Diagnostic solutions for antimicrobial resistance:

Identifying unmet clinical needs

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VAXINFECTIO

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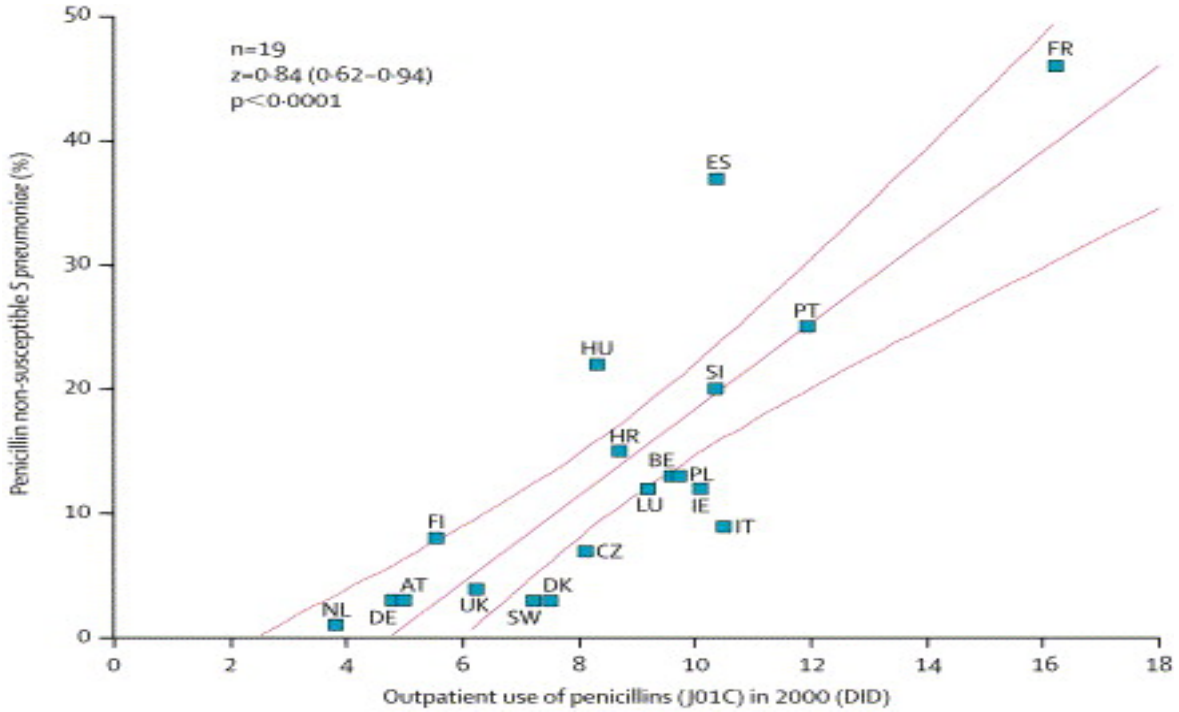
I identified eight (because I was only given 20 min) unmet diagnostic needs for antimicrobial resistance and (sometimes) will provide solutions

1

We need rapid diagnostic tests to reduce antibiotic prescribing and hence the selective pressure



Goossens et al, 365: 579-87, Lancet 2005

- 80% of antibiotics are prescribed in primary care
- Acute RTIs most common reason for GP consultation
- Most infections are due to viruses
- Evidence of over prescribing by GPs
- Overprescribing is linked to increased antibiotic resistance


YOU HAVE A VIRUS...
...NEXT!....
YOU HAVE A VIRUS...
...NEXT!....
DR. DUMA

2

We need rapid diagnostic tests to decrease broad-spectrum toxic antibiotics and hence morbidity and mortality

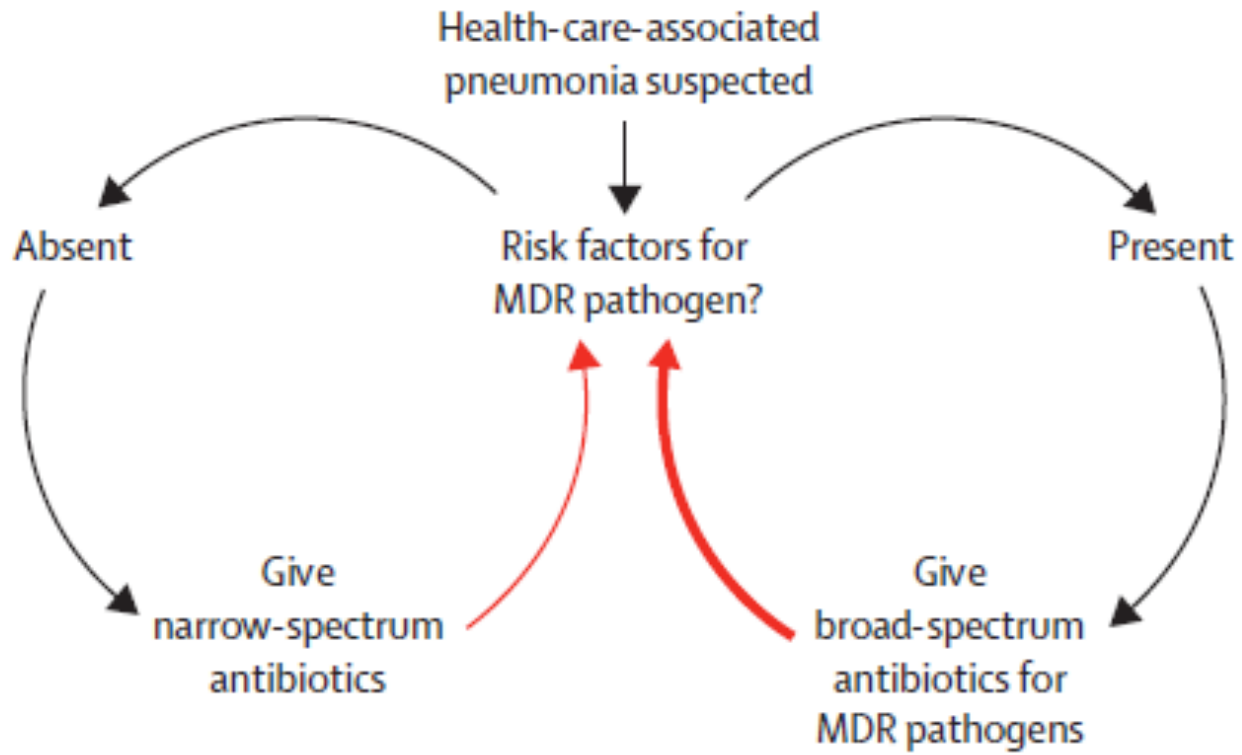
	Compliant treatment (n=129)	Non-compliant treatment (n=174)	p value
Survival through day 28 (total population)	65% (3)	79% (4)	0·004
Baseline CPIS <7	68% (6)	80% (4)	0·063
Baseline CPIS ≥7	63% (6)	78% (5)	0·037
Survival through day 28 (patients with *Pseudomonas* spp infection*)	55% (9)	82% (9)	0·064
Resource use, after pneumonia (days)			
Mechanical ventilation support (total population)	8 (3–15)	9 (2–18)	0·44
Length of stay in ICU (total population)	12 (7–22)	13 (5–20)	0·57
Length of stay in hospital (total population)	16 (9–28)	17 (10–26)	0·52
Mechanical ventilation support (survivors to day 14)	8 (2–18)	9 (2–18)	0·81
Length of stay in ICU (survivors to day 14)	14 (7–23)	13 (5–21)	0·15
Length of stay in hospital (survivors to day 14)	18 (11–32)	18 (10–28)	0·55

Data are Kaplan-Meier % (SE) estimates of survival or median (IQR), unless otherwise stated. ICU=intensive-care unit.
*We isolated *Pseudomonas* spp for 50 patients (33 patients in the compliant group and 17 in the non-compliant group).

