

MRSA: Politics, Policy and Paul Simon?

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Workshop Aims

To reflect on the various bottlenecks that we encounter to prevent and control the rise of MRSA and learn from each other as to how we can alleviate these?

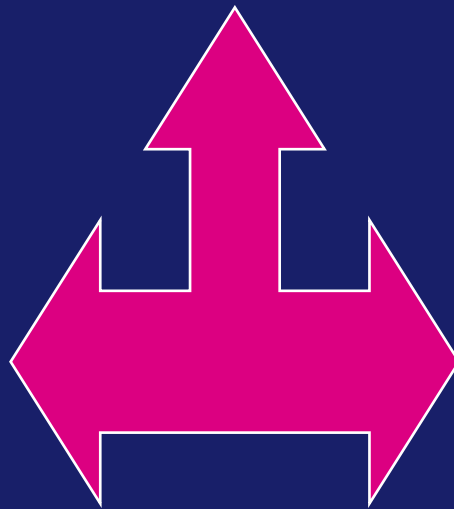
Pathogenesis of Infections

The Boxer
Seed

(Microbes)

Climate
(Environment)

Soil
(Patients)



Old Friends

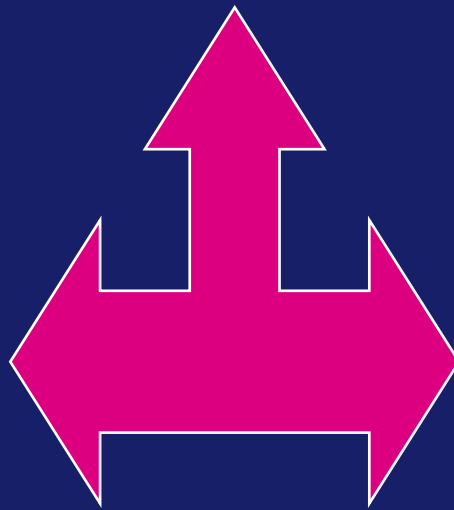
Keep the Customer Satisfied

Pathogenesis of Hospital-Acquired Infections

Pathogens and “Commensals”

Environment

Invasive procedures,
Devices (catheters,
tubing, lines),
Antimicrobials,
Healthcare delivery
(re-admissions, nursing homes,
Hospital transfers, staff
shortages, length of stay, inter ward transfers...)



Patients

Young, Aged,
Immunosuppressed

&

Carers

MRSA Pathogenesis

Microbial (Seed) Factors

Identification of MRSA

- Well standardised (disc-diffusion, E-test, automated methods, *mecA* detection, PBP 2a detection)
- Hetero-resistant strain in the Netherlands...
- Problem could be a small-colony variant: the only reliable methods are *mecA* detection or PBP 2a detection (modified)*

*Kipp F.J Clin Microbiol, 2004;42:1277

Typing of MRSA

Phenotyping:

1. Resistance profiles – not discriminatory because of multiresistance
2. Phage typing – not all isolates typable; great expertise required

Typing of MRSA

Genotyping

1) **Image-based methods** – able to distinguish clonal spread from unrelated isolates during an outbreak

- **PFGE** is the gold standard (still) today
- Plasmid profile analysis
 - Restriction analysis (REA, RFLP, Southern blotting)
 - PCR analysis : AP-PCR, Rep-PCR, **RAPD**, **SCCmec**

Future: VNTR....(coa, spa....)



Typing of MRSA

Genotyping

2) Sequence-based methods

MLST– multilocus sequence typing of housekeeping genes

- Able to address the long-term global epidemiology (expensive) **WITH SCCmec**
- suitable for database storage and software analysis

Typing of MRSA

Genotyping

2) Sequence-based methods

newer targets suitable for local epidemiological analysis
e.g. *spa* sequencing (expensive and not available
everywhere)

Lab. Healthcare Associated Infection (LHCAI)-Led
HARMONY Project: European EMRSA

Five Major International EU EMRSA clones :

A - “Iberian clone”:.:

Belgium EC-1: Finland E7, 10: France A, B, C:

N. German I: Spain E1 : Sweden: Portugal

B - Belgium EC-3: Finland E1

**C - UK E3: South German II: Slovenia: Finland :
Belgium**

**D - UK E16: Sweden II, Denmark: Finland E5:
Belgium, (Turkey, US, Australia)**

E - UK EMRSA –15: Germany: Belgium, (Australia)

Pharmaceutical Industry is withdrawing from the market!

