Changing diagnostic paradigms for microbiology

(AAM report 2016)

Universum, C.Flammarion, gravure sur bois, Paris 1888.

Point of care testing

Is it obvious?

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Clinical Microbiology, University Hospital of Liege,
University of Liege, Belgium

Changing diagnostic paradigms for microbiology

(AAM report 2016)

Point of care testing

Is it obvious?

- **Clinically ?**
- **Technically ?**
- **Regulatory ?**
- **INAMI ?**

Outline

- Definitions & Background
- Types of POC tests
- Implementation
- Oversight of Near-Patient and Point-of-Care testing
- Evaluation
- Take home messages

Definitions

- **POC** (Point of care)
  - **At the time and location at which patient services are delivered**
- **POCT** (Point-of-care testing) or **NPT,** Near-patient testing
  - **Medical testing and diagnosis carried out at, or close to, the site of patient care**
    - **For in-patients**, at bedside, in a regular exam room or in critical care facility (ED, ICU, etc.)
    - **For outpatients**, at home, at a local pharmacy, at local clinic's examination room, at physician's office, at nursing home or age-care centre
  - **Performed by specially trained healthcare professionals but not laboratory personnel.**
  - **Usually short TAT** (few minutes → 1 or 2 hours)
    - Rapid actionable results to improve outcome and reduce cost of care

XXIst century, Medical evolutionary background

Factors impacting on development and daily practice of microbiology

- **Evolution of lab landscape**
  - **Centralization of core laboratories**
    - Serving more decentralized patients in network affiliated with a hospital
- **Medical environment**
  - Increasing emphasis on **evidence-based medicine** and adherence to **guidelines**
- **Evolution of technological background**
  - Exponential progress: molecular biology and robots
  - New platforms from “sample-in / result-out”
  - Continuation of advance to accelerate in the near future
- **Economic environment**
  - Cost-effective use of available resources
  - Reimbursement system, regulation

- **Quality assurance, traceability, LIS**
- **Global increase of antimicrobial resistance**

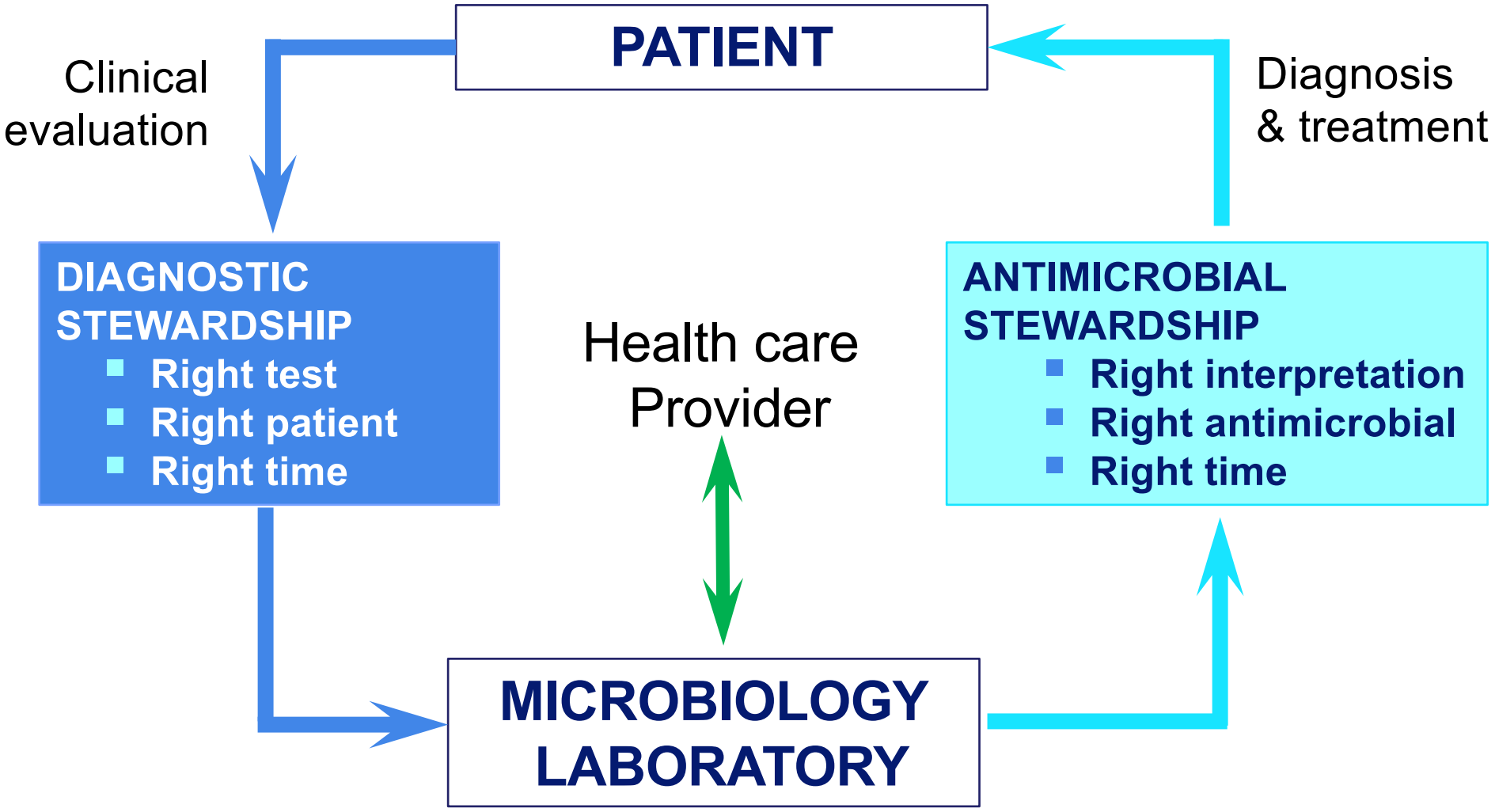
What the clinician seek from the clinical microbiology laboratory

Three basic truths

- ❑ **Is my patient infected ?**
- ❑ **If so, with what ?**
- ❑ **If so, what will treat it ?**

Roles of diagnostic and antimicrobial stewardship

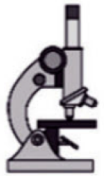
(Adapted from J Clin Microbiol 55:715-723)



HOME

COMMUNITY

CLINIC/HEALTH POST
(Out-patient)



PERIPHERAL LAB
(Microscopy center)

HOSPITAL
(In-patient)

Turnaround time

collection and transport of specimen

Too slow for optimal management of patient

Specimen Analysis

Central lab – Specialized expertise, high-complexity testing, batch testing, but

Results

(0 -) ≥ 2 days ?

limited operation hours 8h-18h ?

