Advances in Medical Microbiology - Are the Patients Better Off?

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Objectives

- To describe major changes that have occurred in microbiological diagnosis of infectious diseases.
- To identify how these changes have created a new “culture” in the medical microbiology laboratory
- To understand if and how these changes have affected outcomes for infected patients.
- To describe a possible risk management process to identify positive advances for diagnosis of infectious diseases.

Conflict of Interest Declaration

- Chair of Canadian Committee for Antimicrobial Susceptibility Testing (CANCAST)
- Clinical Microbiology Consultant for Thermo Fisher Scientific Microbiology Products – Risk Assessment Analysis.
- Member of ISO TC212 Canadian Mirror Committee (Z252), and Deputy Convener of ISO TC212, Working Group 4 (Microbiology and Molecular Diagnostics).

Important areas of development in medicine and medical microbiology

- Immunology – monoclonal antibodies.
  - For treatment of diseases
  - As diagnostic agents to improve accuracy
- Nucleic acid technology.
  - More rapid and accurate identification of potential pathogens in clinical samples
  - Identification of antimicrobial resistance determinants.
- Phenotypic technology.
  - Rapid identification and speciation of pathogens
  - Early identification of active antimicrobial resistance.
- Systems to improve turn around of samples for infected patients

Measures of assess the value of “advances” in the field.

- Primary
  - Reduced morbidity and mortality
  - Improvement in quality of life measures.
- Secondary
  - Shortened stays in hospitals
  - Reduced burden on health care system
  - Fewer infections.
  - Antimicrobial stewardship, less reliance on antimicrobials,, reduced antimicrobial resistance
  - The patient is “better off”!

Two conflicting measures

- COST- EFFICIENCY
  - Reducing costs by:
    - not doing something
    - reducing testing
    - Technology to reduce reliance on people.

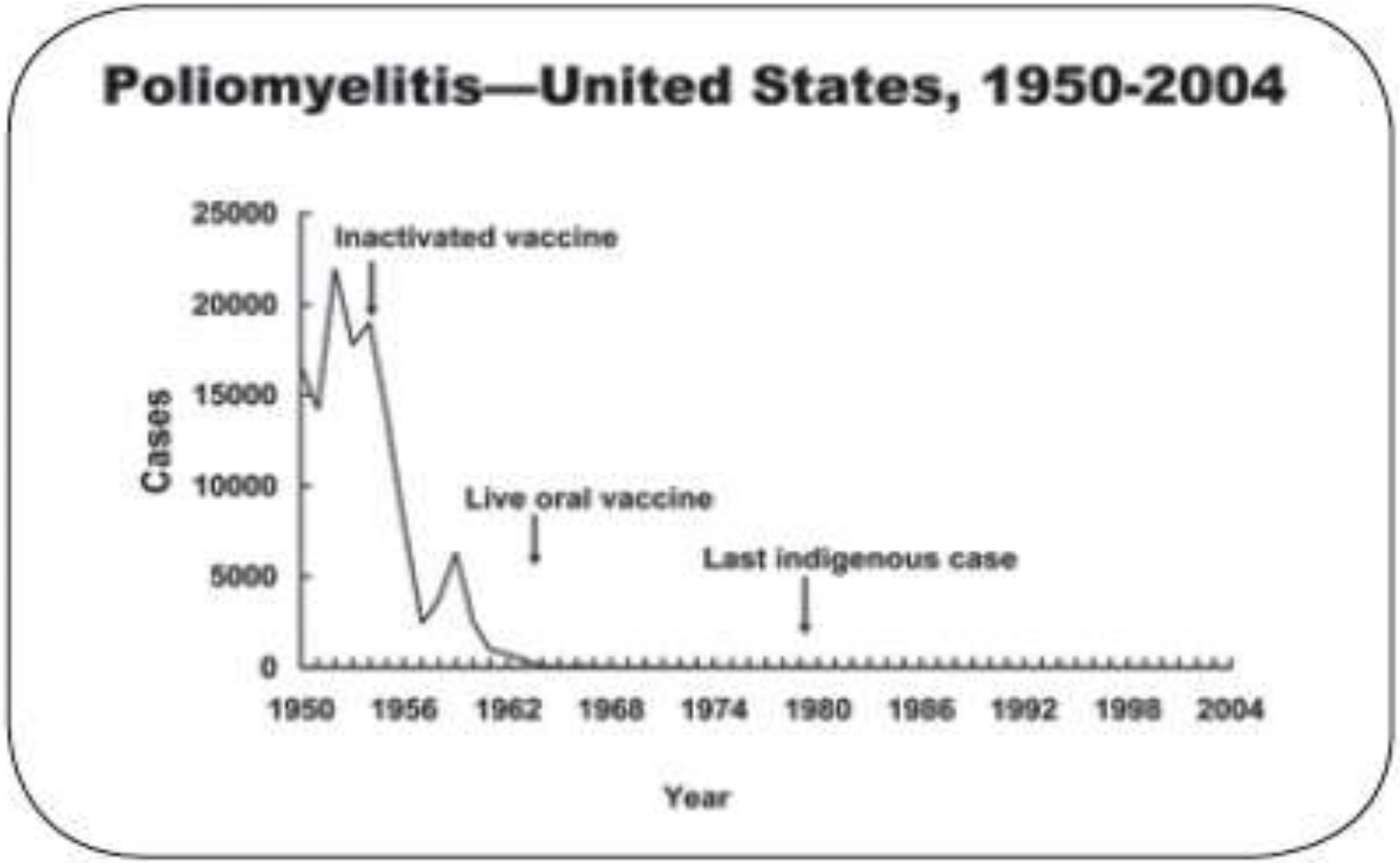
- COST- EFFECTIVENESS
  - Getting the most from the dollars spent
    - Improving the health of patients.
    - Spending some money to save money elsewhere.
    - Best utilization of resources.
    - Determining if technology can meets those goals