- Better returns elsewhere:e.g. statins, anti-rheumatic drugs...
- Short Patents
- Costly development
- “All targets known”
- Additional challenge of resistance

GISA (Mu50) and Hetero-resistant GRSA (Mu3): where have they gone since 1996?

- Described by Hiramatsu et al: thickened cell walls with d-ala-d-ala targets vancomycin binding
- Japan (Arakawa et al, Lancet 2004)
National Surveillance detected none in 1997 or since!
- US and UK <30 strains identified
- Different lineages of MRSA
- Serial passage easy to train resistance
- Cases in UK: resistance lost in laboratory or in serial isolation from patient off vancomycin
- DISCUSS

VanMRSA (VRSA)

- Three cases in US all with *vanA*: Michigan, Pennsylvania and New York
- Two co-isolation of GRE from patients with diabetic foot ulcers
- Third long term care
- No cross infection identified
- All three strains sensitive to many other antibiotics
- We must avoid complacency and plan for emergence elsewhere!
- Creation mechanisms need to be established for VRSA e.g. erythromycin selection pressure?

Community MRSAs

- Genuine “de novo” isolates re?-emerging around the world
- Many different MLST clones, similar characteristics e.g. SCCmec IV, erythromycin resistant, *agr3*
- Panton-Valentine leukocidin (80/81 strains) sometimes present (pneumonia and skin infection)
- Intra-hospital spread not prominent in EU
- Situation elsewhere varied e.g. intra-US
- Watching UK brief : “dosser” drug addicts with same clone (PVL negative)
- DISCUSS: do countries all know?

MRSA Pathogenesis – Host (Soil) Factors (Changes in '90s)