Roles of diagnostic and antimicrobial stewardship

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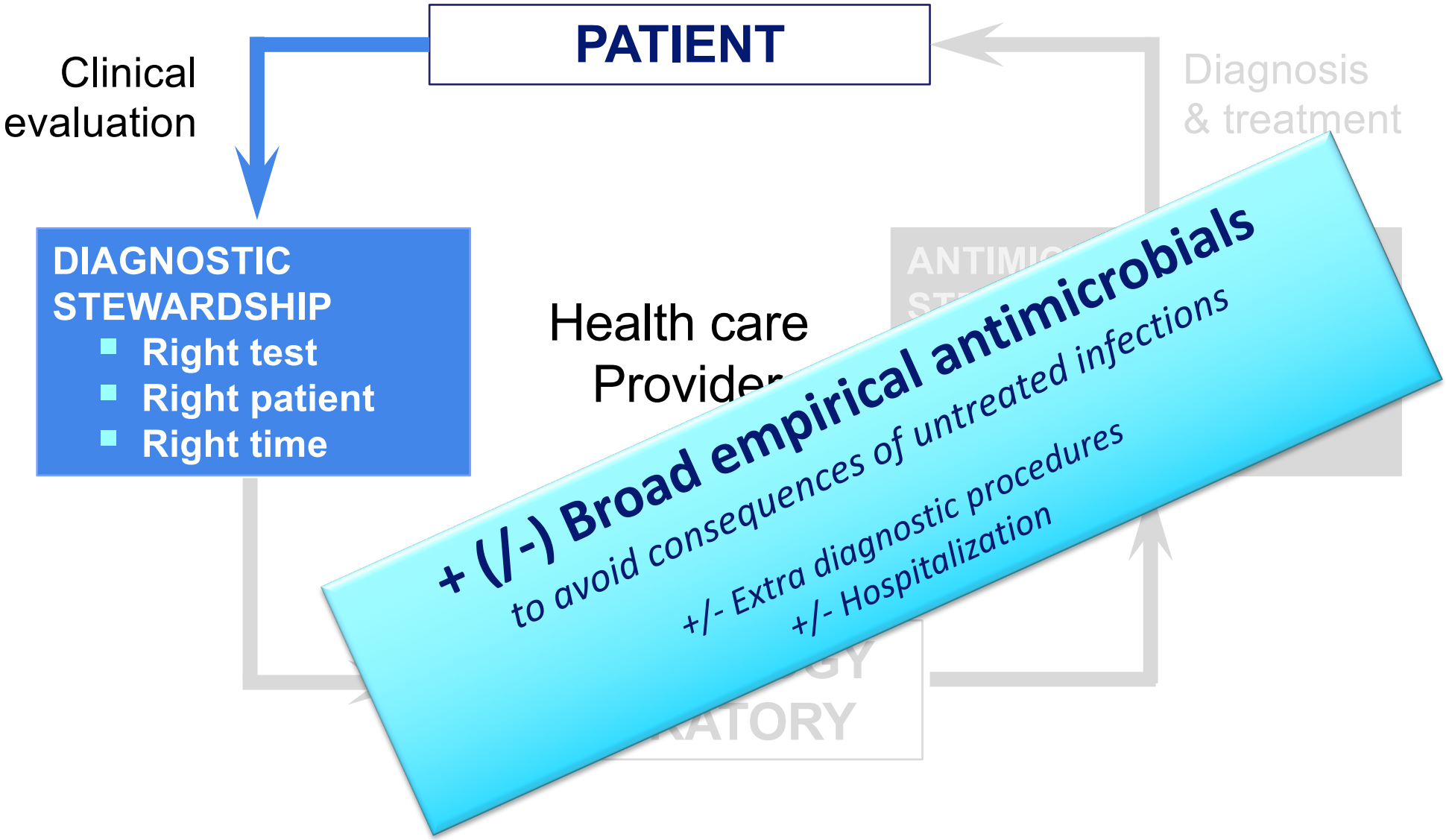

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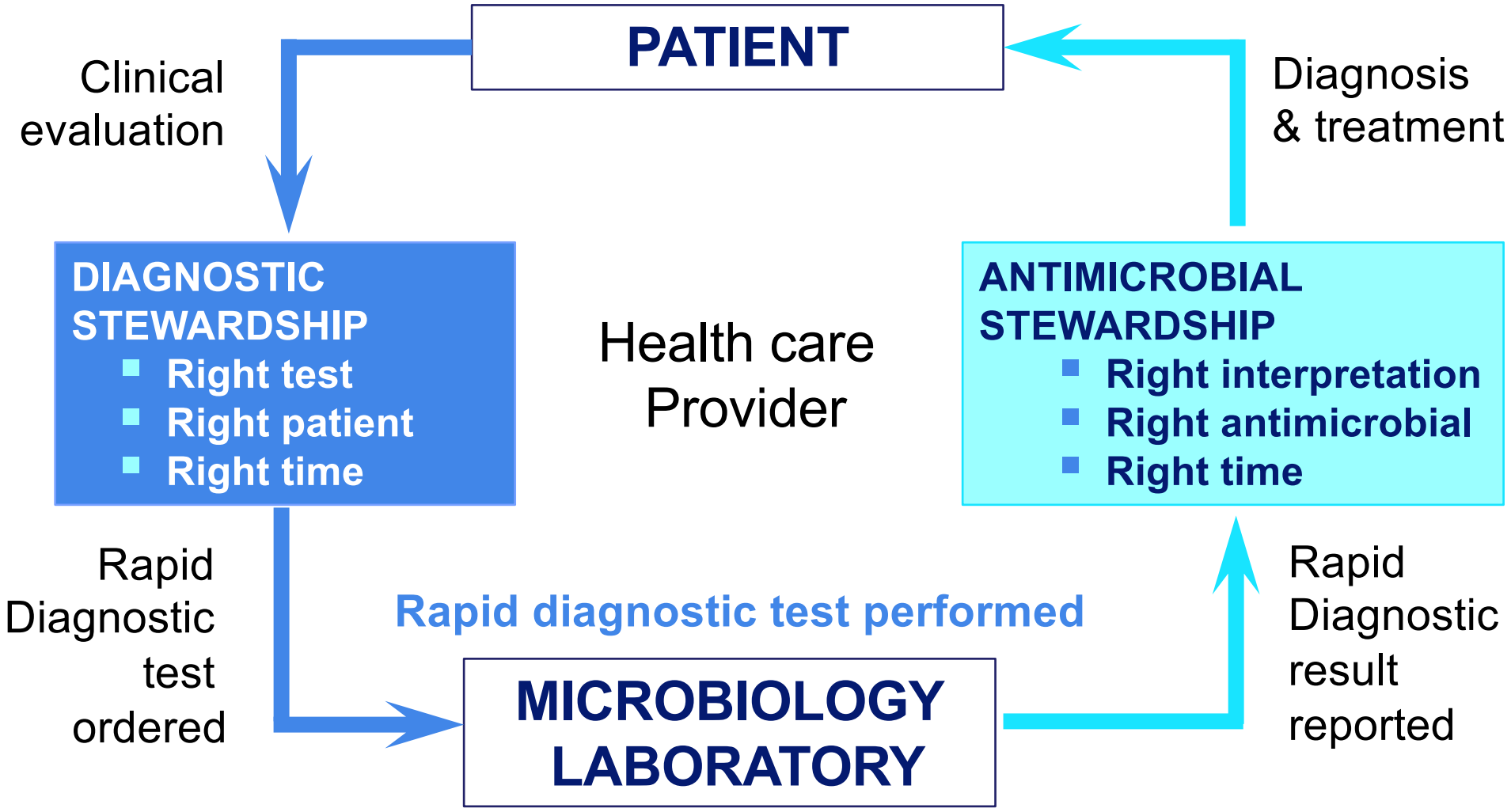