The importance of moving technology forward in medical microbiology

- The most important advances have been in development of tools and reagents to improve the quality of life.
  - Vaccines.
    - Polio, Smallpox, childhood vaccines, prevention of meningitis, pertussis, influenza, etc.
    - New vaccines – hepatitis, other ?
    - Development of vaccines for specific populations. Beta-haemolytic streptococcal vaccines (aboriginals in Australia), pneumococcal vaccines (elderly, socio-economic groups, others).

IN MOST OF THESE INFECTIOUS DISEASES - EPIDEMIOLOGY CLEARLY SHOWS THE VALUE TO HEALTH!

This really does make a difference to personal and public health!



Our laboratories are now full of new and advanced technologies:

What is the evidence for their effectiveness in making the health of patients better and at what cost!
Because we can get a result (sometimes, any result) to the clinician more quickly;

How do we know if patient health is impacted?
What is the evidence?
How can we measure what is being attempted?

Some examples from my own experience and from the literature.

Immunology

- Drug testing using monoclonal antibodies to obtain rapid results that impact the individual and system.
  - Used in a line immunoassay
  - Cross reactions with multiple drugs (the monoclonal antibody is not so monoclonal)
  - The carrier for these tests are commonly gold ions.
  - Quality depends on the purity of the gold – observation that purity may be affected by the price of gold. When gold is up the purity is better (return on investment rather than on the result for the end user).
  - Similar observations have been made in microbiology (rapid *Strapt, C. difficile*, etc.
- Monoclonal antibodies used in treatment of various diseases (or as reagents).
  - Many of the “Mabs”. May be helpful but the list of other issues – primarily infectious can be endless. High risk for TB, HIV, hepatitis, etc, etc, etc.

The promise and perils of nucleic acid technology.