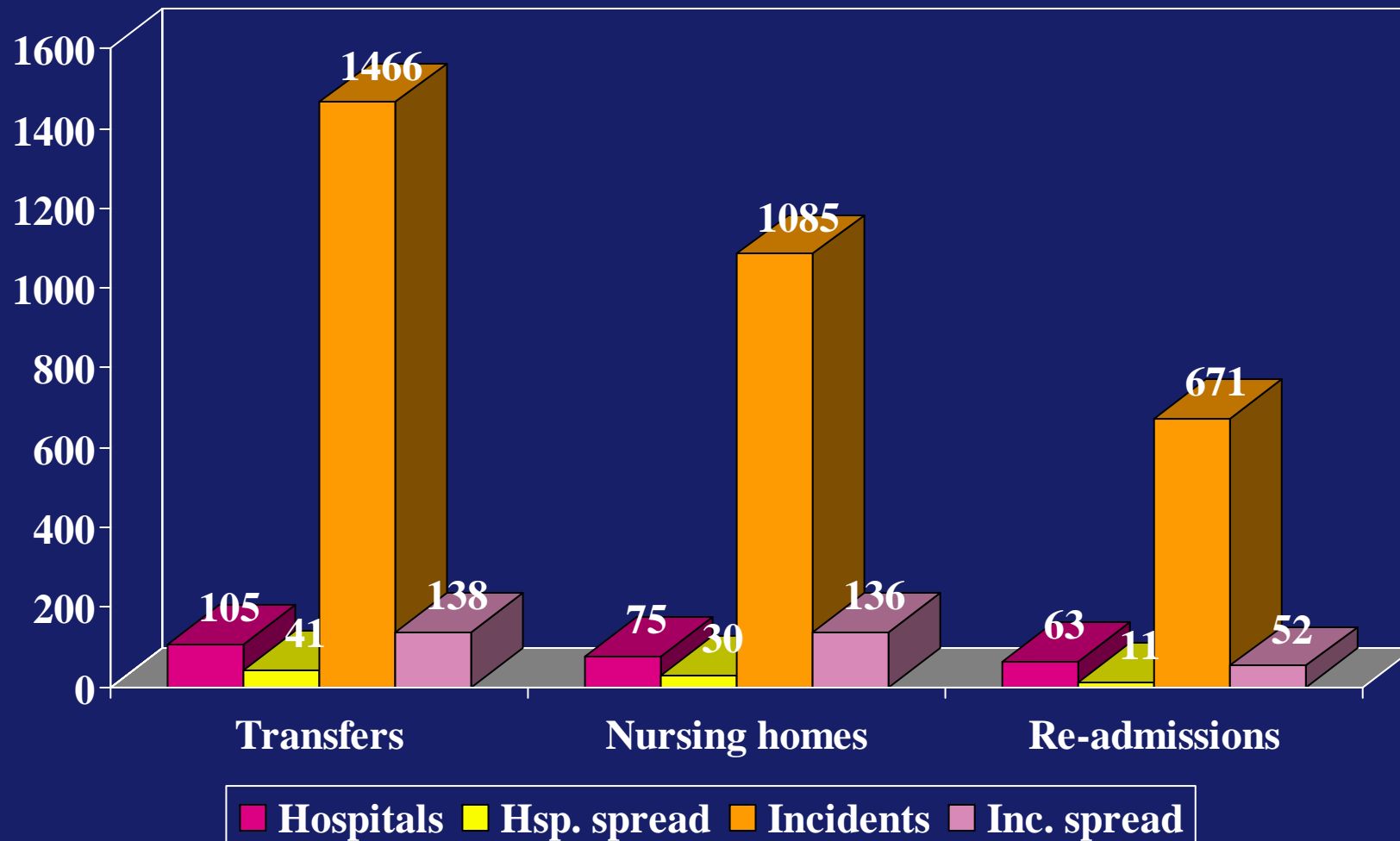
- Aged:
 - Most of the EU has become increasingly aged
 - “Elderly” (>65) – more prone to MRSA carriage
 - Elderly are fitter for longer and undergoing more dramatic surgery, orthopaedic surgery and Intensive Care Unit admissions
- Sacral and Varicose ulcers colonised with EMRSAs : contributing to this reservoir in the community
- Evident in the literature that Neonates are becoming more affected