Roles of diagnostic and antimicrobial stewardship

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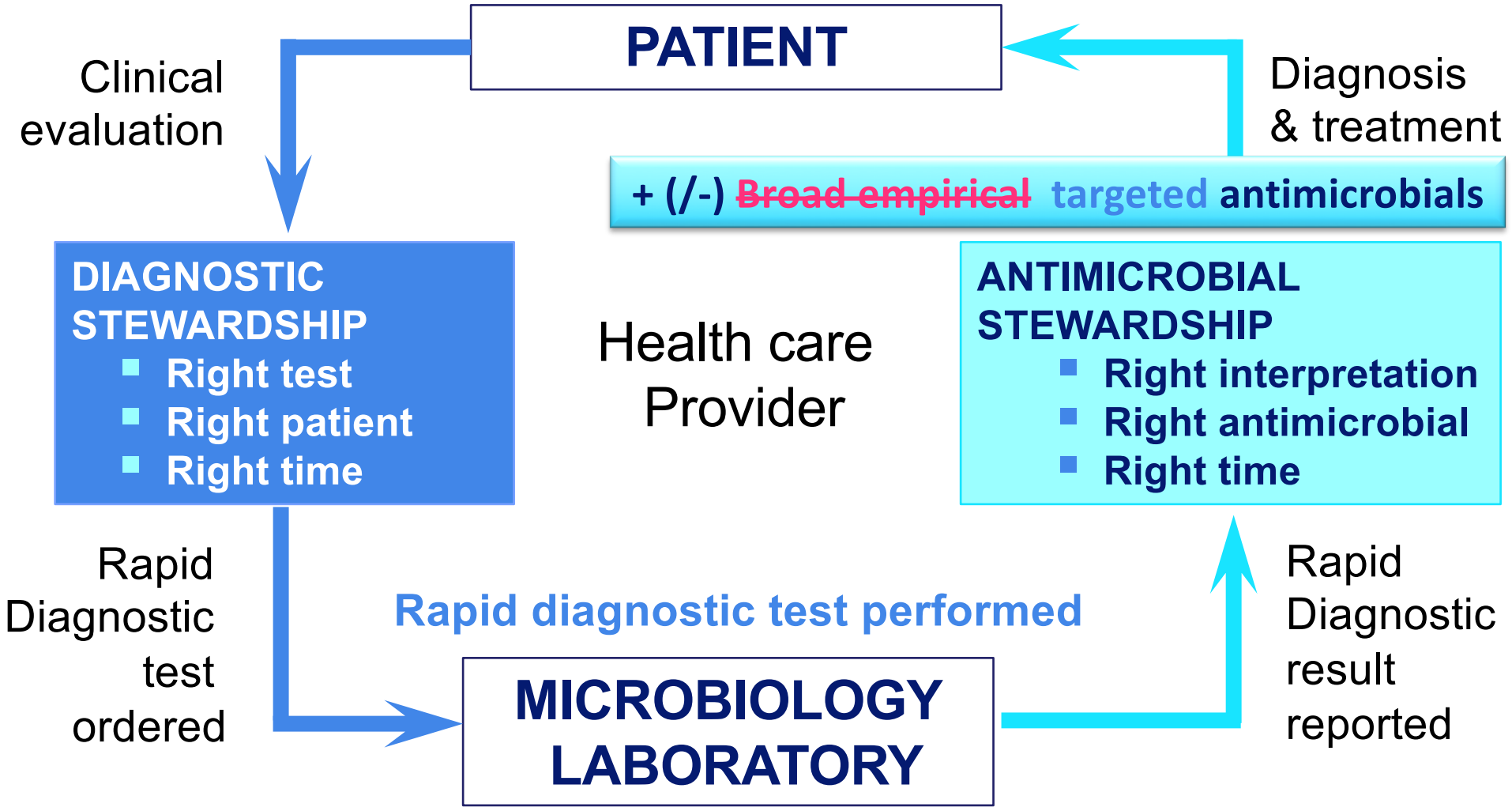


Diagnostic and Antimicrobial Stewardship

Theranostic approach:

timely results to inform diagnosis and treatment

Turnaround time

collection of specimen

Optimal management of patient

“on-demand” Specimen Analysis “POCT” ?