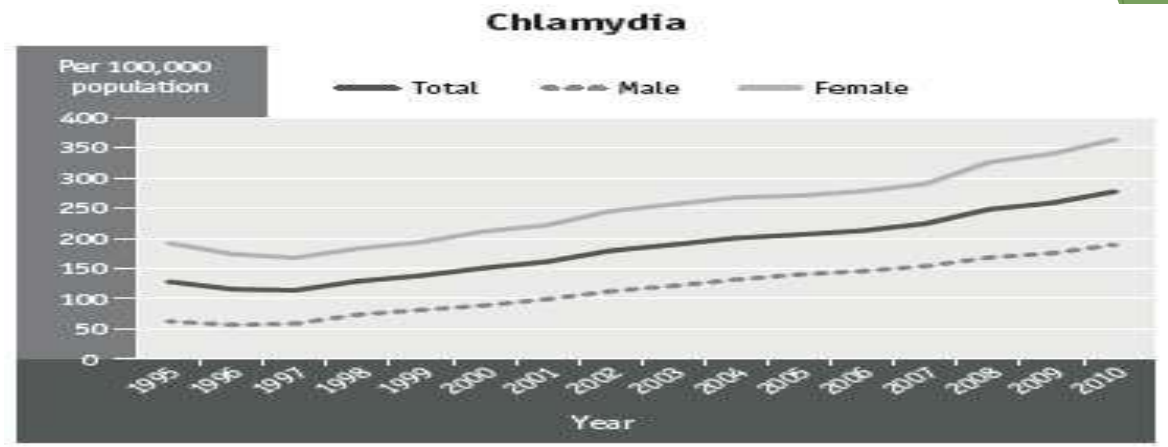
- NAAT for CT/GC
- Multiplex – PCR - RVP, RPP
- Hepatitis and HIV, and viral load testing
- Identification of resistance genes

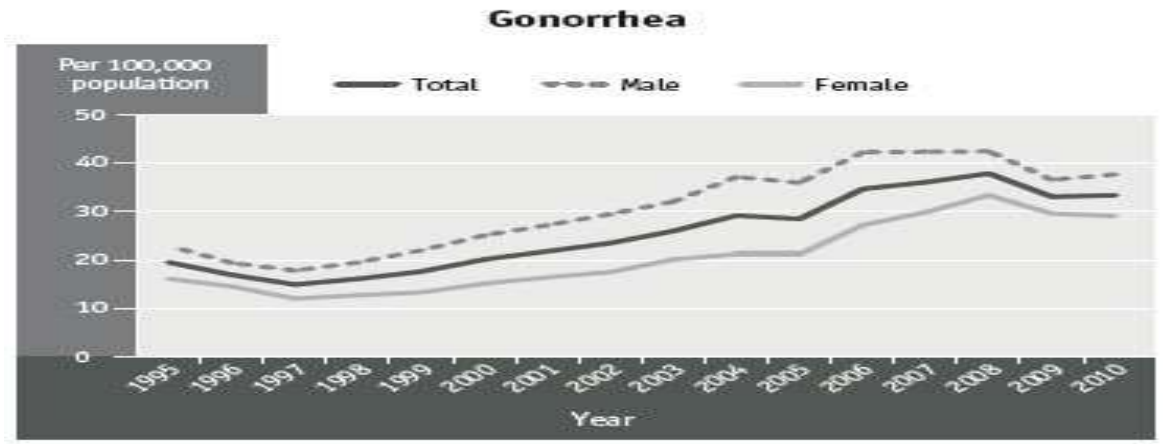
GC/CT laboratory diagnosis.

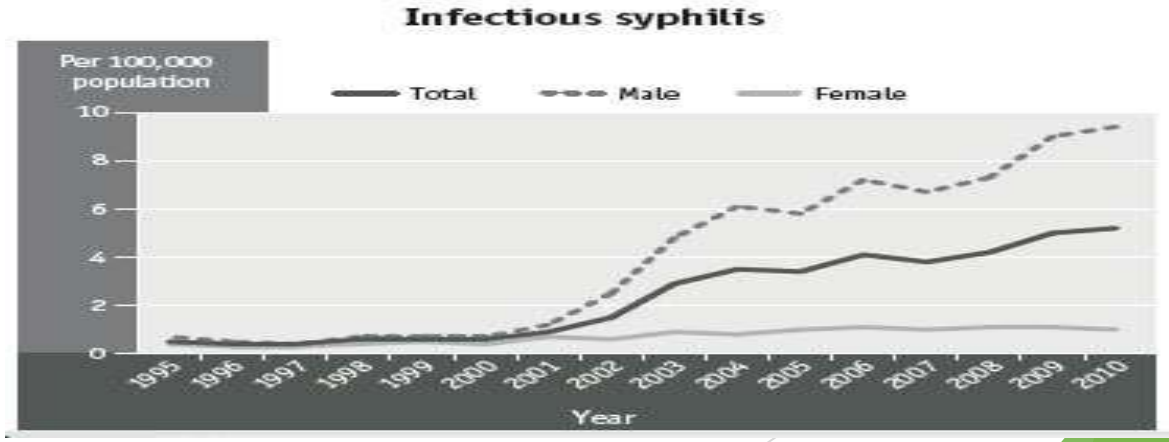
- Previous.
  - Culture or cell based investigations.
  - Slow, but accurate.
  - Identification of changing antimicrobial susceptibility

- Now.
  - Nucleic acid based. (Introduced in Canada in the late 1990's)
  - Multiple specimens. (Swabs, urine)
  - More rapid.
  - Does not detect changing antimicrobial susceptibility
  - Is there a positive effect on epidemiology and patient care?

