Clinical Microbiology : in search of a future ?

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- Limited clinical impact of clinical microbiology on infectious disease management
  - Increasing impact of evidence-based guidelines
- How to increase impact of clinical microbiology
- Brave New Lab : the lure of the integrated laboratory

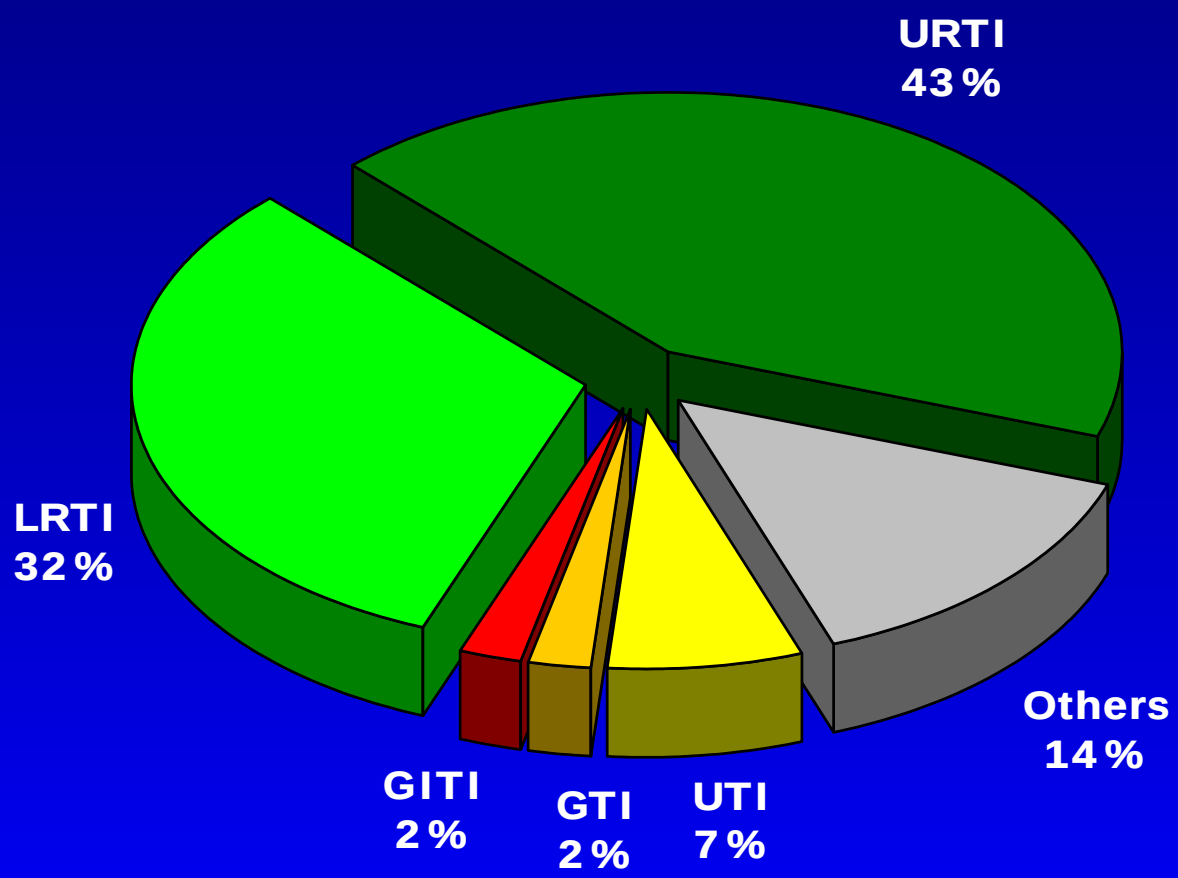
Impact of clinical microbiology on infectious disease management

- near absence of microbiological investigation in out-patient setting

- in 60% of hospitalised patients with diagnosed infection, no microbiological investigation was performed

» PSG Hospital anti-infective audit database 1995

Antibiotic prescriptions in Belgium outpatients (Q4/99)