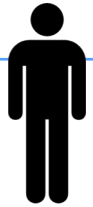
Results

Rapid, 24 hrs/7 d, robust

& cost-effective

Rapid & accurate identification of a pathogen

Prime importance for effective provision of care to patients with infectious disease



The faster you identify pathogens,

the quicker you can react to it,

- **Supporting rapid initiation or cessation of atb treatment**
- **Implementing targeted treatment according to rational use of antibiotics when needed**
- **Preventive measures and control of infections**
- **Enhancing surveillance of pathogens and infectious diseases**

Benefits are also for

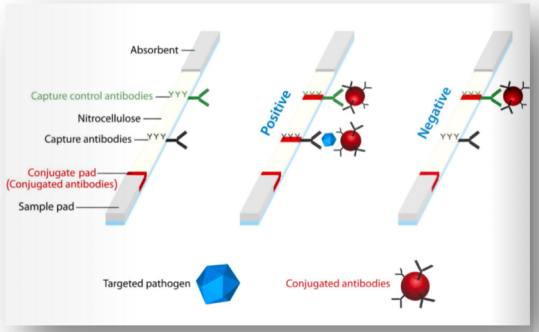
The community, hospital and control measures

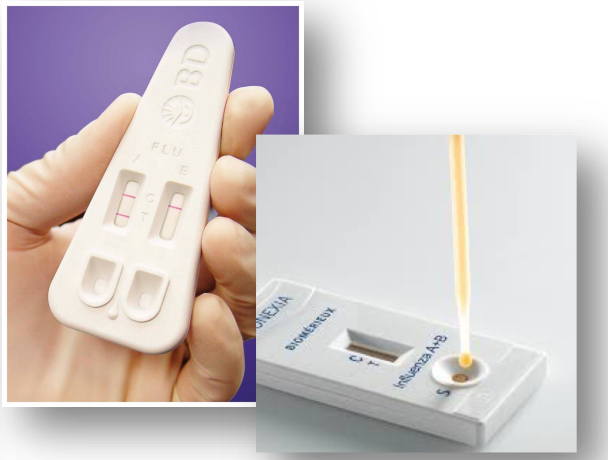
POCT: types of tests

Shifting from antigen-based testing to nucleic acid amplification-based testing, including multiplex syndromic panels

1. Antigen, antibody tests

- **Mainly lateral-flow immunochromatographic membrane-based assays (LFIA)**
- **Lower Sensitivity and specificity than NAAT**
- Influenza A&B, Group A Streptococcus, infectious mononucleosis, Respiratory syncytial virus, HIV, *Treponema pallidum, Streptococcus pneumoniae*, *Legionella pneumophila* serogroup1, etc.





POCT: types of tests

2. Nucleic Acid Amplification tests (NAAT)

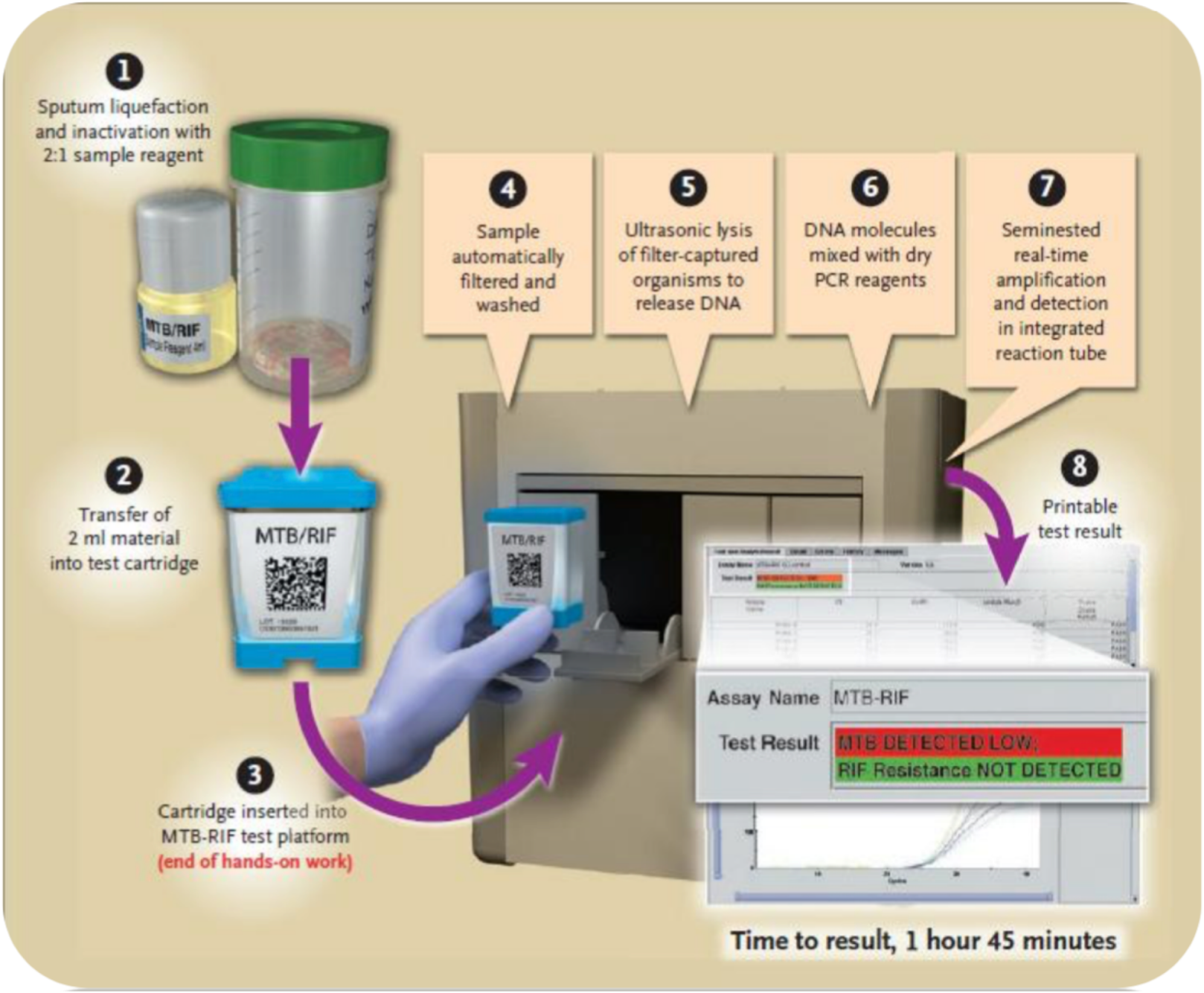
- **Detect DNA or RNA sequences specific to a particular target** (present in a specific pathogen or antimicrobial resistance determinant)
  - FLU A/B; RSV, MRSA, CT/NG, C.difficile, Norovirus, GAS, GBS, Trichomonas, TB/Rif, etc.
- **Different amplification methods**
- **Costly and need of specialized equipment**
- **Increased sensitivity, but limitations** (contamination → F+; mutation → F-)