Table 5: **Treatment outcomes, grouped by empirical treatment compliance**

Kett et al, Lancet Infect Dis 2011;

Vicious circle within the HCA-pneumonia guidelines



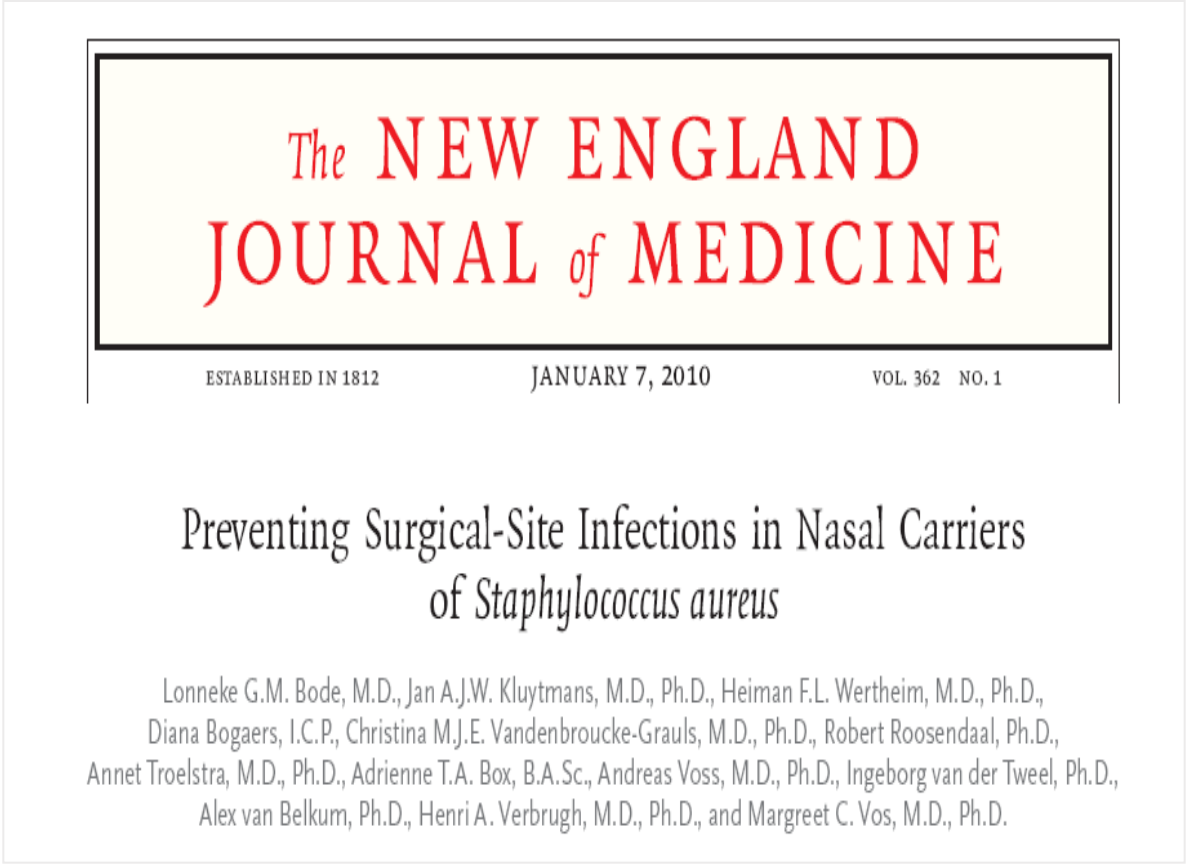
Yu, Lancet Infect Dis 2011; 11: 248-52

3

We need “diagnostic-friendly” healthcare delivery systems

‘Surgical-site *S. aureus* infections acquired in the hospital can be reduced by rapid screening & decolonizing of nasal carriers’

Bode L *et al*. *NEJM* 2010;362:9-17

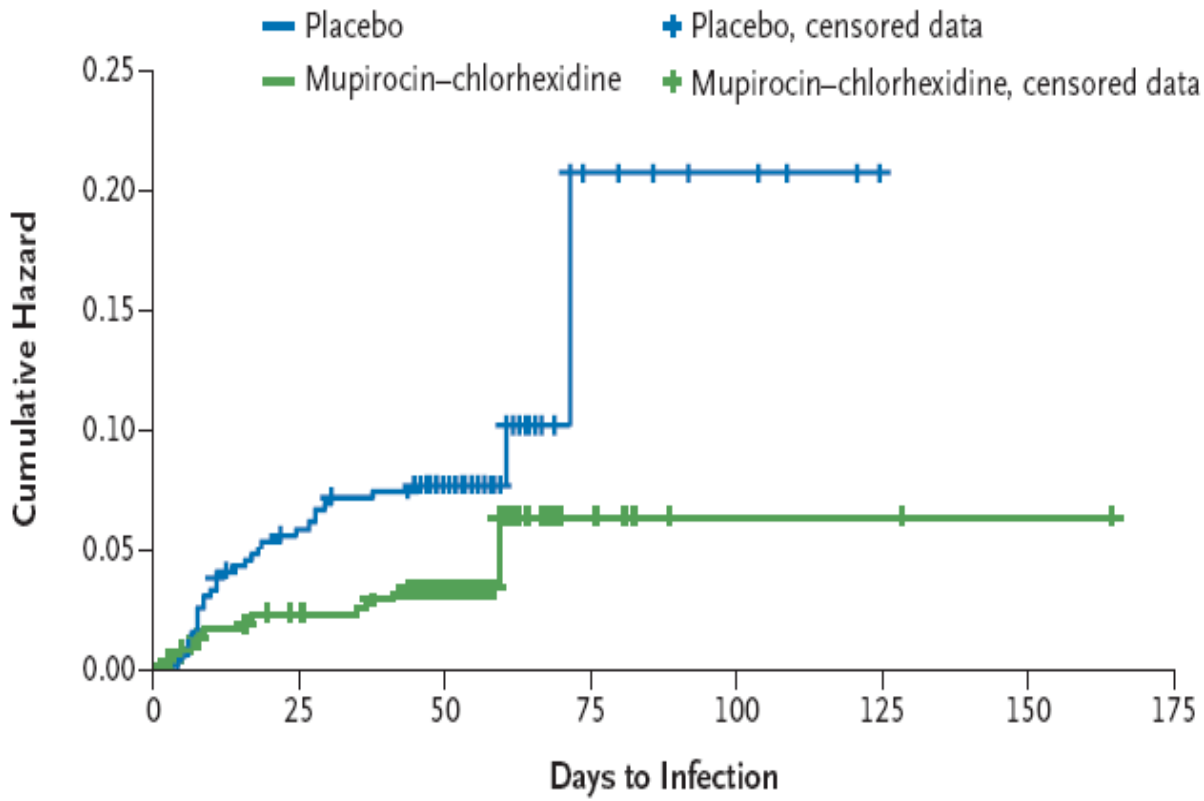


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 7, 2010 VOL. 362 NO. 1

Preventing Surgical-Site Infections in Nasal Carriers of *Staphylococcus aureus*

Lonneke G.M. Bode, M.D., Jan A.J.W. Kluytmans, M.D., Ph.D., Heiman F.L. Wertheim, M.D., Ph.D., Diana Bogaers, I.C.P., Christina M.J.E. Vandenbroucke-Grauls, M.D., Ph.D., Robert Roosendaal, Ph.D., Annet Troelstra, M.D., Ph.D., Adrienne T.A. Box, B.A.Sc., Andreas Voss, M.D., Ph.D., Ingeborg van der Tweel, Ph.D., Alex van Belkum, Ph.D., Henri A. Verbrugh, M.D., Ph.D., and Margreet C. Vos, M.D., Ph.D.



