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Clinical Impact of New Lab Technologies

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Better tests better care:
Syndrome-based diagnostics

Prof. Pierrette Melin

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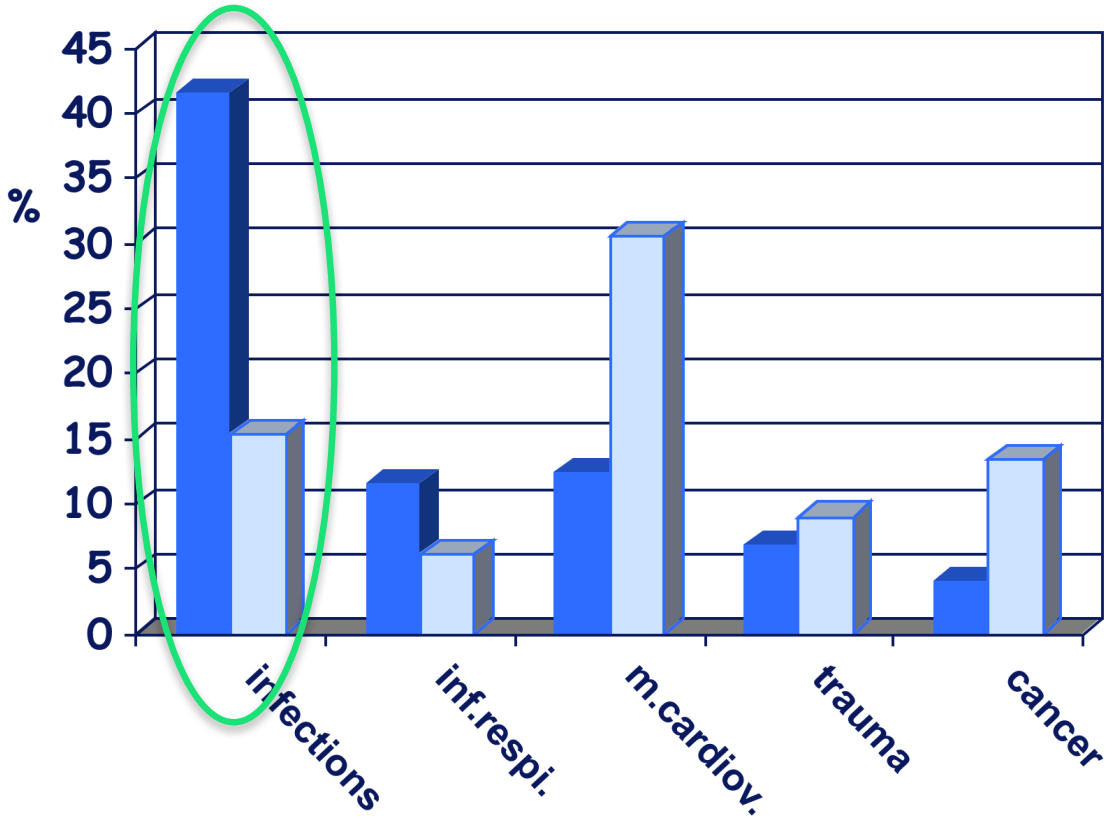
Infectious diseases in the XXIst century: Burden, threats and challenges