Impact of clinical microbiology on infectious disease management in out-patients: CAP

- If CAP is diagnosed, antibiotics are started immediately and empirically without waiting for results of eventual microbiological investigations. Delaying therapy results in increased incidence of complications and higher mortality.
- When a pathogen is identified, a targeted, narrow-spectrum therapy is instituted

» IDAB, Diagnosis and therapy of CAP in adults, 2000

Impact of clinical microbiology on infectious disease management

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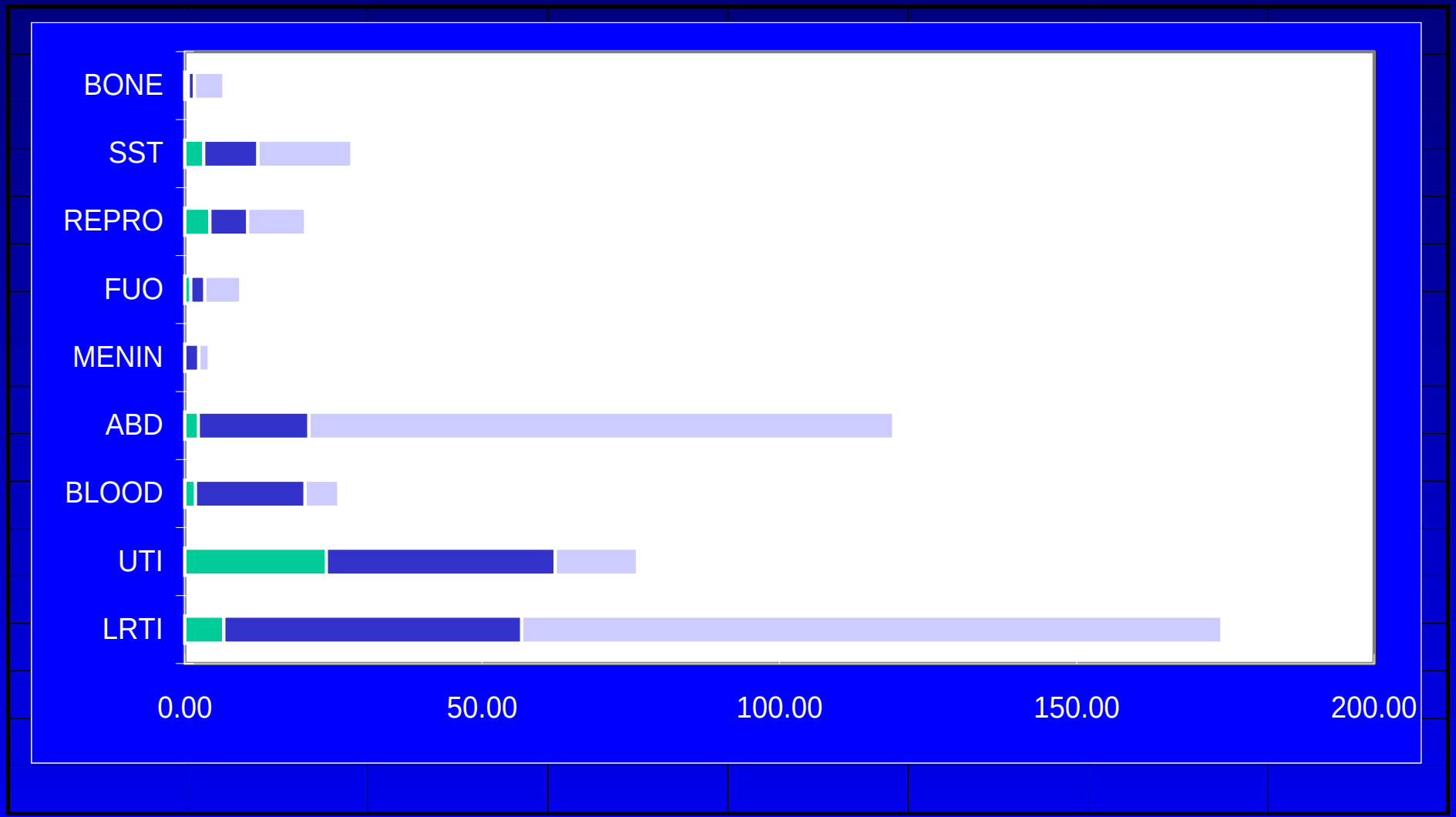
Availability of antibiogram in hospitalised patients with infections
Belgium 1995