No. at Risk						
Mupirocin–chlorhexidine	504	484	240	6	2	1
Placebo	413	386	204	7	4	0

Figure 3. Kaplan–Meier Curves Showing Cumulative Hazard of Hospital-Acquired *Staphylococcus aureus* Infection in the Study Groups.

Data were censored at the end of the follow-up period or at the time of death.

Bode L *et al*. *NEJM* 2010;362:9-17

4

We need rapid diagnostic tests to enrich patient population in clinical trials:

- **to reduce costs**
- **to develop narrow spectrum antibiotics**

A *P. aeruginosa* - Focused VAP Programme

- Standard non-inferiority Phase 3 study[1]
  - Need 336/arm or 672 evaluable patients total
- If only 10% yield *P. aeruginosa*,
  - We need 6,720 patients … for ONE trial!

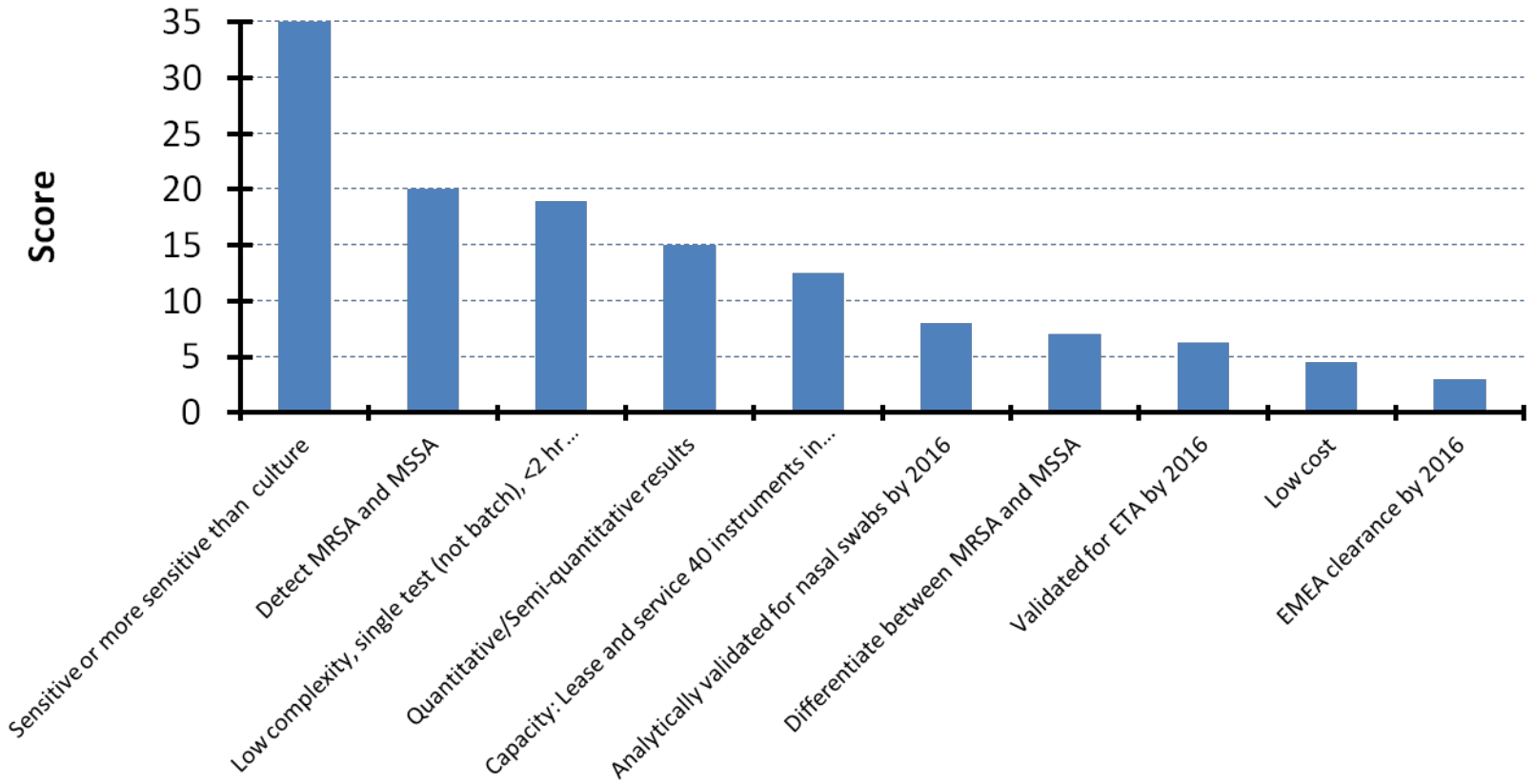
[1]Assumes 80% success rates, 10% margin, and 90% power.

Courtesy: John Rex

Examples of clinical trials in IMI where rapid diagnostics are needed

- Phase II RCT with anti-α-toxin staphylococcal antibody MEDI4893 for prevention of HABP/VABP (MedImmune):
  - Diagnostic test needed: rapid detection of *S. aureus* in ETA
- Phase II RCT trial with anti-pseudomonas antibodies MEDI3902 for prevention of HABP/VABP (MedImmune)
  - Diagnostic test needed: rapid detection of *P. aeruginosa* in ETA

S. aureus ETA Rapid Dx Weighting



Rapid Diagnostic for POCT for *P. aeruginosa* colonization in endotracheal aspirates in patients on a mechanical ventilator

Required diagnostic specifications:

- High sensitivity (<10^2 cfu/mL) to identify patients as they become colonized (versus infected/pneumonia)
- High specificity also desired
- Validated for endotracheal aspirate samples (ETA)
- Minimal hands on time (<30 min) for specimen processing
- Rapid turn-around time for result (<2 hr)
- Test can be run on demand without need for batching
- Test can be performed outside of microbiology (ICU or step down unit)
- Low cost (<$40)

- Supply up to 100 instruments to sites across Western Europe
- Service and Technical support for the instruments and assay kits
- Supply ~x,xxx tests between 2016 and 2020

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CEPHEID ANNOUNCES DIAGNOSTIC COLLABORATION WITH MEDIMMUNE AND COMBACTE TO FACILITATE CLINICAL TRIALS OF NEW MONOCLONAL ANTIBODIES TO PREVENT SERIOUS INFECTIOUS DISEASES

GeneXpert Systems and Xpert Tests Expected to Enhance Efficiency of Clinical Trials

SUNNYVALE, CALIF. — January 13, 2016 —Cepheid (Nasdaq: CPHD) today announced a collaboration with MedImmune, the global biologics research and development arm of AstraZeneca, and COMBACTE, a European public/private partnership set up to promote the development of new drugs in the anti-infectives field, to develop a series of rapid diagnostic tests to identify *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) in respiratory secretions of mechanically ventilated patients. These tests will be used to help identify patients for MedImmune's MEDI4893 and MEDI3902 clinical programs, which are being conducted within the COMBACTE consortium to explore the use of biologics in preventing ventilator associated pneumonia (VAP) infections in intensive-care-unit (ICU) patients.