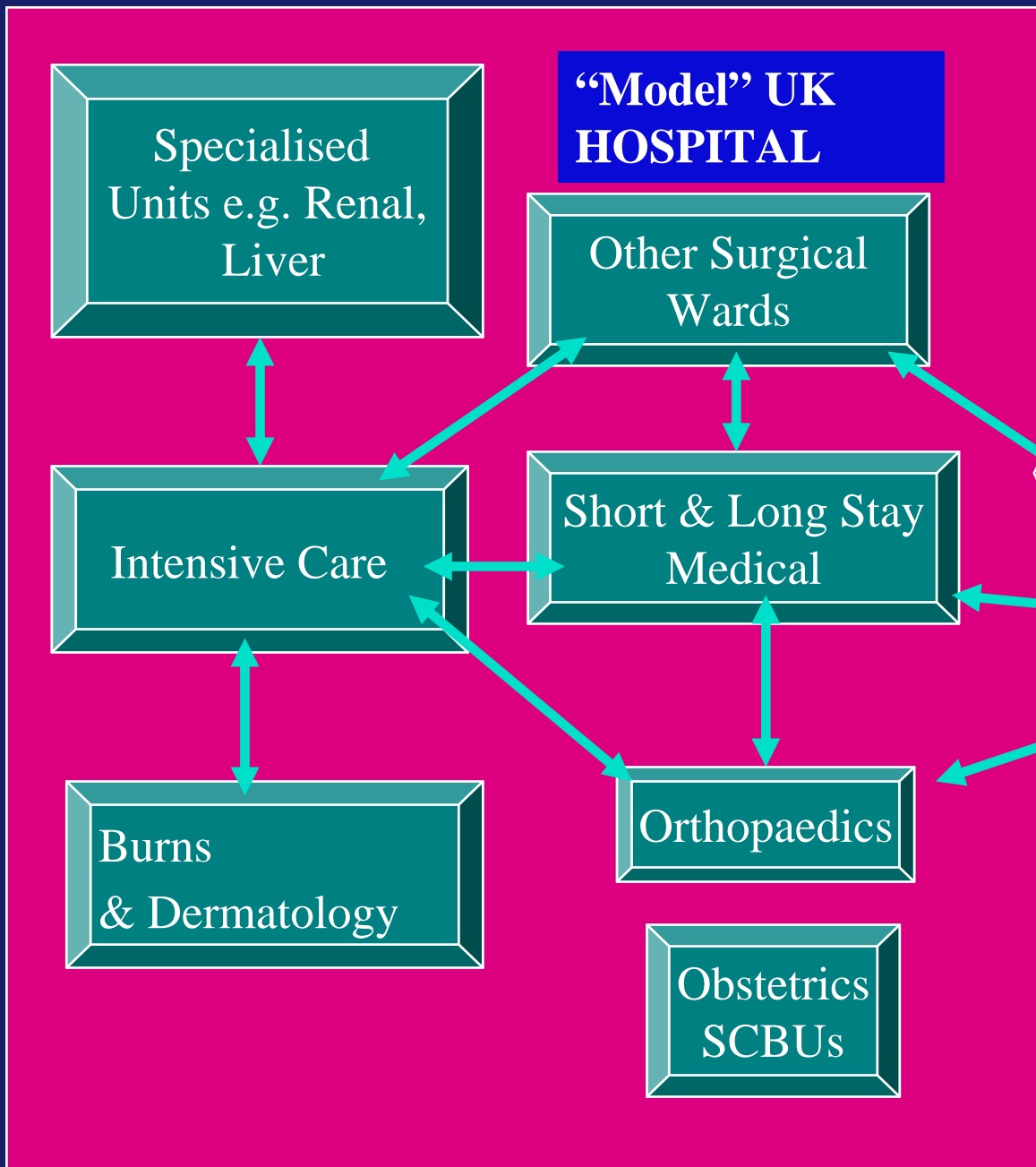
MRSA Pathogenesis – Environment (Climatic) Factors

- A multitude!
- *“The way we deliver healthcare to-day is almost designed to spread multiple resistant organisms like MRSA”*

Barry Cookson quote from the Times

1995 : UK ICTs experience of different ways MRSA was acquired and spread in their hospitals





MRSA Challenges

International and Inter-Hospital Patient and Staff Transfers

Re-Admissions

Nursing Homes

“De-novo”?

**“Endemic MRSA”:
constant challenges
to the hospital**

Decreasing lengths of stay:

- **Decreases likelihood of MRSA acquisition**
- **Infections present after discharge (Loss of Alert Organism Surveillance)**
- GPs are more aware of this now

- Bed Occupancy in the UK ~90% parts are >100%
- Pressures on waiting lists make it difficult to lower
- Most EU countries have ~85% occupancy
- Some data show hospitals may be more efficient if operate ~85%