HEALTH CANADA REPORT 2013: Increasing rates of STIs in Canada







Luminex Respiratory Pathogen Panel – FDA approval.

- *ABLE 1. Pathogens*

Bacterial Targets

- *Chlamydophila pneumoniae*
- *Mycoplasma pneumoniae*

Viral Targets

- *Influenza A*
- *Influenza A H1*
- *Influenza A H3*
- *Influenza B*
- *Respiratory Syncytial Virus A*
- *Respiratory Syncytial Virus B*
- *Human Bocavirus*
- *Coronavirus 229E*
- *Coronavirus OC43*
- *Coronavirus NL6*
- *Coronavirus HKU1*
- *Human Metapneumovirus*
- *Rhinovirus/Enterovirus*
- *Adenovirus*
- *Parainfluenza 1*
- *Parainfluenza 2*
- *Parainfluenza 3*
- *Parainfluenza 4*

NxTAG Respiratory Pathogen Panel Targets		
Viral Targets		
Influenza A	Rhinovirus/Enterovirus	Adenovirus
Influenza A H1	Parainfluenza virus 1	Coronavirus HKU1
Influenza A H3	Parainfluenza virus 2	Coronavirus NL63
Influenza B	Parainfluenza virus 3	Coronavirus 229E
Respiratory Syncytial Virus A	Parainfluenza virus 4	Coronavirus OC43
Respiratory Syncytial Virus B	Human Metapneumovirus	Human Bocavirus
Bacterial Targets		
Chlamydophila pneumoniae	*Mycoplasma pneumoniae*	

Health Canada VS. FDA Approval for Luminex RPP

- Viral targets – same as U.S.A.
- Bacterial targets. *Chlamydophila pneumoniae, Mycoplasma pneumoniae* PLUS *Legionella pneumophila* (type not-specified)
- Health Canada approved:
  - nasopharyngeal swabs, bronchoalveolar lavages (BALs), nasal and tracheal aspirates, nasal washes, sputum, and throat swabs – not data available on sensitivity and specificity according to sample type.
  - No information presented in IFU on sensitivity and specificity for any samples or on reactivity especially for *Legionella*.
- FDA:
  - Legionella not included.
  - Nasopharyngeal swabs only for all targets . Extensive data presented only for that specimen type.

The impact of rapid respiratory diagnostic tests on patient outcomes and health system utilization

F. Ko and S. Drews. Expert Review of Molecular Diagnostics 2017
https://doi.org/10.1080/14735179.2017.1372195

- Review of 31 studies on rapid testing for Influenza and RSV
  - Either rapid antigen or rapid molecular testing modalities. Most for influenza.
  - Results revealed a paucity of information of patient outcomes.
- Major Positive observations.
  - Early diagnosis
  - Better cohorting of patients with influenza A or B.
  - Improved utilization of antiviral agents.40% of the studies
- Negative observations.
  - Limited effect on patient and clinical indicators.
  - No apparent clinical change management.
  - Difficulties in getting results to clinicians –
  - Almost 40% of the studies – no control or pre-study group results.

Rapid Phenotypic Bacterial identification and susceptibility

- Identification
  - Conventional Automated systems.
  - MALDI-TOF.

- Susceptibility
  - MADI-TOF Screening (MRSA, TB – INH resistance)
  - Accelerate technology.

Identification.