My lessons learned on role of diagnostics

to aid patient enrolment in COMBACTE clinical trials with narrow-spectrum drugs (4/9 intervention trials)

Unclear function and performance characteristics	How will test be used? What are required performance characteristics to aid patient enrolment?
Schism between pharma and diagnostic companies	Pharma: limited number of organisms in a specific sample Diagnostic companies: broad range tests
Unclear exploitation	How is the test developed into labeled product? Who will pay for the test?
Regulatory blind-spots	Potential regulatory needs discussed too late and/or conflicting feed-back
Demand of pharma to perform test outside of microbiology lab	Purchasing and logistical challenges Challenges to organise, track and train HCW Maintenance, Q-controls and test support Miscommunication between pharma, diagnostic company, micro lab, and CRO

5

We need to drive reimbursement prices of rapid diagnostics to fight AMR based on by their medical & societal value

Tsunami of instruments

Fast systems

Alere: i

Isothermal amplification: NEAR

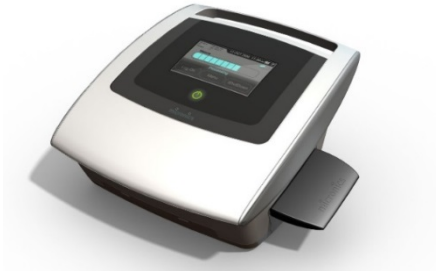
15 min Influenza test

Handheld devices

Micronics: PanNAT

1 hour 3 targets test

H: 20 cm / Depth= 34.5 cm / Width: 12 cm



Multiple targets

bioMérieux: FilmArray

Reverse transcriptase

Turn RNA into cDNA

TAT: 1 hour

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

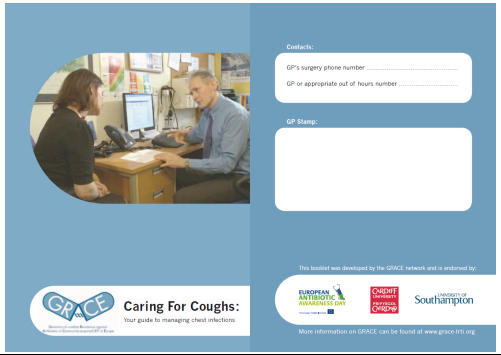
> "I can either prescribe $4 penicillin" on the chance that a patient has a strep infection, Dr. Beasley says. Or he can order a $51 strep test to make certain the person does. For a patient struggling to make ends meet financially, he says he prefers the $4 penicillin.

6

We need to address psychological, social, and organisational barriers to support the uptake of diagnostics for antimicrobial stewardship

GRACE Intervention Trial

- Countries: UK, Poland, Spain, the Netherlands, Belgium
- Baseline in 6,774 patients and 4,358 patients post-test
- 2x2 factorial design (Communication, CRP, Usual care)



	Usual care	Communication
Usual care	Usual care 58%	Communication training 41%
CRP	CRP training 35%	CRP + Communication training 31%

Little et al, Lancet 2013

Mean (SD) CRP concentration by microbiological diagnosis for LRTI subjects with (n=141) and without CAP (n=2963)

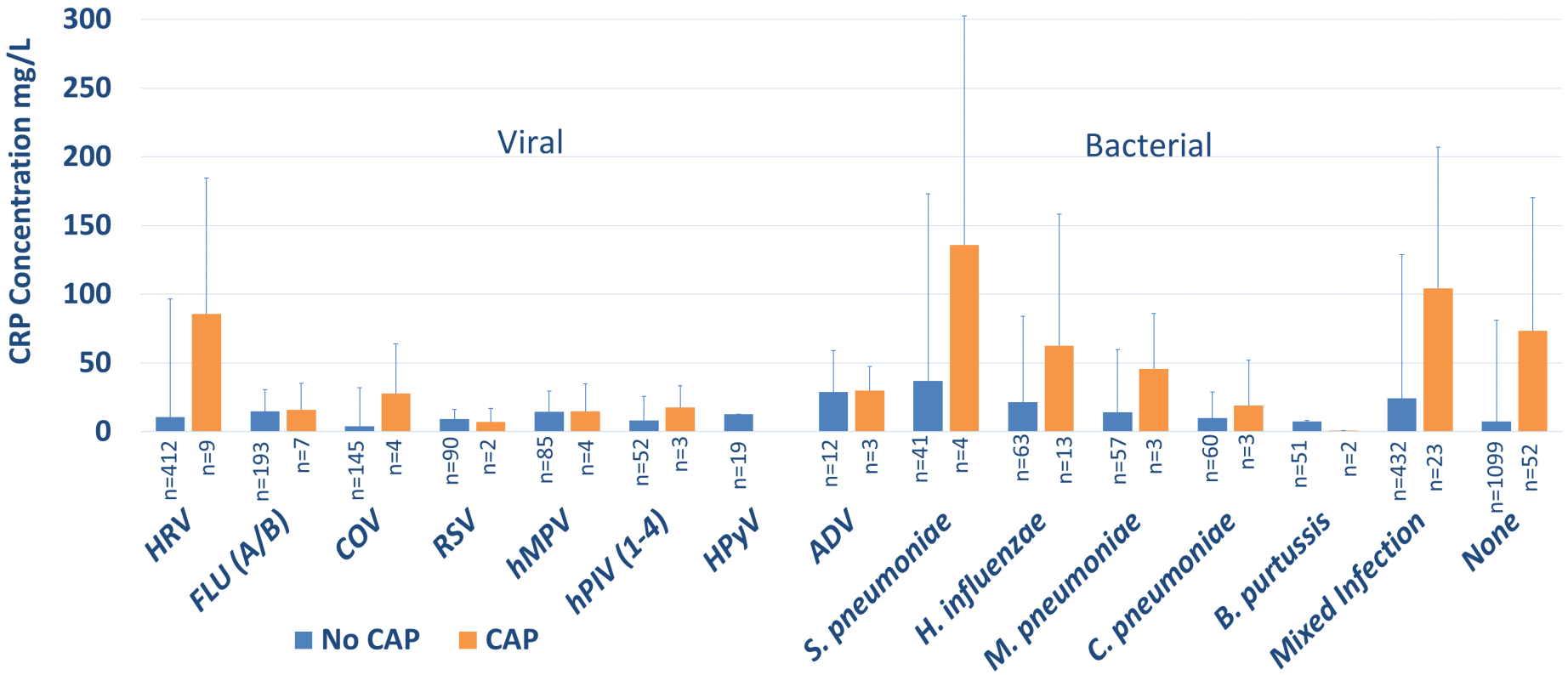


TABLE 5: Overall and country-specific cost-effectiveness (Cost-utility analysis)