BACKGROUND

Causes of mortality *(WHO 2008 & 2012)*



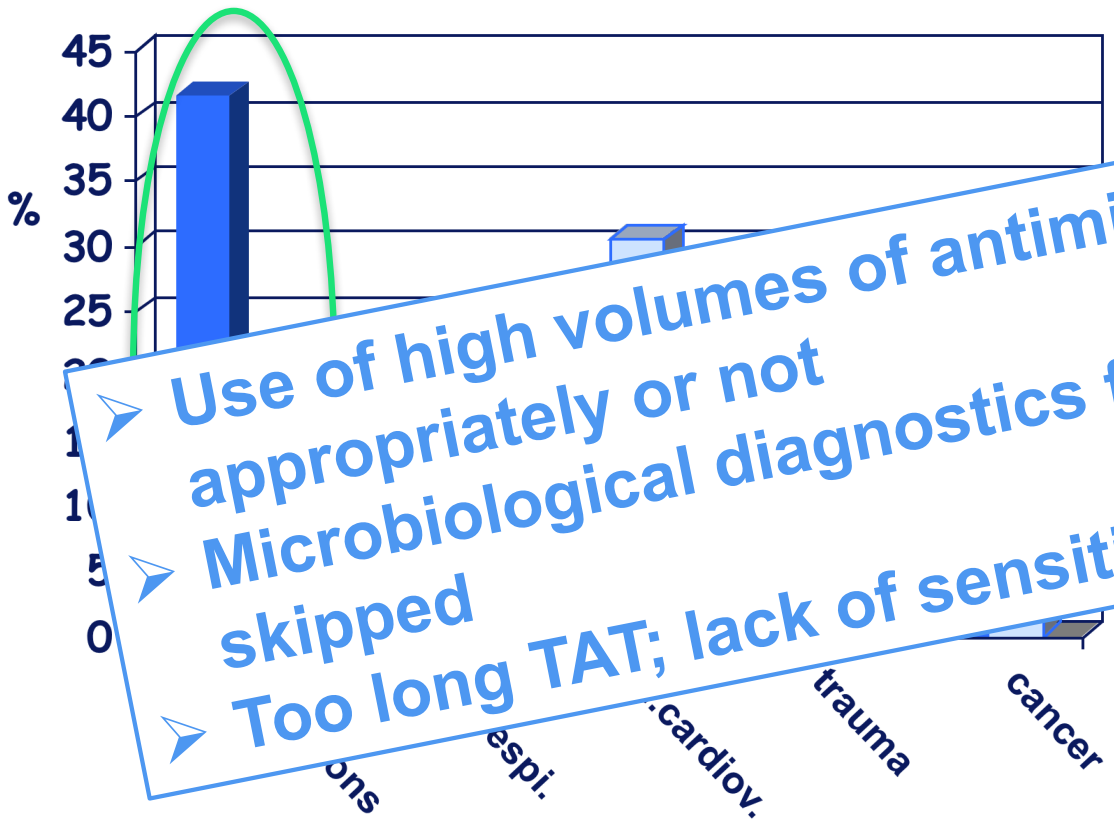
Global death rate related to infections
= 20-25%

INFECTIONS
= second cause

Low income countries *(Africa, Asia, …)* **death rate related to infections**
= 40%

INFECTIONS
= first cause

Causes of mortality *(WHO 2008 & 2012)*



- Use of high volumes of antimicrobial agents appropriately or not
- Microbiological diagnostics frequently skipped
- Too long TAT; lack of sensitivity