PSG Hosp. anti-infect. aud. database

Impact of clinical microbiology on infectious disease management in the hospital

- 50 % data ever used by clinicians.
  - Matsen ‘81: Rapid methods & automation in microbiology. ASM
- 52 % clinicians aware lab results 72 h after reporting
  - Matsen ‘85: Diagn. Microbiol. Infect. Dis. 3, 73S
- 50 % recommended AB therapy changes implemented
  - Trenholme ‘89: JCM 27, 1342
- utilisation lab results 60 % of the time
  - Koontz ‘87: Ann. Meeting ASM, abstr. C303
- 50 % recommended AB therapy changes not followed
  - Koontz ‘94: Adv. Exp. Med. Biol. 349, 27

Impact of clinical microbiology on infectious disease management: VAP

- IDAB ‘VAP diagnosis and treatment guidelines’ 2002:
  - Anti-microbial treatment cannot be withheld in clinically suspect patients with negative direct microbiological results (including ICO in PSB or BAL)
    - Niedermann ‘94, Papazian ‘95, Marquette ‘95, Torres ‘94, Blot 2000, Fabregas ‘99

Impact of clinical microbiology on infectious disease management: VAP

- IDAB ‘VAP diagnosis and treatment guidelines’ 2002:
  - Sensitivity of (direct) microbiological examination is insufficient and is even lower in the presence of prior anti-microbial treatment, particularly when introduced recently
    - » Jorda ‘93, Ruiz 2000, Kirtland ‘97, Dotson ‘93, Souweine ‘98
  - Inadequate initial therapy or delay in starting initial empirical therapy are associated with excess morbidity and mortality
    - » Rello ‘97, Kollef ‘99, Luna ‘97

Impact of clinical microbiology on infectious disease management: VAP

- A positive direct microbiological examination in a clinically suspect patient may increase diagnostic accuracy although this has not unequivocally been proven

» Fabregas ‘99, Timsit 2001, Blot 2000

Impact of clinical microbiology on infectious disease management: VAP

- IDAB ‘VAP diagnosis and treatment guidelines’ 2002:
  - No improvement in patient outcome if initial ‘inadequate’ empirical treatment adapted after 48 hours based on culture results

    » Sanchez-Nieto ‘98, Luna ‘97
  - discontinuation of therapy on the basis of a negative culture after 48 hours in a patient that has not received antibiotics has no effect on outcome

    » Bonten ’97

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How to increase impact clinical microbiology

- faster turn-around time: same day reporting, point of care testing
- do more and do less : more reliable & clinically (therapeutically) meaningful results

Impact of rapid reporting on infectious disease management

- 300 pts - various infections: 49 % impact on AB choice , 21 % change in empirical therapy
  - » Matsen ‘81: Rapid Methods & Automation in Microbiology. ASM
- 173 pts - bacteraemia: in 32 of 48 cases, AB changes made more rapidly
  - » Doern & Scott ‘82, AAC, 21, 1023
- 268 pts - surgical unit : 14.5 % changes in rapid vs. 8.8 % in conventional method
  - » Vincent ‘85, Presse Med. 14, 1697
- 226 pts - bacteraemia : 11 % recommendations not followed rapid vs. 50 % with conventional method
  - » Trenholme ‘89, JCM, 27, 1342