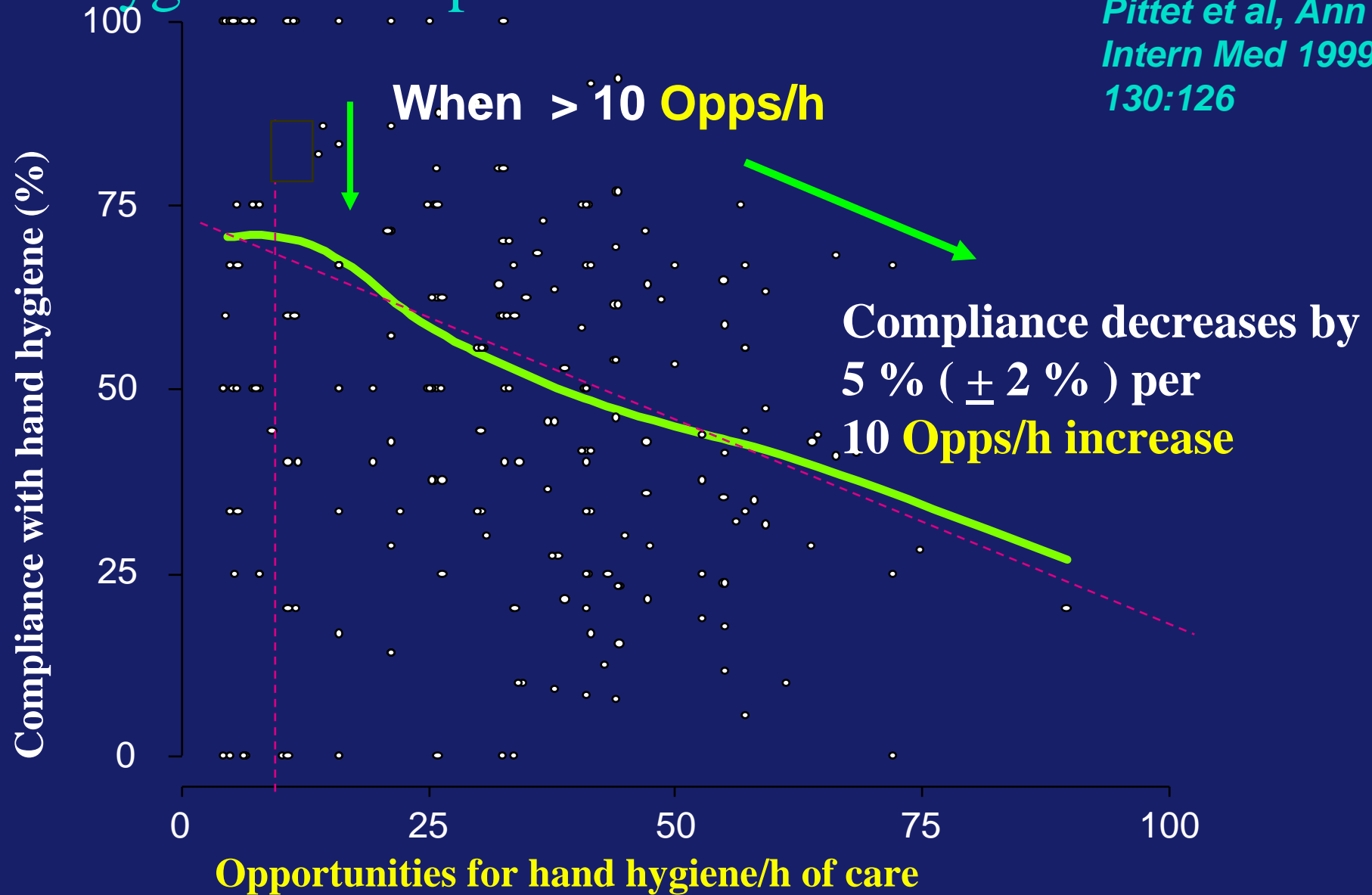
- Inter-Ward Transfers: difficulties in retrospective & prospective case tracking:
3 papers shown this and another in preparation
- Consultant teams can change too!
- Many hospitals cannot quickly produce data

Nurse shortages
- a global problem
but a complex story

High patient workloads
and stress are significant
factors in failure to comply
with infection control
procedures

Hand Hygiene Compliance and Workloads

Pittet et al, Ann Intern Med 1999, 130:126



Issues relating to reliance on Agency staff: moonlighting, quality assurance of training, inter-hospital transfer

ITU AGENCY NURSES EMPLOYED

Month (1986)	Nurses	Sessions AM/PM/Night	
January	10	17	
February	19	33	
March	15	69	
April	40	84	
May	34	112	
June	26	54	
July	10	16	ITU SPRING-CLEAN
August	25	76	
September	18	51	
October	23	37	
November	13	26	
December	26	46	
TOTAL	259	621	

Relationship between Nurse/Patient Ratios and Staffing levels

- Many different systems of assessing intensity of care: perceptions depend on underlying stress
- Several studies show relationships between infection and colonisation rates Haley et al, 1997, Vicca, 1999, Anderson 2002,
- ARPAC study in November 2004 ...