	Cost	QALY	ICER	ICER (compared to UC)
Overall (n=4264)				
CRP&Comm	94.36	0.0648	Dominated by Comm	Dominated by UC
Usual care	92.46	0.065	Dominated by Comm	N/A
CRP	87.41	0.0651	Dominated by Comm	Dominates UC
Comm	83.21	0.0651	N/A	Dominates UC
Belgium (n=318)				
Comm	93.28	0.0651	3450	7120
CRP&comm	92.59	0.0649	7343	8038
CRP	87.45	0.0642	12900	12900
Usual care	86.16	0.0641	N/A	N/A
Netherlands (n=329)				
CRP&Comm	84.99	0.0649	Dominated by CRP	Dominated by UC
Usual care	75.52	0.065	Dominated by CRP	N/A
CRP	73.41	0.0656	27186	Dominates UC
Comm	54.38	0.0649	N/A	N/A
Poland (n=1419)				
Usual care	143.41	0.0663	49129	N/A
Comm	114.37	0.0656	Dominated by CRP	N/A
CRP&Comm	110.95	0.0652	Dominated by CRP	N/A
CRP	109.02	0.0656	N/A	N/A
Spain (n=1318)				
CRP&Comm	78.71	0.0648	Dominated by Usual care	Dominated by UC
CRP	70.86	0.0656	Dominated by Usual care	Dominated by UC
Usual care	66.46	0.0659	1000	N/A
Comm	65.86	0.0653	N/A	N/A
UK (n=880)				
CRP&Comm	106.57	0.0641	Dominated by Comm	25050
Usual care	101.56	0.0639	Dominated by Comm	N/A
CRP	98.75	0.0645	Dominated by Comm	Dominates UC
Comm	98.05	0.0648	N/A	Dominates UC

Confidential; manuscript in preparation

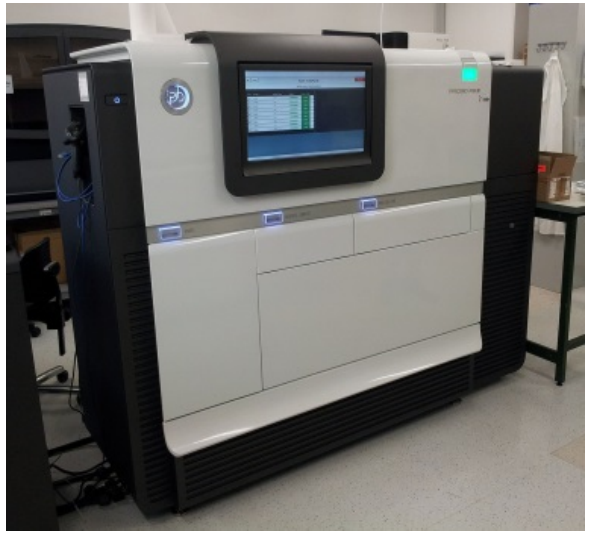
Long road to successful uptake of diagnostics

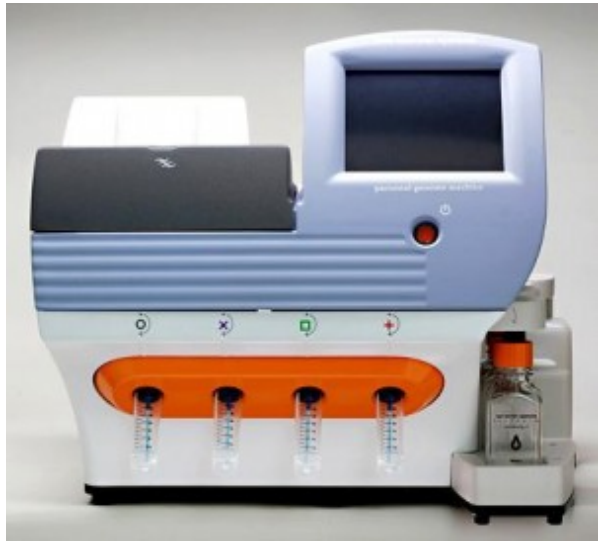
- Rapid and cheap test available
- Demonstrated benefit in reducing antibiotic prescribing in a multinational, cluster, randomized, factorial, controlled trial (published in The Lancet)
- Supported by microbiological and cost-effectiveness research
- Reimbursed in the Netherlands
- Yet not used in primary care

7

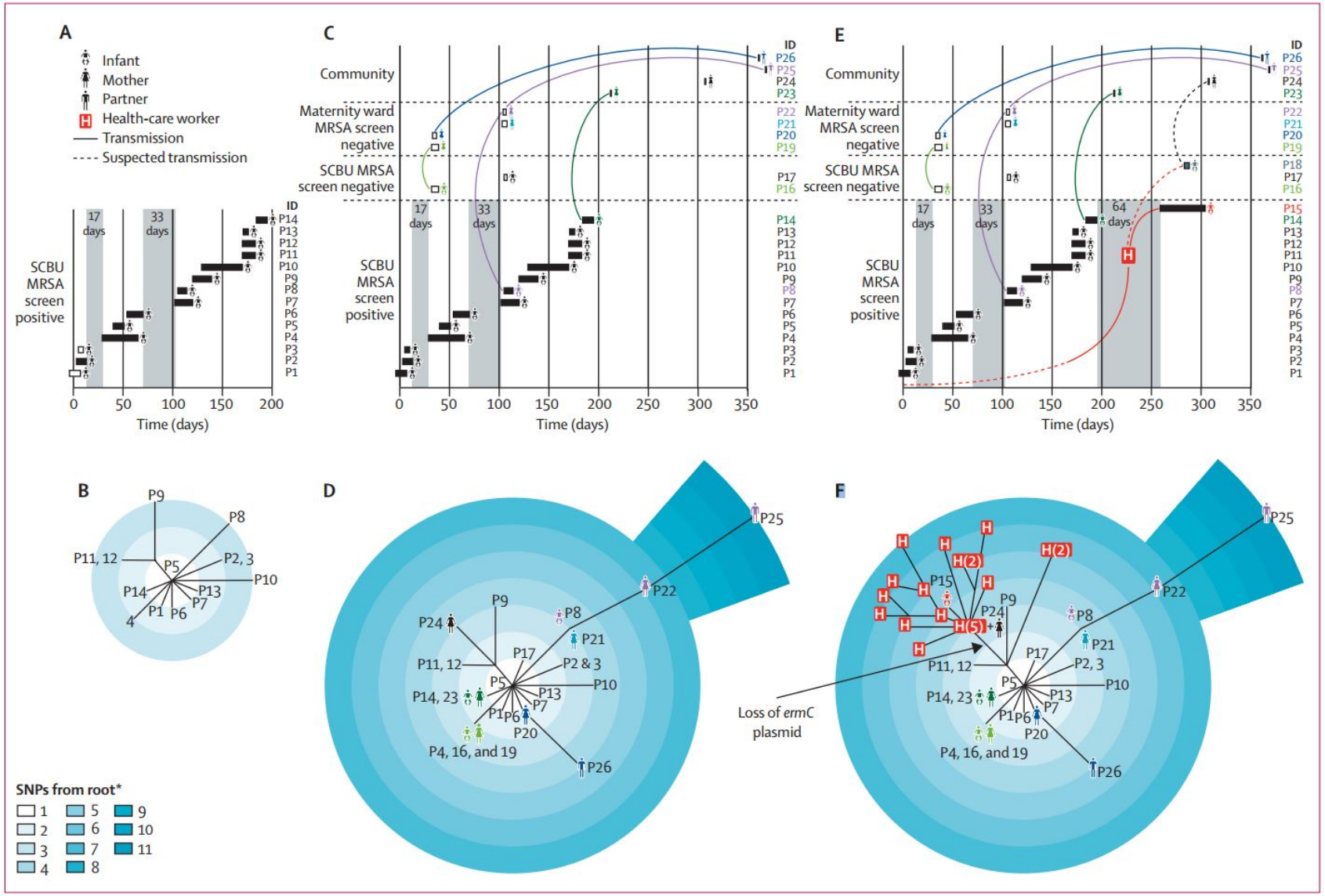
We need different business models to support uptake of new, innovative, and expensive diagnostics