Impact of rapid reporting on infectious disease management

- 273 pts vs. 300 pts
- mortality rates: 8.8 % vs. 15.3 %
- mortality rates attributable to infection: 7.0 % vs. 12.7 %
- Total hospitalisation costs: 15,062 US$ vs. 19,256 US$
- days in ICU: 1,320 vs. 1,904
- fewer laboratory studies, imaging procedures, days of intubation
- shorter time to alterations in AB therapy

Doern et al, JCM, 1994, 32, 1757

Impact of rapid reporting on infectious disease management

- 242 pts vs. 523pts
- average turn-around-time: 39.2h vs 44.4 h
- mortality rate: 7.9% vs 9.6%
- average length of stay: 10.7 days vs 12.6 days
- average variable cost per patient: 4,927$ vs 6.677$
- change to appropriate AB within 48 h: 94% vs 77%

» Barenfanger et al, JCM, ’99, 37,1415

How to increase impact diagnostic microbiology

- faster turn-around time: same day reporting, point of care testing
- do more and do less : more reliable & clinically (therapeutically) meaningful results

Clinically relevant reporting in microbiology

Aim of diagnostic microbiology: assist physician in infection management

- “Clinical impact taxonomic identification related to its ability to direct antimicrobial therapy”
- “Rapid identification that exceeds diagnostic/therapeutic necessity is of limited value”

» Staneck, Diagn. Microbiol.Infect. Dis., 1985, 3, S51

Clinically relevant reporting in microbiology : the surgeon's view

- 'I don't care what it is, just tell me what kills it'
  - identification relevant if it precedes ABgram
  - identification relevant if needed to interpret ABgram
  - identification relevant if it helps understanding the infection

Clinically relevant reporting in microbiology : the infectious diseases specialist view

- Identification relevant for interpretation of ABgram
- Identification relevant for disease diagnosis, origin, progression and outcome, clinical significance of isolates
- Identification relevant for epidemiological surveillance
- Identification relevant for identifying known/unknown organisms causing new diseases

Clinically relevant bacterial identification : the therapy oriented setting

- outpatients, non-complicated, non-compromised hospitalised patients
  - establish presence of infection
  - limited identification/susceptibility testing that is relevant to therapy
  - speed
  - symptom/problem oriented e.g. sore throat, LRTI, cystitis, vaginitis, diarrhoea

Clinically relevant bacterial identification : the added value oriented setting

- Recurring, chronic and complicated infections, compromised patients
  - full identification
  - added value identification : clinically and prognostically more relevant information
  - MIC-based antibiotic dosing

How to achieve rapid reporting: phenotyping versus genotyping

- Phenotype based methods:
  - 18 hrs incubation + 3 hrs (identification)
    + 5 - 16 hrs (AST)

- Genotype based methods: 2 - 4 hrs

Clinically relevant reporting: from phenotypic species to genotype

genotypes are clinically more relevant than phenotypic species

→ unit of pathogenicity, predictive value of virulence gene detection and expression

→ unit of epidemiological behaviour, prediction of epidemicity, clinical relevance

From phenotype to genotype: genotype based identification of clones → most pathogens are clonal

Species	Total number clones	Number clones commonly isolated from infections	% of infections due to common clones
B. bronchiseptica	21	3	87
B. pertussis	2	2	100
H. influenzae b	104 60	6 3	81 78
L. pneumophila	50	5	52
S. sonnei	1	1	100