Are there regional variations in the diagnosis, surveillance and control of MRSA

H.Richet, ICHE 2003

- 90 hospitals in 30 countries worldwide
- Low incidence rate ($<0.4/1000$ ptdays)
High incidence rate ($\geq 0.4/1000$ ptdays)
- Higher mean No of beds/ICN was the ONLY factor significantly associated with higher incidence rate:
834 versus 318 (p: 0.02)

HARMONY – some of the experience in other EU countries with UK strains

- **Sweden**

- Most patients in side or two-bedded rooms!
- Polish strain in Stockholm, E-16 in Gottenburg
- Poor infection control policy implementation

- **Finland**

- Currently low inter-hospital patient transfers, even lower inter city
- EMRSA -3 and -16 outbreaks intra-city

- **The Netherlands**

- EMRSA-15 and 16 spread rapidly intra-wards but control possible with search and destroy

- **Staffing shortages reported in all countries**



Summary of Key parameters for MRSA control

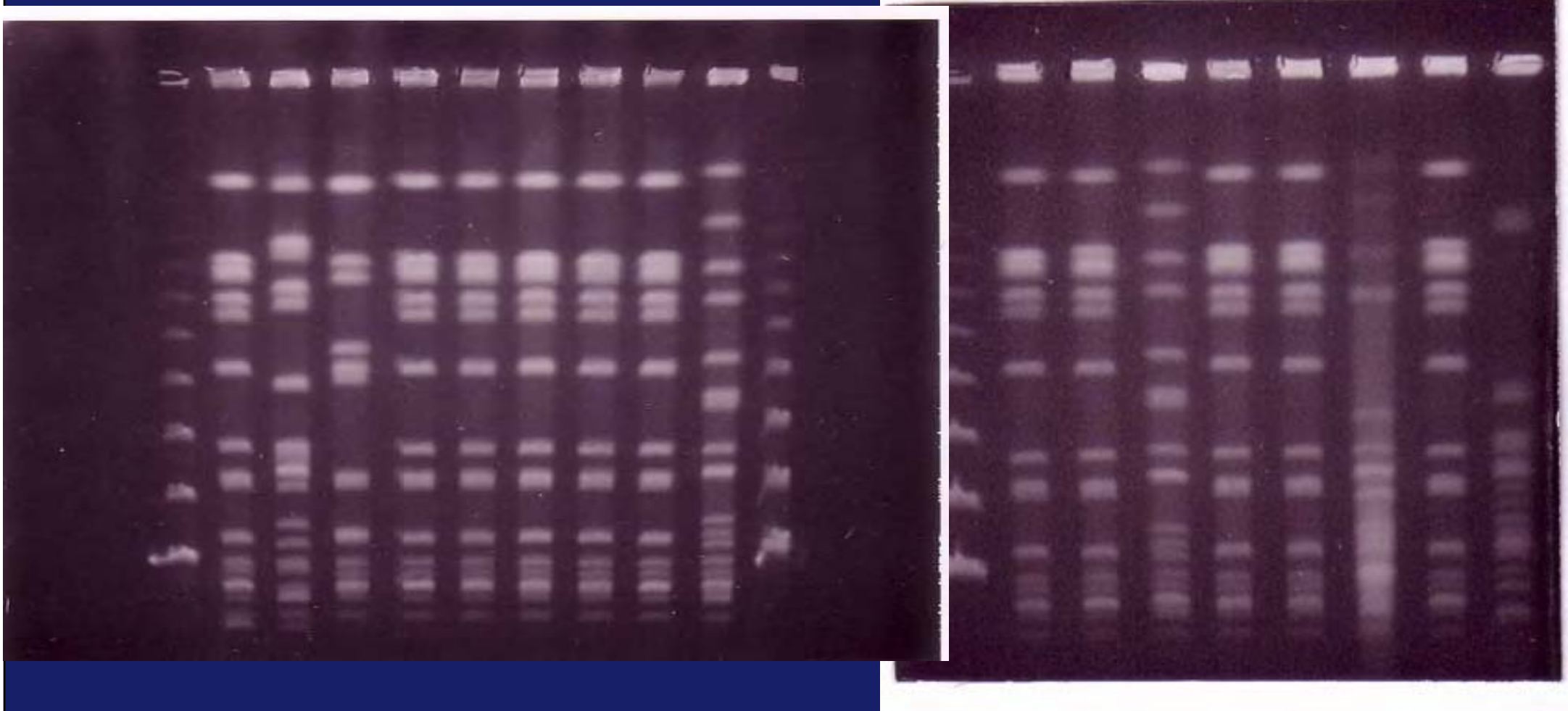
- **Reduce antimicrobial use:** selection pressure
- **Reduce MRSA reservoir** and potential for spread: ward closures, patient decolonisation and early discharge
- **Infection control measures to prevent spread**
 - Promote and improve hand hygiene (alcohol hand rubs)
 - Effective isolation measures e.g. targeted and cohort nursing, monitored universal precautions, side-rooms, MRSA bays or wards.
 - Screening e.g. identify reservoir, use of MRSA acquisitions as a quality indicator