POCT: types of tests

NAAT considerations

Diagnostic of Tuberculosis

- **Challenge for low resources countries**
- **Improvement of diagnostic of TB, particularly in developing nations with high prevalence and often associated to HIV.**
- **NAAT to replace direct microscopy** (sensitivity 50-60%) _ GeneXpert TB **(+/- culture, suboptimal, too long)**
- **High sensitivity of NAAT**
  - **98% of smear positive and 75% of smear negative patients**
  - Results delivered within 2 hours → initiation of treatment the same day of healtcare visit !!
- **Rapid, sensitive and specific :**
  - Potential to replace microscopy
- **Ability to identify rifampicin-resitant TB**
- **Minimum technical training required to run the test**


1
Sputum liquefaction and inactivation with 2:1 sample reagent
2
Transfer of 2 ml material into test cartridge
MTB/RIF
3
Cartridge inserted into MTB-RIF test platform
(end of hands-on work)
4
Sample automatically filtered and washed
5
Ultrasonic lysis of filter-captured organisms to release DNA
6
DNA molecules mixed with dry PCR reagents
7
Seminested real-time amplification and detection in integrated reaction tube
8
Printable test result
Assay Name MTB-RIF
Test Result MTB DETECTED LOW
RIF Resistance NOT DETECTED
Time to result, 1 hour 45 minutes

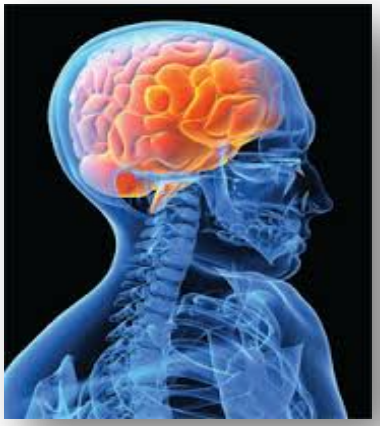
Desirable features of POC devices or on-field assay

- **Quick reliable response**
- **Short Turn Around Time (TAT) < 1 hour ?**
- **Accuracy: high sensitivity, specificity, negative and positive predictive values**
- **As simple as possible, compliance with basic rules of GLP**
- **Ease of use: to perform and to interprete** *(clear-cut result)* **by unskilled minimally trained people**
  - *Low rate of invalid / error results*
- **Workflow; very limited hands-on-time**
- **Limited training**
- **Long shelf-live, minimized waste**
- **Availability 24h/7d**
- **Cost-effective**
- **Internal QC / embedded process control / control for presence of specimen on board**
- **Fully automated and robust test & platform**
- **Traceability, connectivity to electronic medical files**
- **Multiplexing capacity**
- **Small footprint, low noise level**

Why do we need better rapid POCT ?

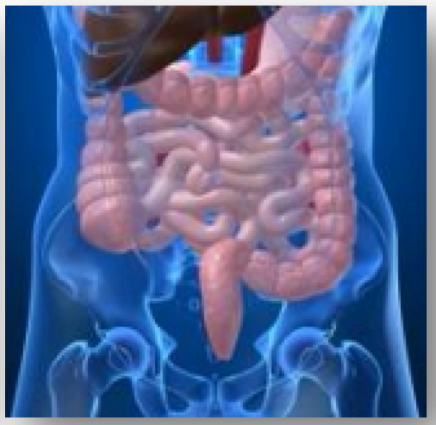
In many cases a clinical presentation may be caused by a number of possible pathogens

- **Syndromic diseases**
  - **Characterized by the abnormal presence, simultaneously, of a group of signs and symptoms**

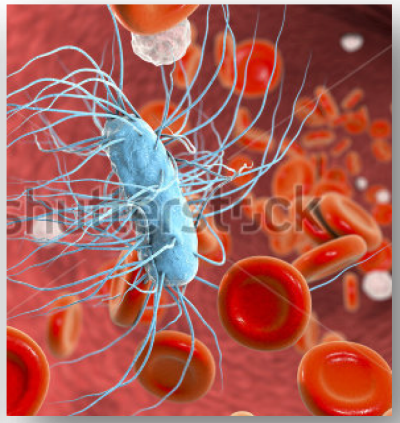


CNS infections

Respiratory tract infections



Gastro-enteritis



Bloodstream infections

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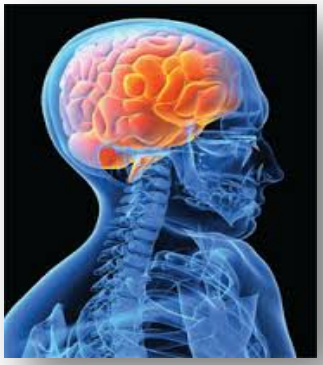
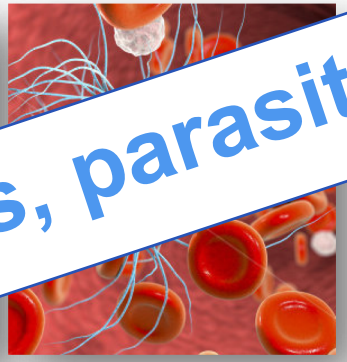


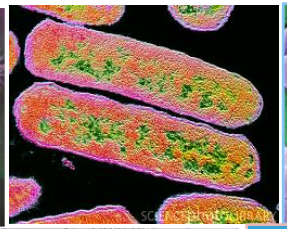
CNS infections

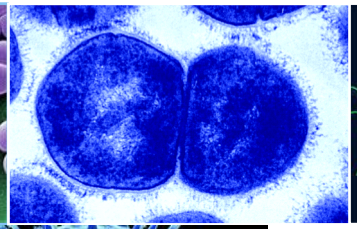
Gastro-enteritis

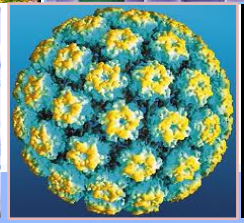


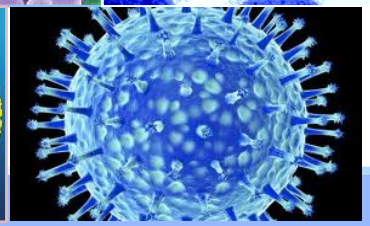
Bloodstream infections

Bacteria, fungi, viruses, parasites









Microbiological diagnostic approaches Transition

- From conventional (aetiological) approach
  - *« Is a specific pathogen present in the specimen? »*
  - **Step by step, on demand** (primarily directed to typical bacteria)
  - **Varied individual methods**
  - **TAT : minutes to days or even weeks**