elated to

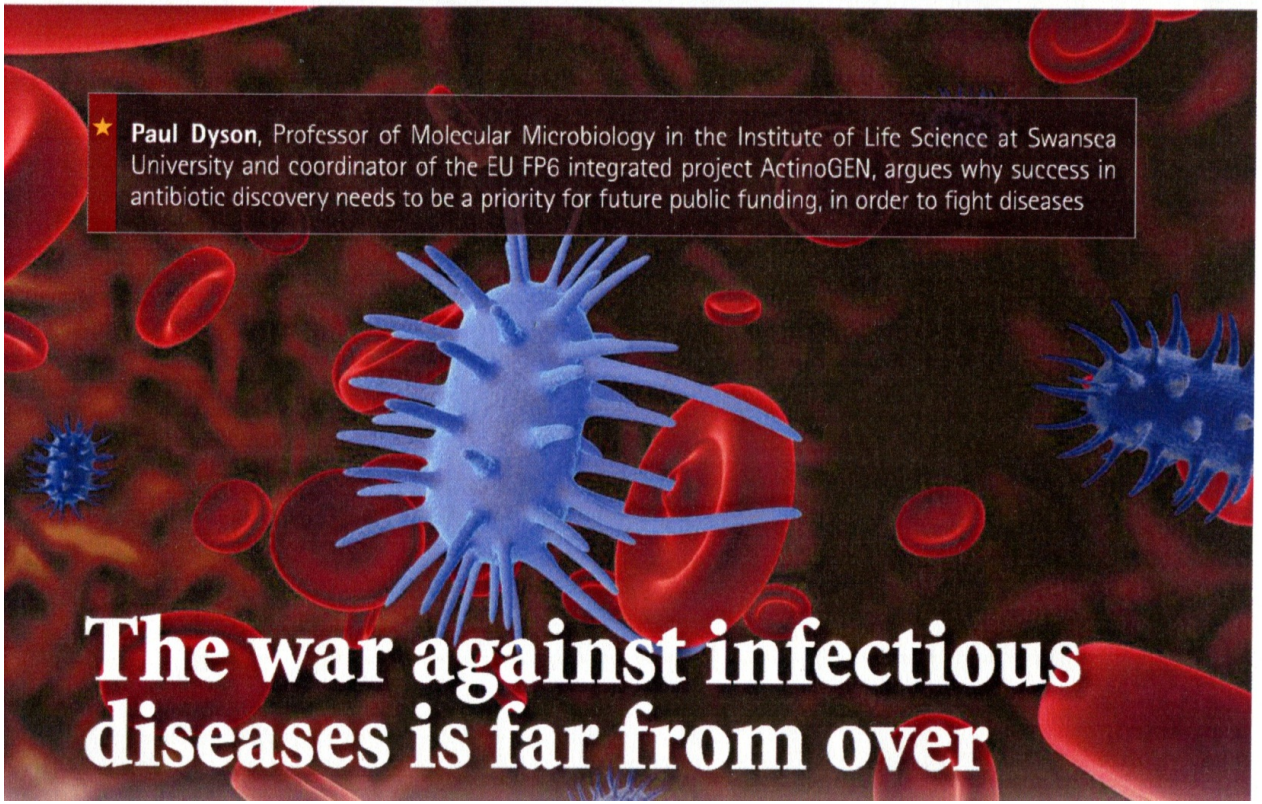
ECTIONS
= second cause

Low income countries
(Africa, Asia, …) death rate
related to infections
= 40%

INFECTIONS
= first cause

Worldwide major threat:
Bacteria are doing resistance
Global increase of antimicrobial resistance
Emerging superbug

→ ***and our small inventory of antibiotics continues to dwindle due to increasing levels of resistance***



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, implementing

- **Treatment according to rational use of antibiotics when needed**
- **Preventive measures and control of infections**

Benefits are also for

The community, hospital and control measures

Missions of clinical microbiology laboratory

TO IMPROVE THE MANAGMENT OF INFECTIOUS DISEASES

Diagnostics & rational use of antibiotics

To provide useful, accurate and relevant results

CONTRIBUTION TO DIAGNOSTIC

Presence /absence of pathogens
Identification +/- quantification

Bacteria, fungi, virus, parasites

CONTRIBUTION TO CHOICE OF ANTIBIOTHERAPY

Probabilistic, targeted

Antimicrobial susceptibility testing, identification of resistance mechanisms and resistance genes

SUPPORT TO INFECTION CONTROL

POSITIVE IMPACT ON

- **Therapeutic decision?**
- **Optimized management of patients?**
- **Morbidity, mortality?**
- **Hospitalization? Length of stay?**

- **Control of nosocomial infections?**
- **Antibiotic use?**
- **Control of antimicrobial R ?**
- **Management of outbreak**

OK, if reduction of Turn-Around-Time for result and its notification to clinician

XXIst century
Medical evolutionary background

Factors impacting on development and daily practice of microbiology

- **Medical environment**
  - Increasing emphasis on evidence-based medicine and adherence to guidelines
- **Economic environment**
  - Cost-effective use of available resources
  - Reimbursement system, regulation
- **Technological background**
  - Exponential progress: molecular biology and robots
  - New platforms from “sample-in / result-out”
  - Continuation of advance to accelerate in the near future
- **Quality assurance, traceability**
- **Global increase of antimicrobial resistance**

Reduction of time for microbial detection and identification
Holistic approach

“NEED FOR SPEED”
“SYNDROME-BASED APPROACH”
Desirable improvements

Need for speed *(& near the patient)*

24h/7d

Delayed results are un

€€€
Cost-effective

- Sample-in result-out integrated device
- Full automation
- With internal QC
- Easy to perform, to interprete
- Reduced training

Turnaround tin
collection of specim

Optimized management of patient and Infectious diseases

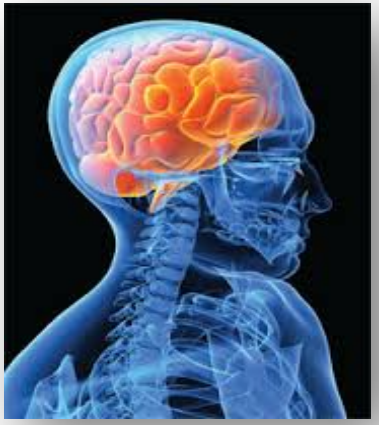
Identification
AST

pecimen Analysis: Relevant pathogens

- High Sensitivity
- High Specificity

Microbiological diagnostics of syndromic diseases

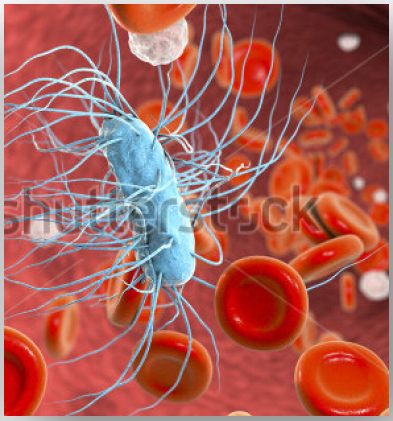
- **Syndromic diseases**
  - **Characterized by the abnormal presence, simultaneously, of a group of signs and symptoms**