From phenotype to genotype

The *cag* pathogenicity island and *H. pylori* virulence

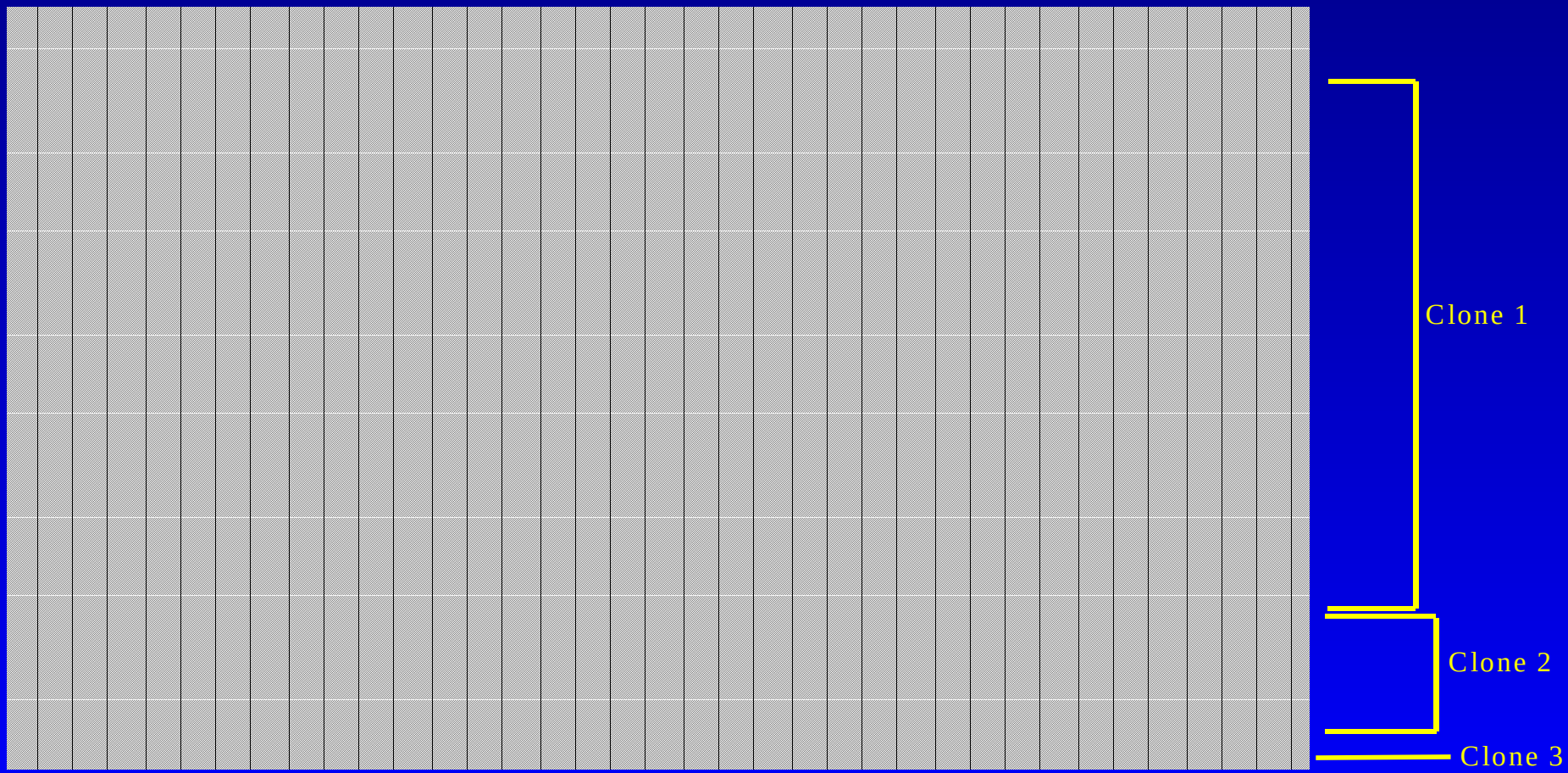
- type I isolates:
  - from peptic ulcer, or severe GI diseases
  - from adenocarcinoma
  - posses *cag* pathogeniticy island
- type II isolates:
  - from asymptomatic carriers
  - no *cag* pathogeniticy island

From phenotype to genotype: genotype based identification of clones

- monitoring ‘outbreaks’
- detection nosocomial transmission
- prediction epidemiological behaviour
- study polyclonal infections