- To syndrome-based approach
  - *« Which pathogen is causing this syndrome? »*

Microbiological diagnostic approaches, transition

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- To syndrome-based approach
  - *« Which pathogen is causing this syndrome? »*
  - **Broad panel diagnostic method** (Including atypical agents, viruses, fungi, parasites)
  - **All inclusive testing system** ***« Sample-in / result-out »***
  - **TAT : 1-2 hour(s)**

Point-of-care-test platforms for early diagnosis of infection *(FDA cleared- CE approved)*

To provide an integrated, holistic solution addressing technological challenges

- **For rapid increased detection of bacteria, mycobacteria, fungi, viruses, host markers and resistance to antimicrobial drugs**
  - **To enhance clinical decision-making**
  - **To improve quality of care and clinical outcomes**
  - **To improve targeted therapy and reduce overuse**

- **Specific probes *(pathogens, R markers, virulence markers)***
- **From native patient's samples** (limited volume)
- **Novel methods of sample preparation**
- **Novel molecular solutions**
- **Ultra-high sensitive detection methods**

Results availability

in less than 2 hours for IN/OUT patients

Point-of-care-test platforms for early diagnosis of infection *(FDA cleared- CE approved)*

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- **Novel … …mple preparation**
- **N… … solutions**
- **… …sensitive detection methods**

Res… …availability

in less than 2 hours for IN/OUT patients

Huge challenges and synergies:
Biotechnologies, microtechnologies and clinical practice

All-inclusive systems for multiplex syndromic approach

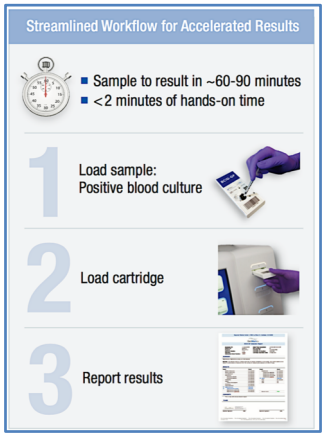
(sample to answer multiplex molecular diagnodtics)

- Systems covering all steps from sample preparation to results
- All reagents freeze-dried in one pouch
- Internal controls for each step!
- Closed system for preventing cross contamination
- Advanced software to run the system, results automatically analyzed and reported in a simple, easy to read format
- Multiplexed testing: for a large number of targets (> 20) per sample
  - Comprehensive Mx panels
- Results available in 1-2 hours following sample injection
- Testing easy to perform with minimal training (24h/7d)
- Bi-directional LIS interface

Among the choice of platforms and assays

BioFire FilmArray System, bioMérieux

ePlex System*, GenMark



- < 2 min of hands-on time
- Sample to result in +/- 60 minutes
- Bi-directional LIS interface
- Scalable system
- Random and continuous access
- In/out the laboratory
- Interpretation of positive results ?

- Meningitis / Encephalitis Panel
- Respiratory Pathogen Panel
- Blood Culture Id Panel
- Gastro-intestinal Panel

Concerns about indiscriminate deployment of syndromic panels when a nuanced approach is needed.

Implementation of POCT

- **Goal**
  - **to collect the specimen and obtain accurate results in a very short period of time at or near the location of the patient.**
- **Advantages**
  - **to bring the test conveniently and immediately to the patient.**
    - Including a variety of remote locations, meeting diverse medical needs.
  - **To increase the likelihood of short TAT to get results quicker**
  - **To enable clinicians to support the timely diagnosis, triage, monitoring and treatment of patients if needed.**
  - **A lean process, less steps; redisigning workflow**
- **Caveats**
  - **Many limitations if analysis procedures are not adhered to.**
    - Essential that POCT is undertaken correctly to ensure accurate and reliable results and interpretation.
  - **Are other results needed from non-POCT to manage patient?**

Implementation of POCT

- **Goal**
  - **to collect the specimen and obtain accu… in a very …**
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- **Caveat…**
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  - **Are other results needed from non-POCT to manage patient?**

When over utilized or incorrectly performed, POCT presents a significant patient risk and potential for increased healthcare costs.

An incorrect test result can result in the wrong treatment and potentially life threatening consequences

International standards & quality assessment

- **International standard for POCT : ISO 22870**
  - ***Point-of-care testing – requirements for quality and competence*.**
  - **Specific requirements applicable to POCT**
  - **To be used in conjunction with ISO 15189, *Medical laboratories – particular requirements for quality and competence*.**
  - **The requirements of ISO 22870** "apply when POCT is carried out in a hospital, a clinic, or healthcare organisation providing ambulatory care"

- **Internal Quality Control**
- **External Quality Assessment**
  - **Critical component in assuring the quality of results**

Although POCT provides rapid results and the opportunity for faster medical decisions, the risk of errors with POCT often raises concern over the reliability of test results.

Management / Oversight

- Infrastructure
- Lab must be involved

Testing performed by non laboratory personnel

- Need knowledge of specimen handling, QC, QA, etc.

Analytical quality

- Reliability on results
- Variations in test results from multiple testing platforms

Regulatory

- Waived vs non-waived

Training and competency assessments

- Need to track for all operators
- Differing requirements between regulatory agencies and for waived or non waived tests

Data management & connectivity

- **Need to capture results electronically** (to reduce errors, incorporate data)
- **Varying connectivity capabilities of POC devices**

Costs & billing

Testing performed by Non-laboratory personnel

- **Nurses, medical assistants**
  - Minimal laboratory knowledge
  - **Focused on patient care**
  - Pressure of fast-paced environment
  - Unfamiliar to importance of proper calibration, instrument maintenance and QC !
  - Risk of mis-use, incorrect performance and mis-interpretation

Why should they handle POCT ?

Isn't it the laboratory role !

The Lab's Responsibility in POCT

- To be part of decision for implementation of a POCT
- Responsible for training
- Organizer and oversight of QA
- To provide guidelines for proper ordering, for interpretation
- To conduct solid, high quality validation studies
  - To balance benefits and harms
  - To evaluate impacts on patient care
  - To evaluate benefits for society as
    - Reduction of transmission of pathogens
    - More appropriate use of antibiotics
  - In one defined setting at a time

POCT Policy

Aims,

- **To ensure that**
  - **POCT is used in a safe and effective way in accordance with best practice.**
  - **Results used for patient care are as near as possible in quality to those issued by accreditated hospital laboratory**

See Leeds Teaching Hospitals NHS Trust (LTHT) website, policy applying to all employees.