CNS infections

Respiratory tract infections

Gastro-enteritis



Bloodstream infections

Microbiological diagnostics of syndromic diseases

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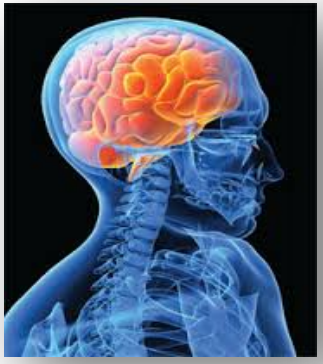
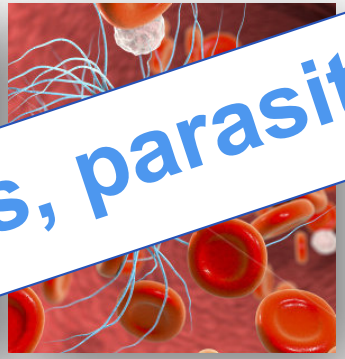


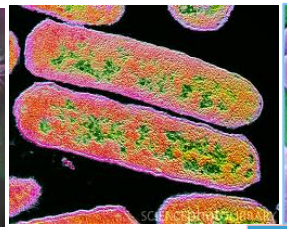


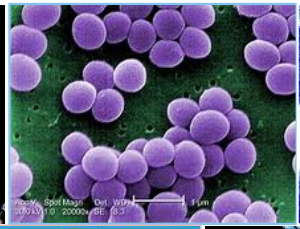
CNS infections

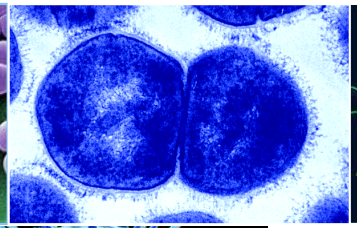
Gastro-enteritis

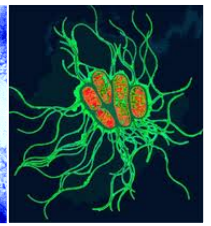
Bloodstream infections

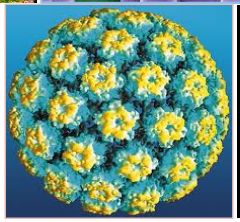
Bacteria, fungi, viruses, parasites

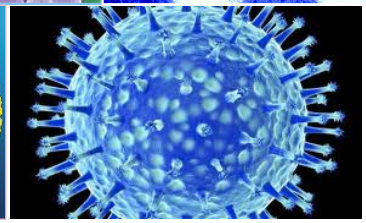


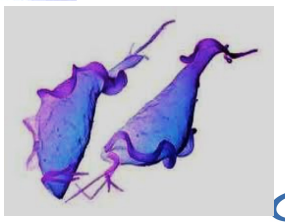












Microbiological diagnostic approaches Transition

- 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

- 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

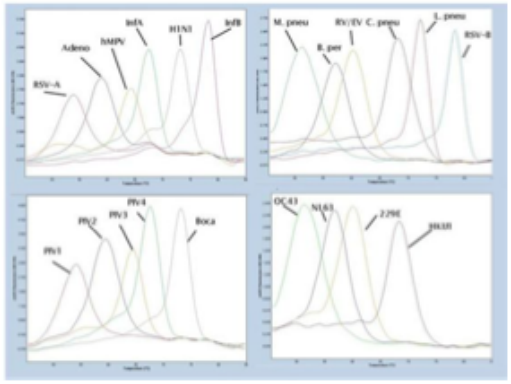
- To syndrome-based approach
  - ***« Which pathogen is causing this syndrome? »***
  - **Broad panel diagnostic method** (Including atypical agents, viruses, fungi, parasites)
  - **All inclusive testing system** ***« Sample-in / result-out »***
  - **TAT : 1-2 hour(s)**

Some commercially Multiplex tests

Cepheid GeneXpert

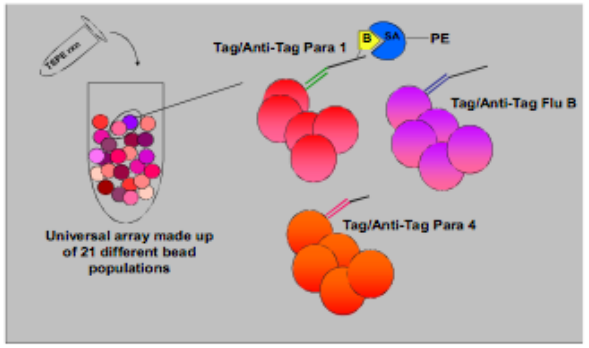
Single use cartridge based
Up to 6 targets
TAT 1.5 to 2/5 hr

