/nat'l/internat'l guidelines **INCL. national HTAs**)
R = Reimbursement (payors (pvt/public) incl. 3rd parties like CHAI, Global Fund, etc)
A = Acceptance by clinicians/users ("acceptability")
M = Management of patients (how does it change management/outcome?) HEOR
S = Support by local admin, hospital, government, NGOs, etc. (gov't, WHO, ….)
+
Price = Selling Price; Actual **Final Price** to patient/insurers/payors

The more the "Market Access" components are achieved, the greater the likelihood of success

THE PROBLEM WITH REIMBURSEMENT & DIAGNOSTICS

- Reimbursement is not linked to MEDICAL and ECONOMIC VALUE
- No harmonized and standardized method for determining “VALUE” of a diagnostic test (i.e. Health Technology Assessment: HTA)
- HTAs, if done, are country-specific and usually not linked to reimbursement or regulatory approval



BARRIERS TO THE DEVELOPMENT OF EFFECTIVE & ACTIONABLE DIAGNOSTICS FOR AMR

Technological challenges

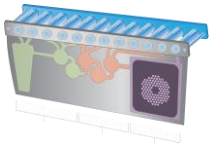
- Aside from specific examples (e.g. biomarkers to differentiate V from B infections), these are NOT the primary or most difficult barriers

Market Access challenges

- **Similar challenges facing antibiotics:** business model, market size, clinical trials with AMR patients, lack of sufficient “push” and “pull” incentives
- **Additional UNIQUE challenges for diagnostics:**
  - Easier to give an antibiotic than to do a diagnostic test first (especially in LMICs)
  - Regulatory landscape is fragmented and non-harmonized, with HTAs & reimbursement highly varied
  - Supply chain issues: equipment, lab structure, trained techs/workers, QC, storage, traceability products & results
  - Behavioral issues: misunderstanding of diagnostics, easier to give antibiotics, “principal-agent” dilemma, corruption

Most importantly, reimbursement is NOT correlated with medical or economic value, unlike novel therapeutics. An antibiotic-sparing diagnostic test is not valued nor reimbursed for this aspect of its benefits, neither for the individual nor for society.