Guidelines for prevention of GBS perinatal diseases

Efficacy, concerns & drawbacks

Room for improvement

POCT FOR GBS,
ISN'T IT CLINICALLY OBVIOUS ?

Concerns about preventive strategies & IAP

	Risk-based approach	Antenatal screening-based approach

No IAP when needed	▪ A lot of missed opportunities
	  ▪ Lack of adhesion
	  ▪ Incomplete assessment of risks
	▪ Up to 65% of cases not associated to RF
		▪ Some missed opportunities
		  ▪ Results not available
		▪ False Negative screening
		  ▪ Change of GBS status
		  ▪ Colonization dynamics
		  ▪ Lack of viability
		  ▪ Transport conditions, antibiotherapy, personal hygiene
		  ▪ Poor sensitivity of culture
		30 - 60 % of true +

Unnecessary IAP	▪ Half up to 80% of women with RF are not GBS colonized
	(except intrapartum fever)
		▪ False Positive screening
		  ▪ Change of GBS status
		  ▪ Colonization dynamics
		Up to 30 % of antenatal positive

Intrapartum screening
Expected advantages & drawback

- ❑ **Inclusion of women without antenatal screening / care**
- ❑ **Identification of women with change of GBS status after 35-37 wks gestation**
- ❑ **Increased accuracy of vaginal GBS colonization status at time of labor & delivery**

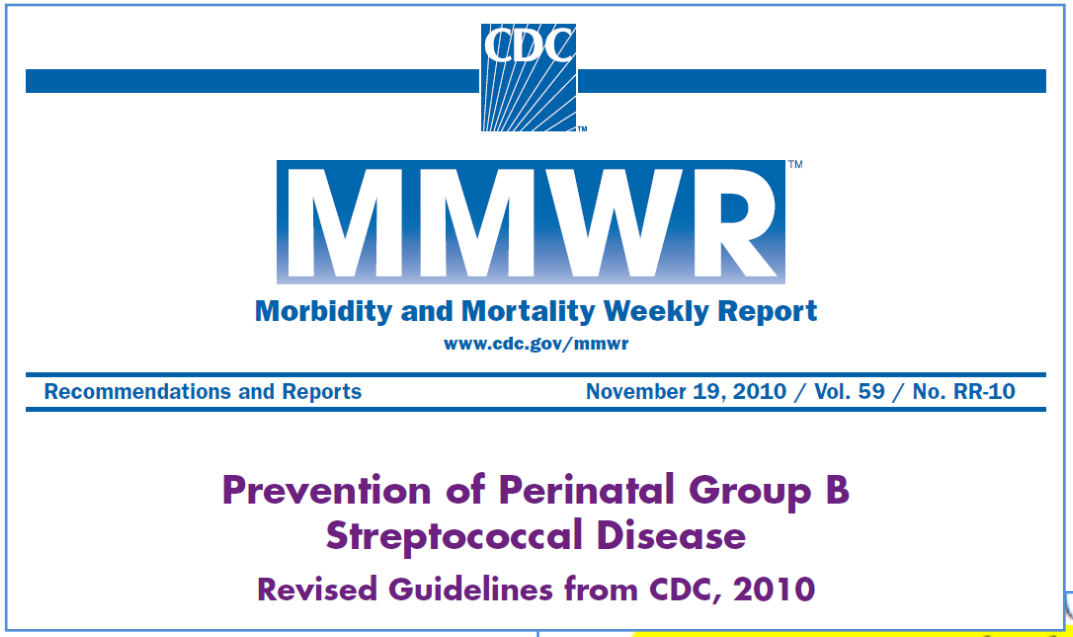
- ❑ **No antimicrobial susceptibility results**

(→ in case of penicillin allergy, antenatal screening)

→ **IAP addressed to right target**

- **Reduction of inappropriate / unnecessary IAP**
- **Broader coverage of « at GBS risk women »**

→ **Improvement of prevention**



CDC

MMWR™

Morbidity and Mortality Weekly Report

www.cdc.gov/mmwr

Recommendations and Reports | November 19, 2010 / Vol. 59 / No. RR-10

Prevention of Perinatal Group B Streptococcal Disease

Revised Guidelines from CDC, 2010

(CIII).

- In settings in which NAAT for GBS is available, obstetric providers can choose to perform intrapartum testing of vaginal-rectal samples from women with unknown GBS colonization status and no intrapartum risk factors (temperature of ≥100.4° F [≥38.0°C] or rupture of amniotic membranes ≥18 hours) at the time of testing and who are delivering at term (CII). If an intrapartum risk factor subsequently develops, antibiotic prophylaxis should be administered regardless of the intrapartum testing results (AIII).
- Women with positive intrapartum NAAT results for GBS should receive antibiotic prophylaxis (AII). NAAT testing is optional and might not be available in all settings.

MMWR
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr
Recommendations and Reports November 19, 2010 / Vol. 59 / No. RR-10

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J Matern Fetal Neonatal Med, Early Online: 1–17
 DOI: 10.3109/14767058.2014.934804

informa healthcare

GUIDELINES

Intrapartum GBS screening and antibiotic prophylaxis: a European consensus conference

When adequate tests available !

G. C. Di Renzo[1], P. Melin[2], A. Berardi[3], M. Blennow[4], X. Carbonell-Estrany[5], G. P. Donzelli[6], S. Hakansson[7], M. Hod[8], R. Hughes[9], M. Kurtzer[10], C. Poyart[11], E. Shinwell[12], B. Stray-Pedersen[13], M. Wielgos[14], and N. El Helali[15]

Old or new tools to detect GBS ?