Genotype-based prediction of epidemiological behaviour

Dendrogram of MRSA genetic relatedness based on macro-restriction analysis



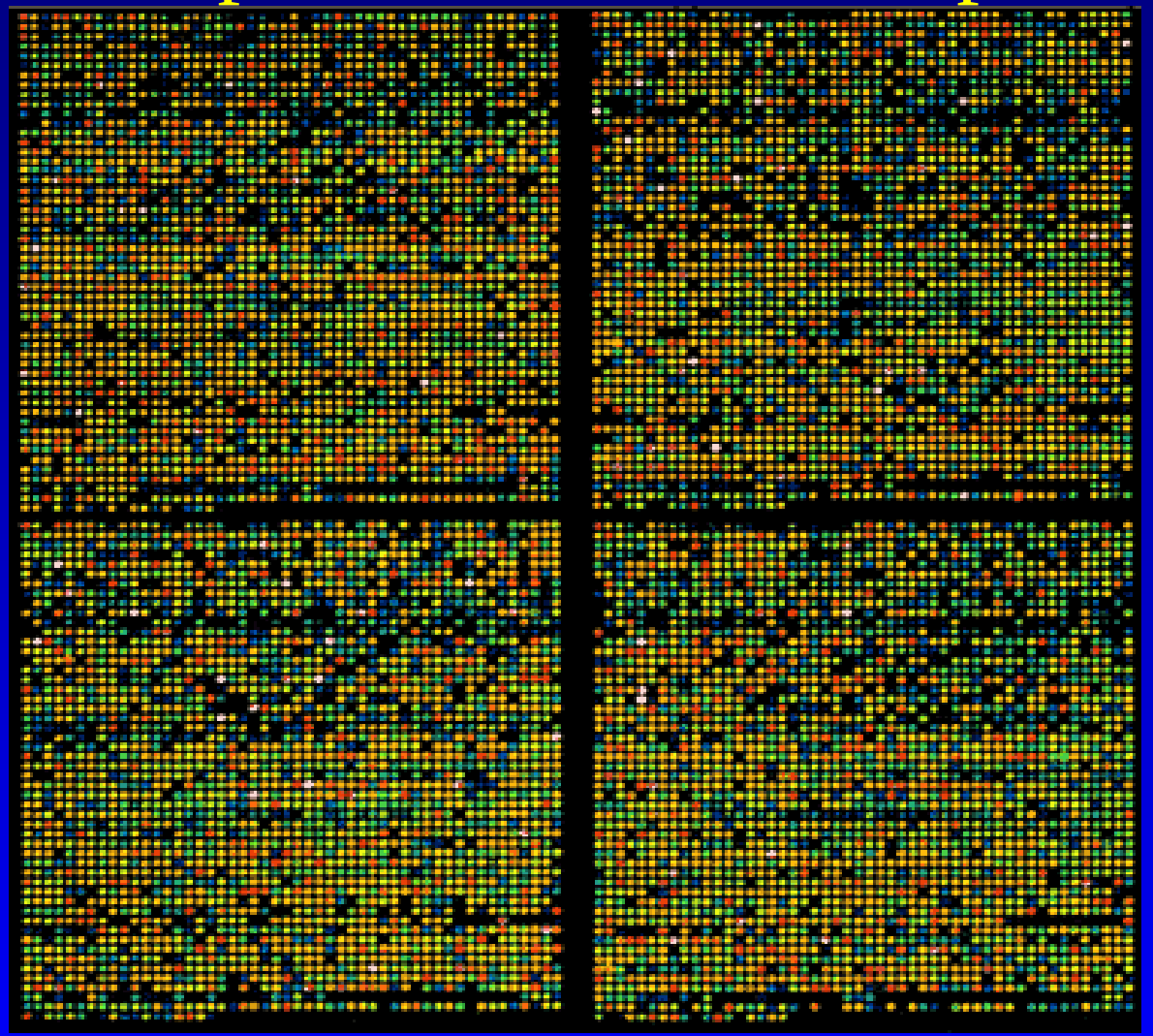
From susceptibility testing to genotype-based susceptibility expert systems

Genotype based susceptibility determination

- detection of resistance genes: e.g.. MRSA, VRE
- detection of mutations: e.g.. Rifampin resistant *M. tuberculosis*
- detection of multiple genetic mechanisms leading to defined resistance phenotype?
- MIC determination?