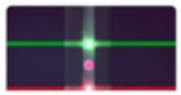
RespiFinder Mx, Pathofinder

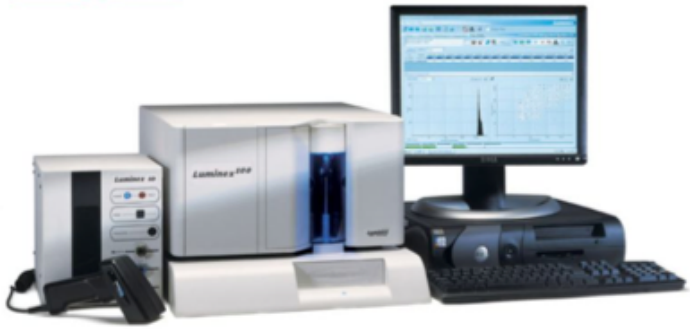


Mx amplification and detection by melting curve analysis
Up to 25 targets
TAT 6 hr

Luminex xTAG Universal Bead Array







Liquid microarray based
Up to 20 targets
RVP 10-12 hr to RVP Fast 4-5 hr

From Pr. Greet leven

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

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- Specific probe… …*markers, virulence markers)*
- From nat… …mples
- No… …ample preparation
- …lar solutions
- …gh sensitive detection methods

Huge challenges and synergies:
Biotechnologies, microtechnologies and clinical practice

Results availability

in less than 2 hours for IN/OUT patients

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

Choice of platforms and assays

BioFire FilmArray System, bioMérieux

- < 2 min of hands-on time
- Sample to result in +/- 60 minutes
- Bi-directional LIS interface
- Scalable system
- Random and continuous access

- Meningitis/Encephalitis Panel
  - 6 bacterial, 8 viral and 2 yeast targets
- Respiratory Pathogen Panel
  - 17 viral targets
  - 3 bacterial (atypical) targets
- Blood Culture Id Panel
  - 8 Gram pos, 11 Gram neg, 5 yeasts, and 3 R markers
- Gastrointestinal Panel
  - 14 Bacterial, 5 viral & 4 parasitic targets

The FilmArray BCID Panel

Simultaneous detection of 27 targets:

Gram + Bacteria

- *Staphylococcus*
- *Staphylococcus aureus*
- *Streptococcus*
- *Streptococcus agalactiae*
- *Streptococcus pyogenes*
- *Streptococcus pneumoniae*
- *Enterococcus*
- *Listeria monocytogenes*

Gram - Bacteria

- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Serratia*
- *Proteus*
- *Acinetobacter baumannii*
- *Haemophilus influenzae*
- *Neisseria meningitidis*
- *Pseudomonas aeruginosa*
- *Enterobacteriaceae*
- *Escherichia coli*
- *Enterobacter cloacae complex*

Fungi

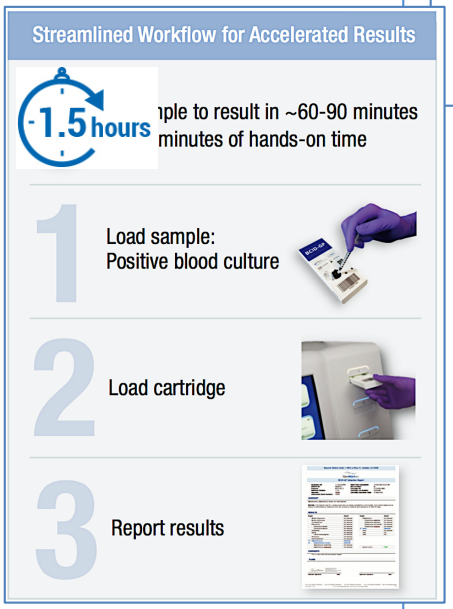
- *Candida albicans*
- *Candida glabrata*
- *Candida krusei*
- *Candida parapsilosis*
- *Candida tropicalis*