- Conventional (combined with susceptibility testing)

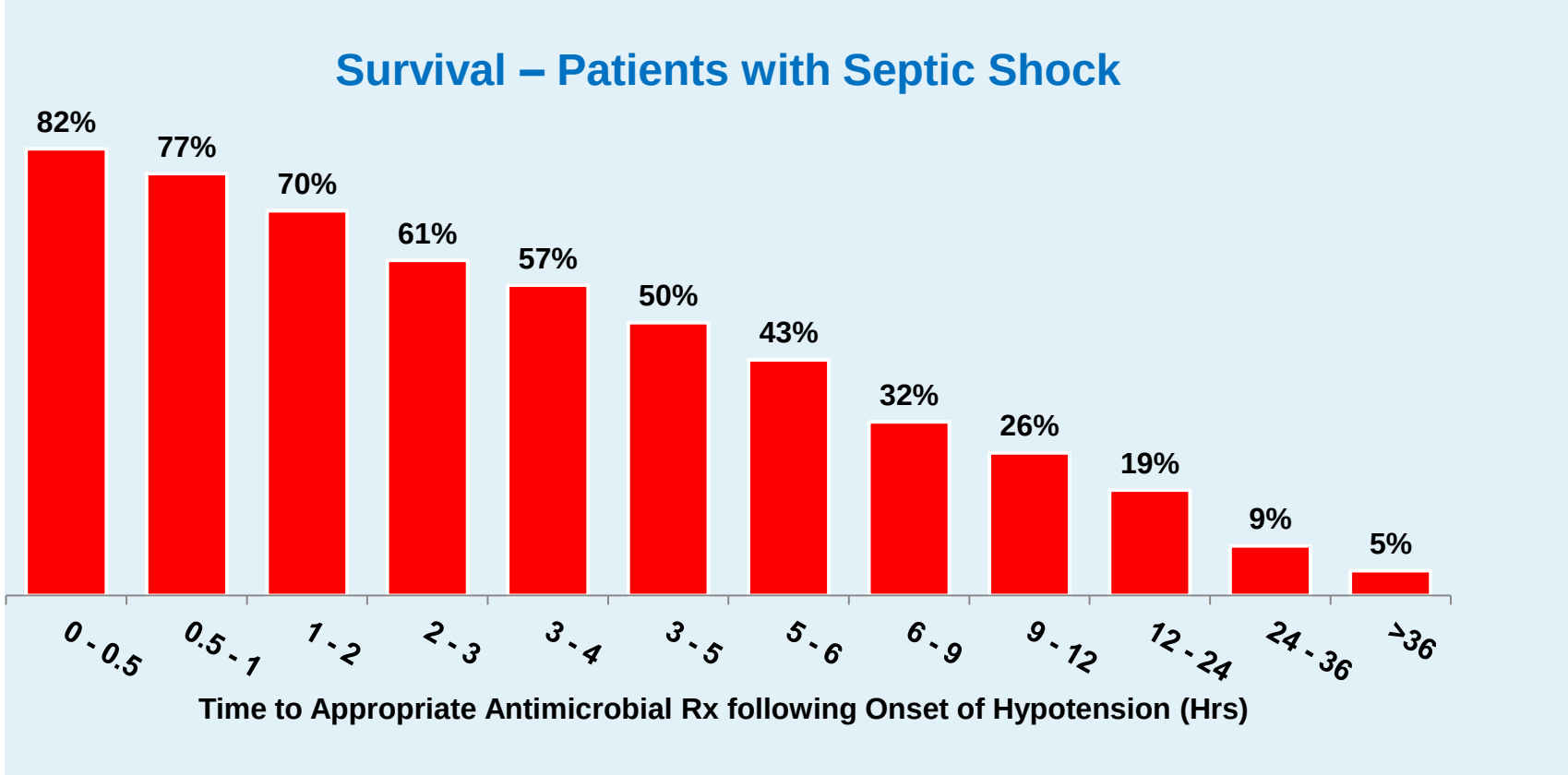
  Barenfanger J et al. 1999 - J Clin Microbiol. 37: 1415.

  - Combined Identification and Susceptibility testing on Vitek II.
  - **Changing shift duties** so that results for both ID and susceptibility read and reported the same day/evening. Using two time periods -
    - LOS – reduced by 2 days (< 0.006)
    - Mortality reduced by 1.6% (NS)
    - Variable cost difference reduced by $1750 (P <0.001)
  - N.B. **Not mentioned in article -** importance of engaging clinicians in the dialogue, evaluation of “expert” systems)

Information gaps may created by advanced technology. An example:

- *Esherichia coli* in urine– no previous isolate from patient.
- Automated susceptibility: Test/BKPT Result/ Extended result*.
  - Cefoxitin – < 4 / S Ertapenem - < 0.5 / S / R*
  - Amox-Clav – >32 / R Meropenem – 2 / I / R*
  - Cefixime – 0.5 / S / R* Other agents – as tested - S, Nitro – 64 / I.
  - Ceftriaxone - <1 / S/ R*
  - "Expert" Comment: "Carbapenemase +/- ESBL" For review
  - MAST testing – No change in zone diameters.
  - Further: Meropenem Etest confirmation MIC = 0.016 – S.
  - Imipenem – 30 mm –S. Fosfomycin – 24 mm – S.
- "Expert" systems may not represent reality. Drive antimicrobial stewardship, technology development and antimicrobial resistance.
- Creates issues for maintaining technologist expertise. Belief in the system

Early, appropriate therapy is key to survival Every hour counts!



Kumar et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006 Jun;34(6):1589-96.

Identification

- MALDI-TOF Beganovic et al. 2017. J. Clin Microbiol 55: 1437.
  - Comparison of MALDI-TOF alone with MALDI-TOF plus antimicrobial stewardship (AMS) for Optimal therapy for bacteraemias.
  - Addition of AMS to MALDI ID
    - Overall Reduction in time to optimal therapy by 32 hr ($p < 0.001$)
    - Gram- Positive reduction in time 24 hr ($p < 0.001$) and LOS 4 days ($p = 0.002$)
    - Gram-Negative reduction in time 35 hr ($p < 0001$), and LOS 7 days ($p < 0.02$)
  - **N.B.** Results support the impact of incorporating AMS into the dialogue.

ACCELERATE: The new kid on the block - Is it ready for prime time?

- Marschal M et al. 2017. J. Clin Microbiol. doi: 10.1128/JCM.00181-17
- ID Direct Approx. 90 minutes. Susceptibility- Approx 7 hrs.
- The Accelerate Pheno™ system correctly identified 88.7% (102 of 115) of all BSI episodes.
- The Accelerate Pheno™ system generated an AST result for 91.3% (95 of 104) samples in which the Accelerate Pheno™ system identified a Gram-negative pathogen. The overall category agreement between the Accelerate Pheno™ system and culture-based AST was 96.4%,
- The utilization of the Accelerate Pheno™ system reduced the time-to-result for identification by 27.49 h ($p<0.0001$) and for AST by 40.39 h ($p<0.0001$) when compared to culture-based methods Gram-negative pathogen.
- Issues: Cost, number of isolates that can be tested, Laboratory workload organization, effect on outcomes.

Automated Front –End Technology

- KEESTRA (BD) ; WASP (Copan)
  - Standardized front-end automated specimen processing.
  - Liquid-based samples improve quality of inoculum
  - Keestra uses pipetter sampling (10 uL)
  - WASP uses classical micro - loop technology
  - Gram-smear preparation.
  - {Photographic technology for examination of plates (some differences in pixelation).

Automated Front –End Technology

- Factors for consideration
  - Reduction in technologist involvement
  - Reduced errors in planting.
  - Standardized spreading of samples.
  - Costs?
  - Impact on laboratory processes. Is there increased cost-effectivenessl

Objective Risk Management Process.

- Identify and score factors in new technology that are purported to improve patient care.
  - Clinical basis for new technology (advancement of the field)
  - Accuracy of results
  - Identification of specific pathogen(s) associated with infection
  - Hands on time , time to a positive result. etc.
  - Direct costs.
- Identify and score factors for optimizing patient care if the new technology was implemented.
  - Patient outcomes – morbidity, mortality, LOS in hospital,
  - Requirements for follow up.
  - Integration of other services; clinical services, antimicrobial stewardship, public health interventions, etc.
- Assess the risks to patient care or public health management if parameters beyond the actual technology are not considered (those would include indirect costs)

Summary

- Quality doesn't only matter in what the lab tests and reports.
- For optimal patient care – need to "Get the Lab out of the Lab".
- New more rapid technologies only matter if the investigations are:
  - Accurate
  - Clinically relevant
  - Followed up in a timely manner by those directly attending the patient.
  - Understood by the clinician. It not just a "test".
- Cost –effectiveness and maintaining laboratory skills should be primary drivers for new advances in medical microbiology.

THIS LAB'S READY FOR YOUR QUESTIONS!