NEXT GENERATION SEQUENCING





Epidemiology and Phylogeny of an Outbreak of MRSA Sequence Type 2371 at a Baby Unit



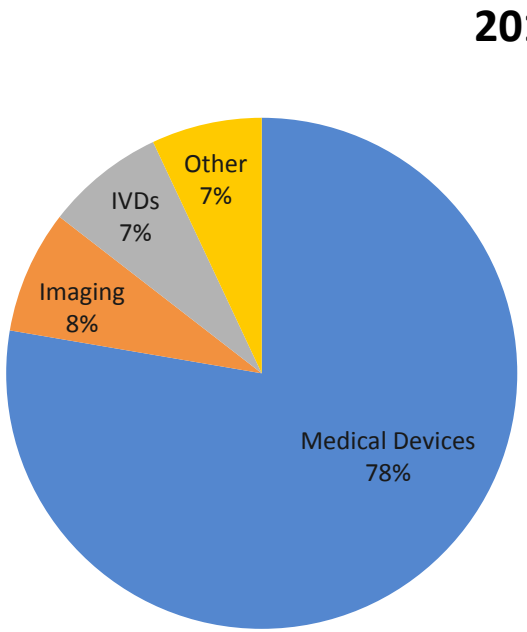
Harris LID 2013; 13: 130-36

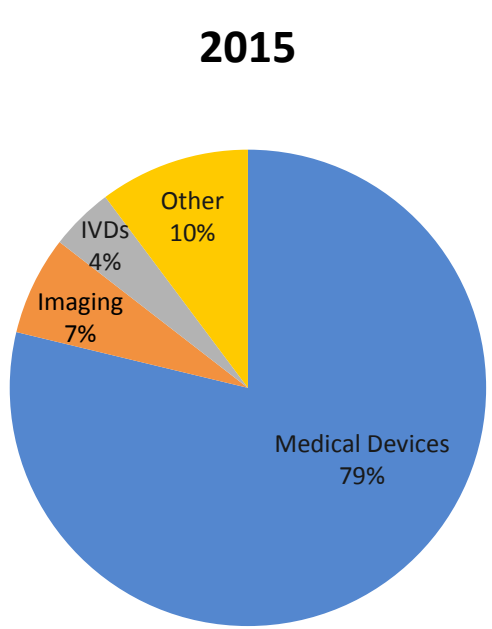
Value-based procurement of IVDs to address AMR

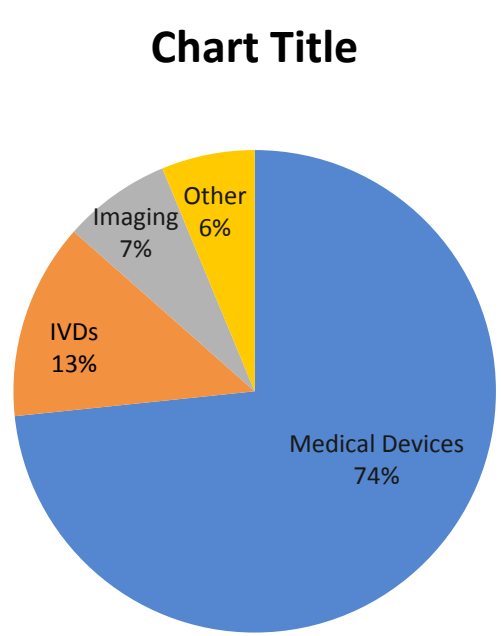
- **Current approach** to procurement based on price-based purchases reduces innovation, discourages the adoption of new technologies, makes the market unattractive for SMEs
- **New EU directive** on public procurement in February 2014
  - Move away from up-front price-only purchase costs
  - Factors in outcome, quality, total costs across the product life cycle and broader socio-economic criteria
- It would encourage IVD companies to invest in innovation
  - Minimum volume assurances
  - Enabling the market to respond to service needs
- Should be based on HTA (next slides)
- Could incentivise clinical value of diagnostics
- Should accelerate regulatory approval
- Should facilitate better reimbursement of IVD tests addressing AMR
- Should be accompanied with measures to address social, psychological, organizational barriers

HTA Reports by medical technology type

	2014	2015	2016
Total HTA reports	372	372	304
Medical Devices (knee replacement, spinal cord stimulation, silver dressing)	289	293	223
IVDs (e.g. serum biomarkers, genetic testing, screening for human papillomavirus)	28	16	40
Imaging (e.g. PET/CT, MRI, Echocardiography)	29	25	22
Others (e.g. sperm washing, ReCell Spray-On Skin, sterile water injections,)	26	38	19







Statistic based on Synergus database (link)

HTA for IVD (of ID / AMR)

- HTA of IVDs represented 8% of all HTA in 2014-2016; HTA of new IVDs in less than 1% (Synergus database)
- HTA for IVD/ID/AMR are very complex (screening, diagnosis, treatment, prognosis, monitoring)
- HTA data requirements/acceptance as evidence, and time points during lifecycle, not aligned between countries and even within countries
- Responsibility and decision power varies between HTA agencies
- HTA are rarely used to inform decision at national, regional, hospital level, community level on access, reimbursement, use, value of IVD
- Need “fit-for-purpose” pragmatic, streamlined, standard HTA of IVDs addressing AMR

SC1-HCO-12-2018: Innovation in healthcare - a CSA towards using pre-commercial procurement and public procurement of innovative solutions in healthcare systems

- Prepare public procurement of innovative rapid diagnostics for tailoring antimicrobial treatment
- Deadline 18 April 2018

SC1-BHC-26-2018: HTA research to support evidence-based healthcare

- Build fit-for-purpose HTA models
- Focus on personalized medicine and companion diagnostics
- Deadline 18 April 2018

SC1-BHC-10-2019: Innovation Procurement: Next generation sequencing (NGS) for routine diagnosis

- Build NGS platform for use of NGS tests in routine diagnostics for personalized medicine
- Deadline 16 April 2019