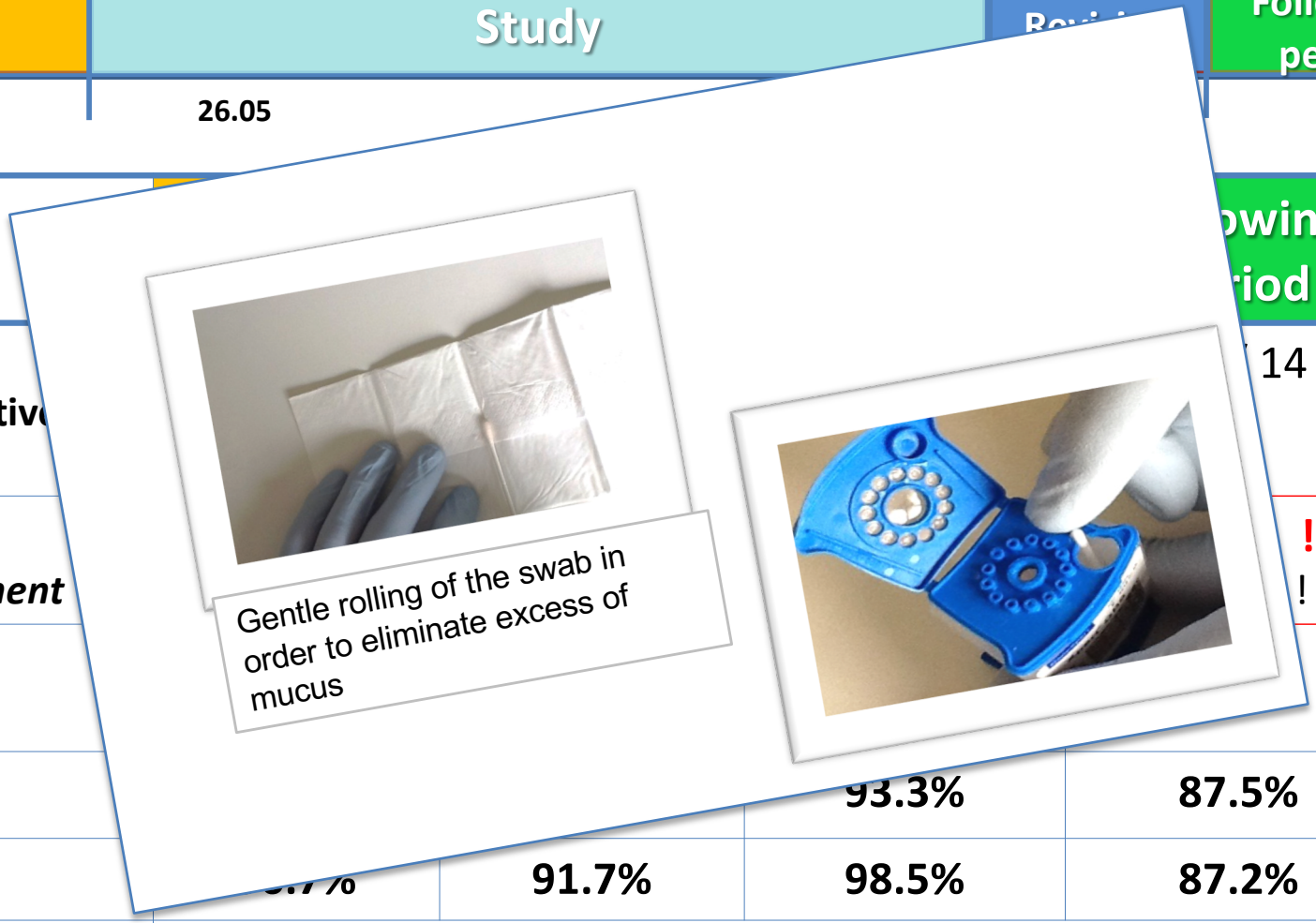
Response to a 30 year “dream” but also an obvious need.

POCT FOR GBS,
IS IT TECHNICALLY OBVIOUS ?

Xpert® GBS results (Liege, 2014)

Intrapartum (IP) culture as gold standard

Number tested / Number GBS Positive Culture				14
Sensitivity *Excluding enrichment*				!! !
Specificity				
PPV			93.3%	87.5%
NPV		91.7%	98.5%	87.2%
Error + Invalid results	3% - 11%			



Xpert® GBS POCT in the delivery room

- High specificity but varying sensitivities !
- Some invalid or error results
  - Time, cost to retest ???
- Some expected improvements to secure the result AND the patient management (specimen control)
- Mucus interference
- Higher Ct when test perform immediately after collection: better results a few hours later

Commutability from lab to POC:

Not always an unconditional success story !

→ **Clinical validation of GBS POCT:**

crucial to be performed (1) on site, (2) by midwives and (3) on fresh specimens

POCT - CONCLUSION
Take home messages

- **Increasingly needed and implemented in new settings**
- **Clinical microbiology laboratory expertise needed**
  - To oversight quality assurance, competency, proficiency testing
- **Integration of POC results in LIS, electronic medical file**
- **Rapidly evolving**
  - Automation, simplification, and miniaturization
  - To associate with the detection of biomarkers
- **Impact on patient outcomes, healthcare delivery models, public health, healthcare costs**
  - Still not clear, to evaluate
- **Need for guidelines**
  - To place orders, to perform, to interprete correctly, to implement
- **Need for new reimbursement rules**
  - Moving from lowest cost per test to total cost of care; focus on medical outcome

Recommendations of AAM, 2016

Implementation

- Redesign clinic workflows to incorporate near-patient and point-of-care (POC) testing.
- Promote proper interpretation of tests to avoid adverse outcomes.
- Provide resources, such as training videos, to support appropriate self-collection of patient specimens.
- Ensure that public health surveillance of infectious diseases is maintained with POC testing.
- Link near-patient and POC test results to the patient's electronic medical record (EMR).

Oversight

- Maintain clinical microbiology laboratory expertise and oversight of infectious disease tests.
- Utilize competent personnel to oversee ordering, testing, and interpretation.
- Educate providers and patients on different types of tests.

Evaluation

- Conduct clinical outcomes and cost-effectiveness studies for near-patient and POC tests.
- Evaluate near-patient and POC tests periodically and undertake regulatory action or reclassification for tests that do not meet performance standards.

References

- **Changing Diagnostic Paradigms for Microbiology**, Report on an American Academy of Microbiology Colloquium held in Washington, DC, from 17 to 18 October 2016. Virginia Dolen, *Rapporteur*
- Messacar K, Parker SK, Todd JK, Dominguez SR. 2017. **Implementation of rapid molecular infectious disease diagnostics: the role of diagnostic and antimicrobial stewardship.** J Clin Microbiol 55:715–723. https://doi.org/10.1128/JCM.02264-16.
- Drancourt M, Michel-Lepage A, Boyer S, Raoult D. 2016. **The point-of-care laboratory in clinical microbiology.** Clin Microbiol Rev 29:429 – 447. doi:10.1128/CMR.00090-15.

… one does not have to wait for the ultimate technical solutions to begin saving lives.

Urdea et al, Requirements for high impact diagnostics in the developing world. Nature, 2006

Time is of the essence in an emergency setting, and can be the difference between life and death.

Thank you !