Genotype-based diagnostic microbiology; is it possible ? DNA-chips

Genotype-based diagnostic microbiology; is it possible ? DNA-chips



Genotype-based diagnostic microbiology is it possible ?

- **Simultaneous identification of 26 different mycobacterial species and rifampin resistance**
  - Troesch et al. JCM ‘99, 37, 49

- **Simultaneous genotyping and species identification using hybridization pattern recognition analysis of generic Mycobacterium DNA arrays**
  - Gingeras et al. Genome Res ‘98,8,435

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The integrated laboratory

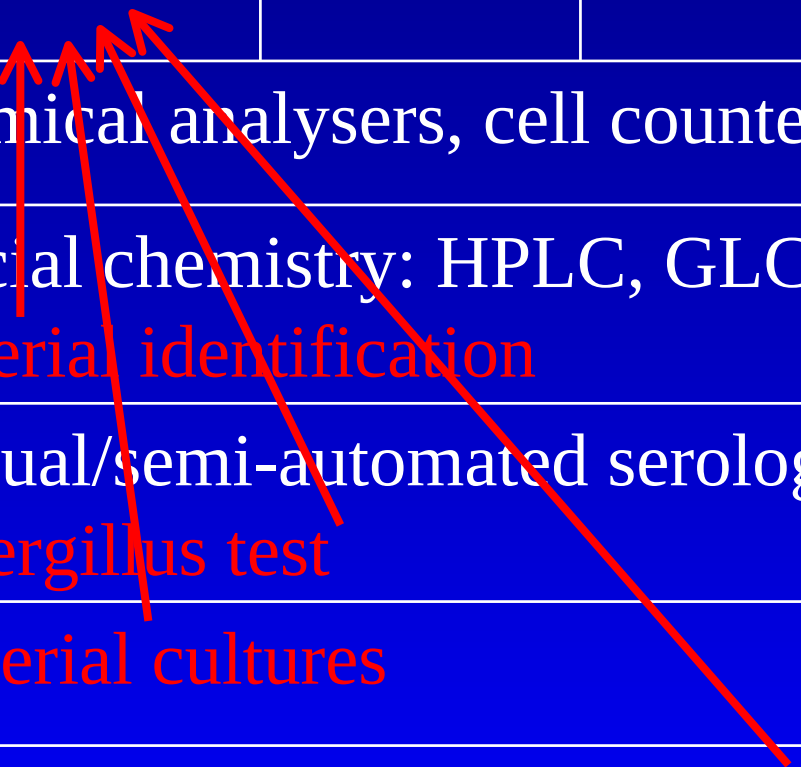
- work flow reorganisation based on common processes and technologies
  - highly automated, cross-capable instrumentation
  - random access, high-throughput
  - cross-trained technologists
  - 24-h-a-day, 7-day-a-week operation

The integrated laboratory

- arguments in favour:
  - economy of scale
  - rapid, quality testing
  - high throughput
- arguments against:
  - loss of quality through decreased proficiency of cross-trained technicians

The integrated laboratory: LAG at UZ Gasthuisberg

	bacterio	viro	hemato	chemistry
PT 1	Chemical analysers, cell counters			
PT 2	Special chemistry: HPLC, GLC, MS: GLC bacterial identification			
PT 3	Manual/semi-automated serology: Aspergillus test			
PT 4	Bacterial cultures			
PT 5	Molecular genetics : *C. pneumoniae* PCR			



Models for change in clinical microbiology

- Less microbiology and more infectious disease management:
  - increase impact on infectious disease management via rapid and situation-relevant testing
  - increasing role for rapid (genotype-based) diagnostics
  - adapt to changing concepts of lab organisation

‘There is a certain relief in change, even though it be from bad to worse; as I have found in travelling in a stage-coach, that it is often a comfort to shift one’s position and be bruised in a new place’

Tales of a traveller
Washington Irving