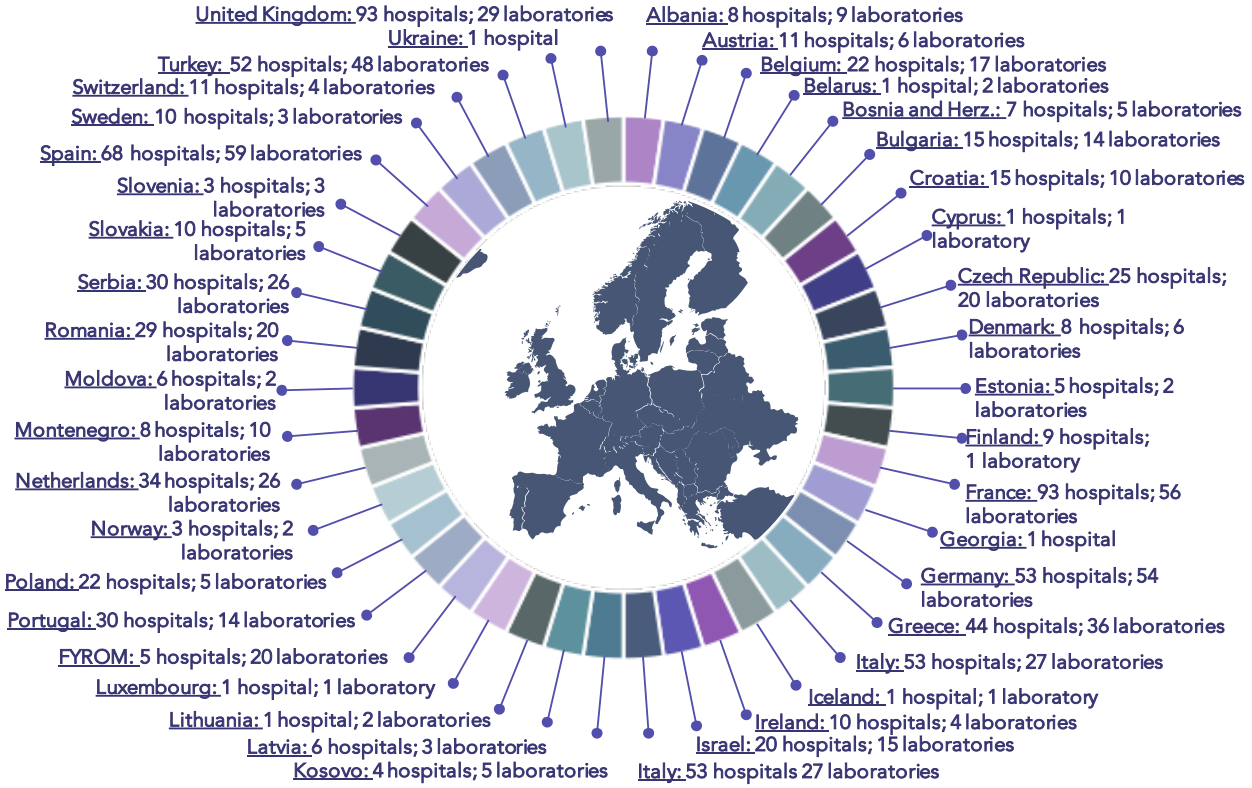
8

We need Clinical Trial Networks to demonstrate the clinical evidence of diagnostics

New IVD Regulation:
Areas of Greatest Impact: Performance Evaluation

- Per **Performance Plan**
- PP to address Clinical Evidence, consisting of:
  - **Scientific Validity**: Literature Search Documented
  - **Analytical Performance**: Per applicable Requirements
  - **Clinical Performance**: Per clinical study, if necessary; Population effects
- Performance Report updated **continuously** throughout lifecycle

IMI- COMBACTE network infrastructure (March 2017)