Antibiotic Resistance

- *mecA*
- *vanA / vanB*
- *KPC*

Choice of platforms and assays

ePlex System*, GenMark

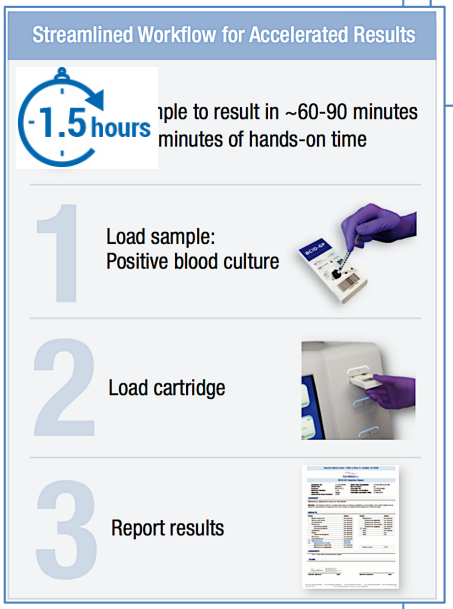


- < 2 min of hands-on time
- Sample to result in 60-90 minutes
- Random and continuous access
- Bi-directional LIS interface
- Scalable system

- **Respiratory Pathogen Panel**
  - 18 viral targets
  - 3 bacterial targets

Choice of platforms and assays

ePlex System*, GenMark



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- **Respiratory Pathogen Panel**
  - 18 viral targets
  - 3 bacterial targets

Coming soon

- ***Blood Culture Id Gram Pos Panel***
  - *20 Specific organisms and 4 R markers*
- ***Blood Culture Id Gram Neg Panel***
  - *24 Specific organisms and 6 R markers*
- ***Blood Culture Id Fungal Pathogen Panel (16 targets)***

Pipeline

- ***Central Nervous System Panel***
  - *Bacterial, viral & fungal targets*
- ***Gastrointestinal pathogen Panel***
  - *Bacterial, viral and parasitic targets*

All-inclusive systems for multiplex syndromic approach

Impact on diagnostics ?

Clinical significance of detected agents ?

Impact on patient management, care ?

Cost-benefits ?

Impact on outbreak management ?

When to use which techniques?

Sequential approach vs Mx detection? For selected patients?

In/Out patients? Severely ill patients? Paediatrics patients ?
Alone or combined with conventional methods?

Will results be able to change empirical behaviour?

All-inclusive systems for multiplex syndromic approach

- **Meningitis/encephalitis BioFire FilmArray**
  - **AL Leber et al - JCM 54, 2016:2251-2261,** Multicenter evaluation- 1,560 CSF: high S and Sp → improved patient outcomes and antimicrobial stewardship anticipated
  - **SH Wootton et al – Ann Clin microbiol Antimicrob 2016 15:26,** 48 community acquired meningitis. Enhancing pathogen Id in patients with meningitis and a negative Gram stain using the BioFire …. Id of pathogens in 22.9% of negative gram stain bacteria, cryptococcus and virus but missed rare pathogens not included in the panel as West Nile virus and histoplasma.
  - **HS Arora et al – The Pediatric Inf dis J 2017 ahead of print,** 62 CSF from newborns (0-3m) with suspected meningitis and compared to culture for GBS and E.coli: 10 GBS and 2 E.coli with BioFire : 5 only positive in culture. Positive CSF only with BioFire originated from newborns who received previosly antibiotic treatment → useful tool for diagnosis of meningitis in pretreated infants

All-inclusive systems for multiplex syndromic approach

- ## Respiratory pathogens BioFire FilmArray
  - **X Qin et al – Ann Clin microbiol Antimicrob 2016 15:28,** Comparison of molecular detection methods for pertussis in children during a state-wide outbreak. Outbreak concurrent to respiratory viral season Home made and BioFire methods were comparable for detection of *B.pertussis*.
  - **DA Green et al – JCM 54, 2016: 2950-2955,** Clinical utility on on demand Mx respiratory pathogen testing among adult outpatients (408) → tested for 20 targets and evaluation of antimicrobial prescriptions: oseltamivir for influenza virus and unecessary ATB use: In adults tested positive for influenza : reduced ATB. For adults tested negative for influenza, positive or negative for other virus: no difference in ATB use→ questionnable benefit from testing other targets than influenza ??
  - **RHT Nijhuis et al – JCM accepted 04.2017,** Comparison of the ePlex Resp Pathogen panel with Laboratory developed real time PCR ….343 specimens, 29 EQA sp and 2 MERS isolates. 97.4 % agreement for 464 pathogens from clinical sp. Excellent performance in a short time-frame with minimal hands-on time