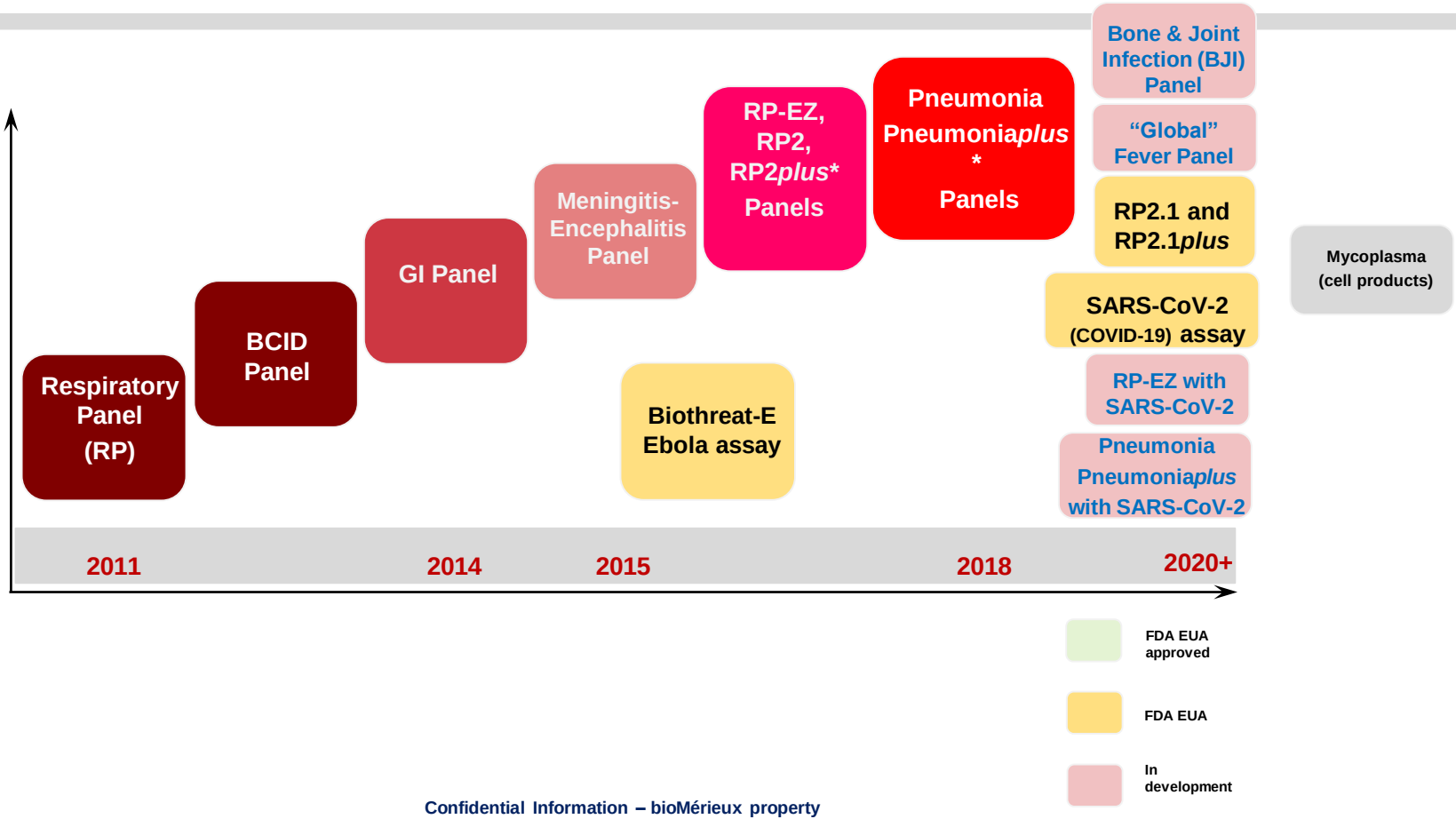
2 SUCCESS STORIES



BIOFIRE BY BIOMÉRIEUX

Vidas B·R·A·H·M·S PCT

THE BIOMÉRIEUX-BIOFIRE PANELS
WORLD LEADER IN THE SYNDROMIC APPROACH



BIOFIRE PRODUCTS:
OVER 30 YEARS OF INNOVATIONS

1990
Idaho Tech, Inc.

1996
Molecular Biology Tools
•LightCycler®

2000
PCR for ID/microbiology
FilmArray™
+
BioThreat Testing

2012
BioFire
(name change)

2014

Markets | Wed Sep 4, 2013 5:04am EDT

BioMerieux buys diagnostics rival BioFire for $450 mln

PARIS, SEPT 4

Related: STOCKS, M&A, MARKETS, EARNINGS

2016
TORCH development

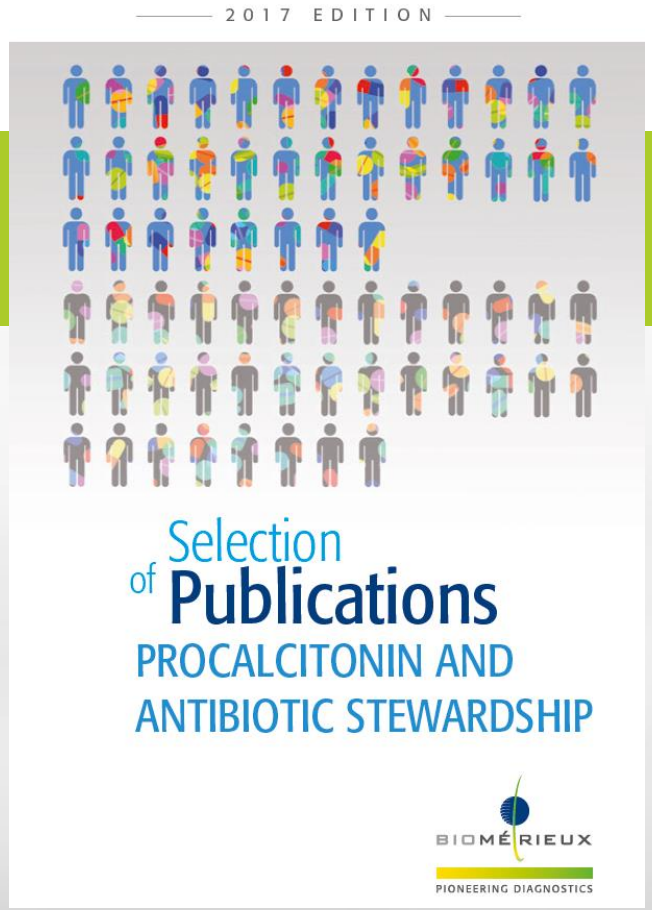
2019-
Enlarge production, sales

2020-

IB: 1,900
Rev: € 150M

IB: 19,000
Rev: € 1,000M

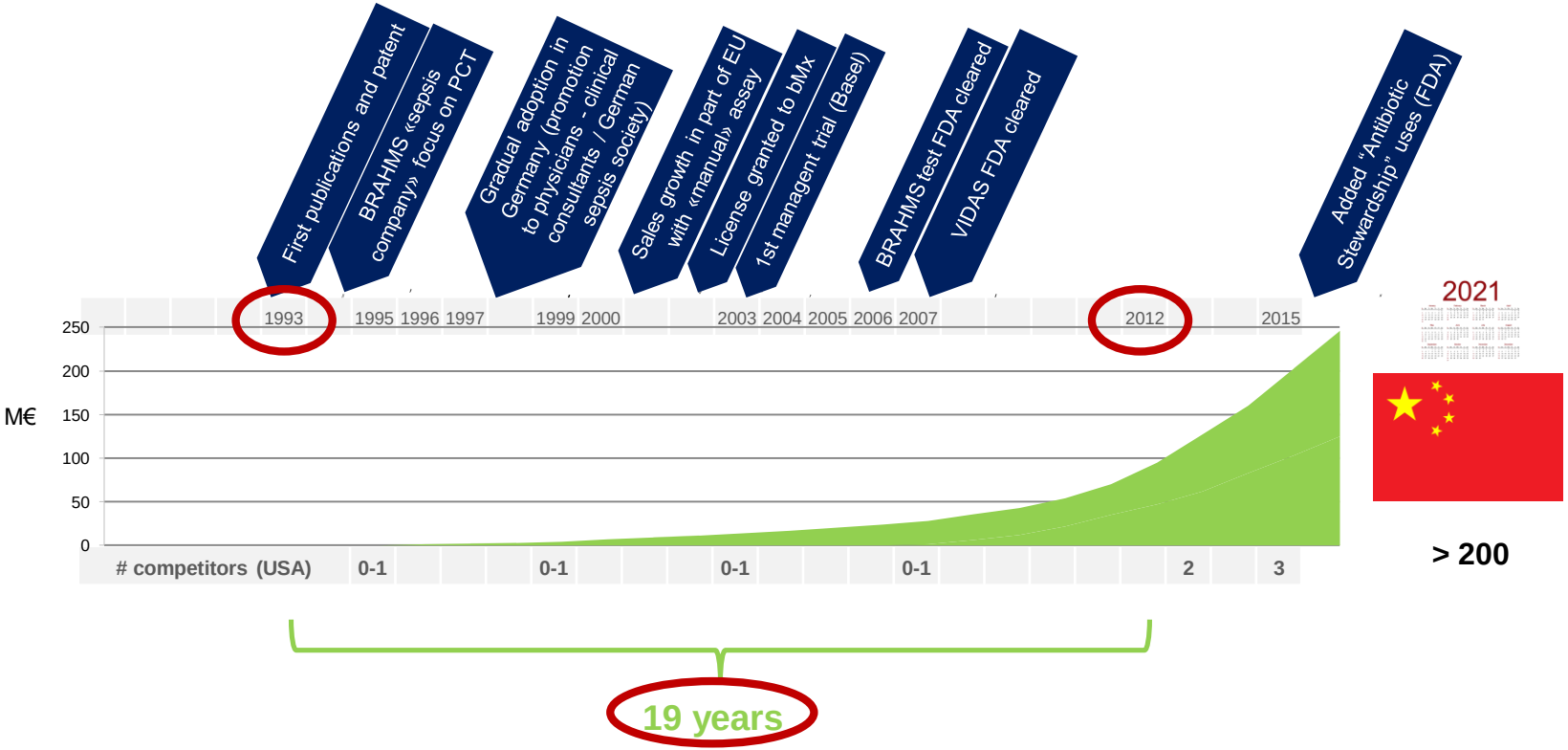
- **2011:** Respiratory Panel (RP)
- **2013:** Blood Culture ID Panel (BCID)
- **2014:** Gastrointestinal Panel (GI)
- **2014:** BioThreat-E (Ebola)
- **2015:** Meningitis Encephalitis Panel (ME)
- **2016:** Respiratory Panel EZ (RP-EZ) "POC"
- **2017:** Respiratory Panel 2 (RP2)
- **2018:** Pneumonia panel (PNEU)
- **2020:** COVID-19 (SARS-CoV-2)
- **2020:** Respiratory Panel w/ SARS-CoV-2 (RP2.1)
- **2020:** Blood Culture ID Panel 2 (BCID2)
- **2020:** Mycoplasma panel (cell products)



PROCALCITONIN

PROCALCITONIN (PCT)

FROM IDEA TO CLINICAL ADOPTION TO MARKET MATURITY



“SIMPLISTIC” CONCLUSION: HOW TO IMPROVE THE ODDS OF SUCCESS

- Start with an important “unmet medical need”
- Take into account the “criteria for commercial success”
- Take into account the “Market Access” components
- Partnerships (esp. with Industry consultation) early on
- Maximize the intellectual property
- Don’t aim for the “perfect” product; aim for the minimal viable product with the maximal impact (a difficult balance)
- Financing: it always takes longer and more money than planned

Thank you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