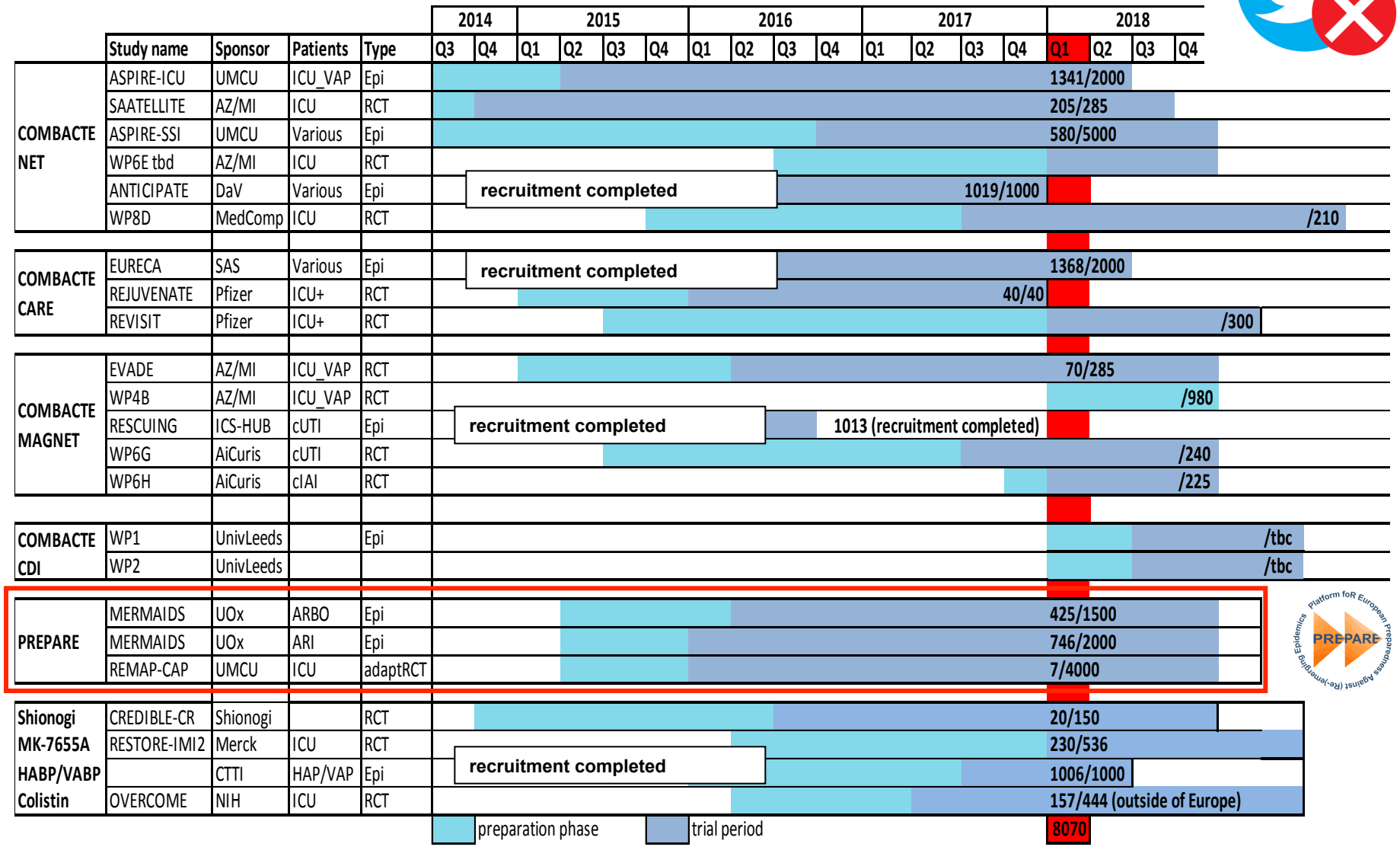


827 hospitals

583 laboratories

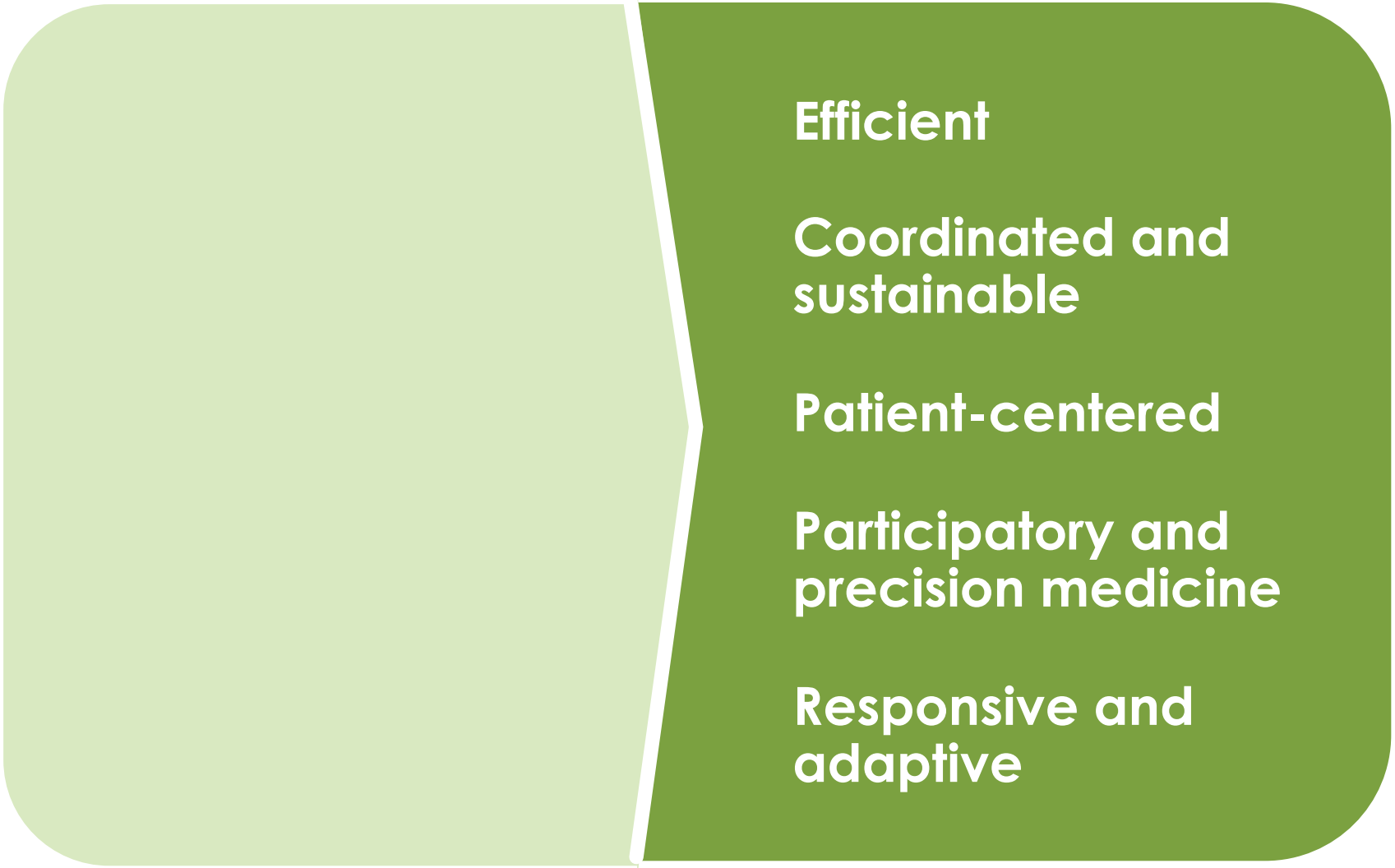
42 countries

COMBACTE Clinical studies

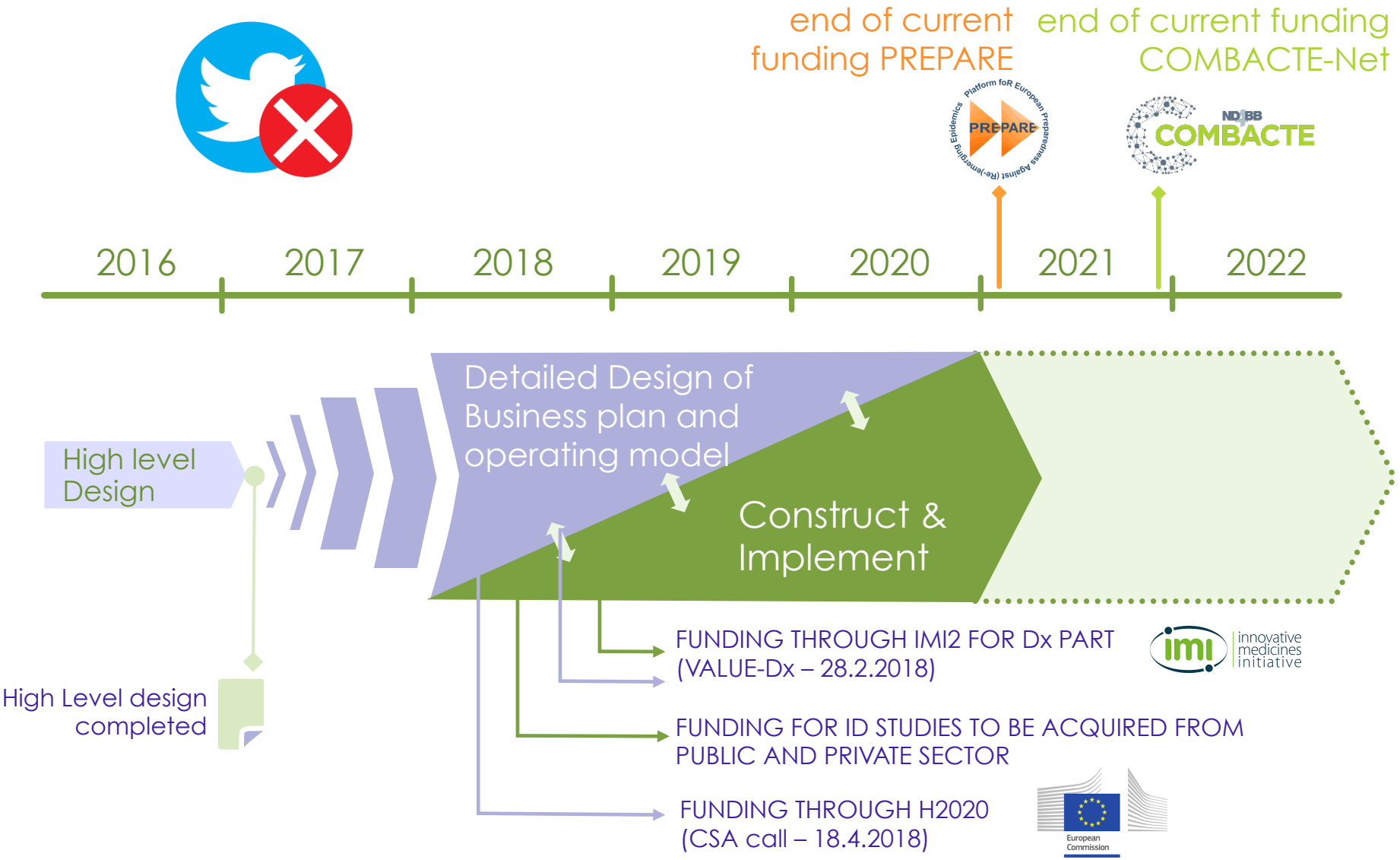


January 2018: 8070 patients enrolled

Time for a Paradigm Shift of Infectious Diseases Clinical Research



ECRAID: Our plan and timelines



SC1-HCO-08-2018: Creation of a European wide sustainable clinical research network for infectious diseases

- Develop business plan to ensure sustainability of a clinical trial network
- Build on PREPATE and COMBACTE
- Deadline 18 April 2018

innovative medicines initiative

Topic 3: The value of diagnostics to combat antimicrobial resistance by optimising antibiotic use

- Develop a business plan for CTN on diagnostics
- Demonstrate the clinical and societal value of rapid diagnostics for AMR
- Build around CA-ART
- Deadline 28 February 2018

Unique opportunities for pharma, academia, the EU and its citizens

- Incentive for pharma to invest in antibiotic discovery
- Allows to broaden the spectrum to other antimicrobial drugs, vaccines, and diagnostic tests
- Allows investigator driven trials
- Allows new models of clinical trials (e.g. Adaptive Platform Trials)
- Creates innovation of the public and private (e.g. SMEs) sector
- Allows rapid clinical research response in the event of a pandemic threat
- Results in improving quality of care delivery to our patients

Many thanks!