All-inclusive systems for multiplex syndromic approach

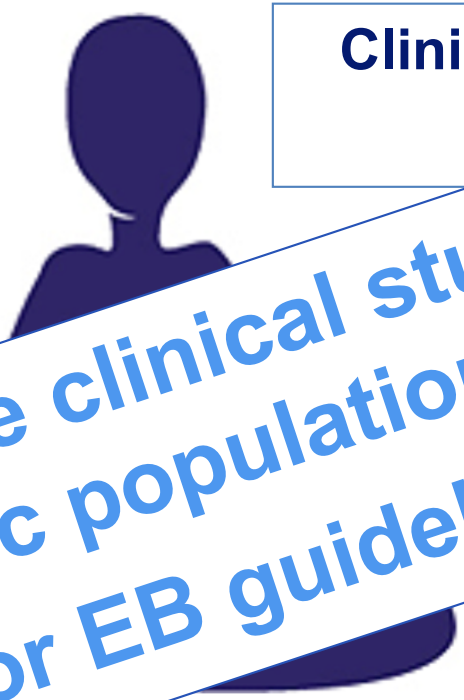
Impact on diagnostics ?

Clinical significance of detected ... nts ?

Impact on patient management, care ?

... its ?

Impact on outh... manag...



Need for more clinical studies in specific populations

Need for EB guidelines

... which techniques?

Sequ... ...ach vs Mx detection? For selected patients?

In/Ou... patients? Severely ill patients? Paediatrics patients ?

Alone or combined with conventional methods?

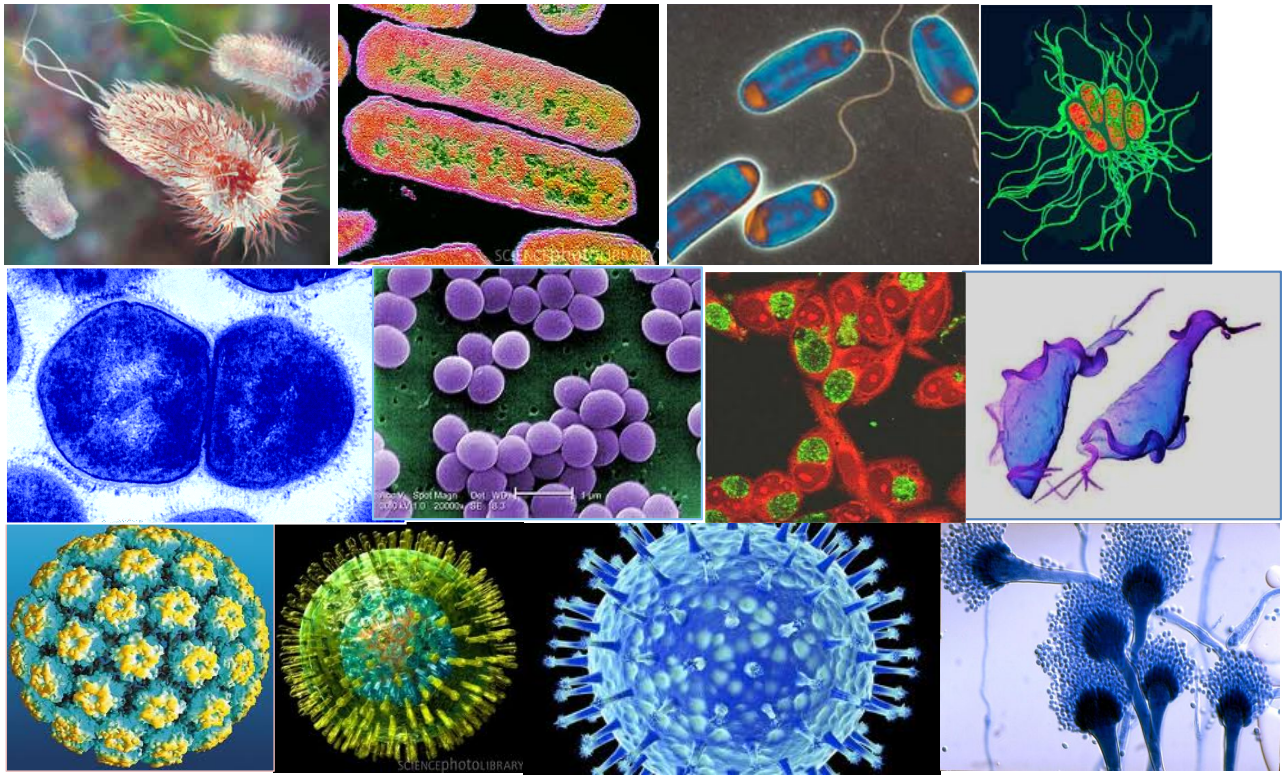
Will results be able to change empirical behaviour?

TAKE-HOME MESSAGES

Mutations & a new culture are necessary to enjoy over the future of microbiology

Multiplex syndromic approach

- Reduction of TAT
- Increased rate of detection for a wide panel of aetiological agents
  - Improved management of patients with severe infections
  - Initiation more rapidly the appropriate rational use of antibiotics
  - Avoidance of unnecessary antibiotherapy
    - Cost avoidance
  - Implementation of control measures for contagious agents
- Complementary to conventional methods



Microbiological diagnostics of syndromic diseases

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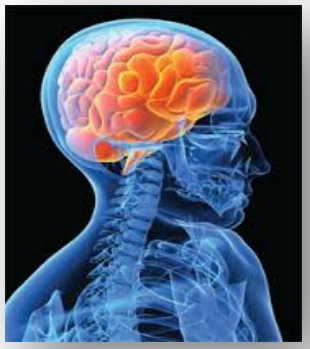
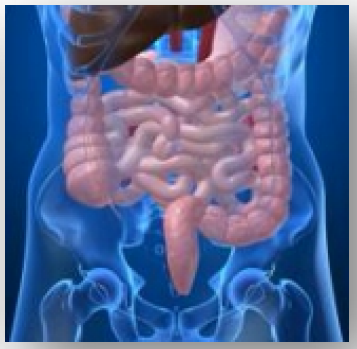
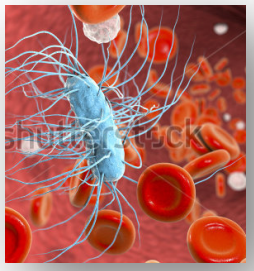


CNS infections



Gastro-enteritis

Respiratory tract infections



Bloodstream infections

Sexually transmitted infections

Multiplex all inclusive tests and system

GenMark Diagnostics

ePlex System

ePlex is designed to revolutionize syndromic infectious disease testing, offering comprehensive panels on a scalable sample-to-answer system

Respiratory panel of 14 viral targets

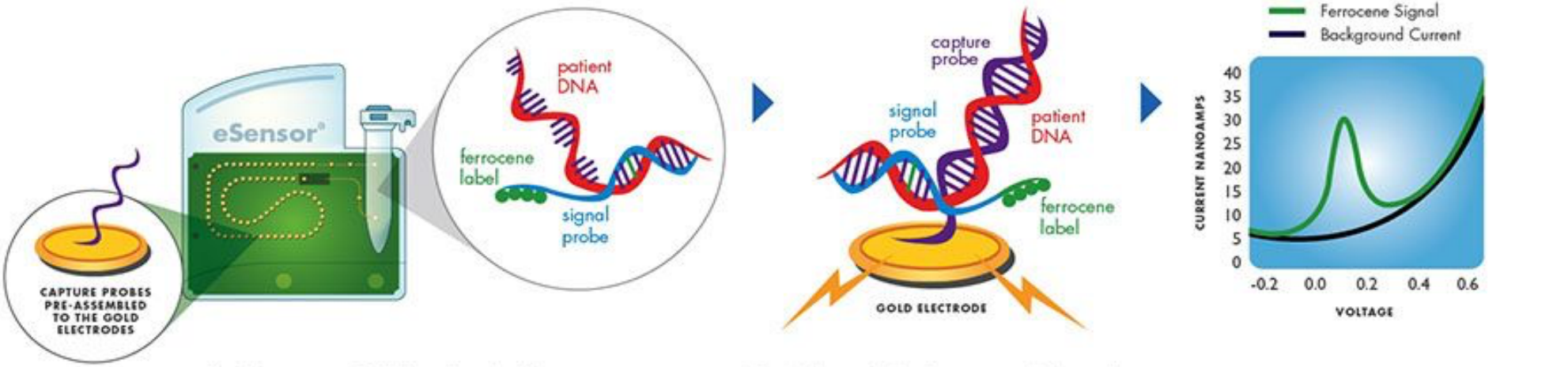
- **Multiplex PCR**
- **Electrochemical detection**
- **3 1⁄2 hours**

Curetis Univero system

Pneumonia panel: 16 bacteria + 1 Fungus and 22 antibiotic resistance markers

- **Endpoint PCR**
- **Array format**
- **4 hours**

ePlex innovative detection technology



1 The target DNA is mixed with the signal probe solution. If the applicable target DNA is present, hybridization to the signal probes occurs immediately.

2 The solution is pumped through the cartridge's microfluidic chamber and the target DNA/signal probe complex completes the reaction with the pre-assembled capture probe.

3 Voltage is swept across each electrode and target DNA is analyzed by electrochemical detection.

CONTENT

- Background
- Desirable improvements
  - Holostic approach
    - Syndrome-based diagnostic approach
- Transition from conventional methods to new technologies
- Discussion
- Take home messages