Croatian MRSA – 2001 Blood isolates

PFGE genotype distribution

- 41/47 MRSA strains examined
- All 9 hospitals
- PFGE; *Sma*I restriction
- Visual comparison

MRSA – blood isolates, Croatia PFGE genotype distribution (2001)



PFGE-type analysis

7 PFGE types

- **Type A: 26/41 - 63% (7 hospitals)**
- **Type B: 6/41 - 15% (5 hospitals)**

- **Type C: 3/41 – 7% (2 hospitals)**
- **Type D: 2/41 – 5% (2 hospitals)**
- **Type E: 2/41 – 5% (1 hospital)**
- **Type F: 1/41 – 2% (1 hospital)**
- **Type G: 1/41 – 2% (1 hospital)**

IFIC 2004 Porec Congress

- Hungary P.25
 - 1993 – first reported outbreak until 2003
 - 70 outbreaks
 - Significant increase beginning the year 2000
 - 21 outbreaks in 2002
 - 36 outbreaks in 2003
 - 708 pts, 74 deaths. ICU, surgical wards
 - Now also Long Term facilities

IFIC 2004 Porec Congress

- Slovenia P.30
 - MRSA eradication in pts with positive surveillance cultures
 - Failure in 70% of pts!
- Romania O.14
 - 23% SA were MRSA in an investigation in neonatal unit
 - 17% in respective Obstetrical Department

HTA MRSA Systematic Review (2003)

Data Extraction & Synthesis

- Systematic assessment Confounders & Biases
- Summary tables; No formal meta-analysis
- Strength evidence evaluated by design, quality data, size effect, presence plausible alternative explanations from confounders or biases & characterised: None, Weak, Evidence or Stronger evidence consistent with effect of interventions on levels of MRSA

Results systematic review

- 4382 abstracts: 254 full article appraisals
- 46 accepted studies
- 18 Isolation Ward
- 9 Nurse Cohorting
- 19 Other isolation
- Most multiple interventions
- Few (4) formally planned prospective studies
- Systematic Assessment & adjustment potential confounders lacking
- Regression to mean effects (7) & confounders (25) provided plausible threats validity
- Predominance unplanned retrospective reports suggest reporting bias (11)
- Statistical Analysis absent/inappropriate (44)
- Little Economic data (40)

Results systematic review: evidence of effect of isolation

- No conclusions could be drawn in one third
- Most of rest: evidence consistent with reduction of MRSA
- In half: evidence considered weak due to poor design, major confounders, systematic bias
- Six studies considered to present stronger evidence: larger, longer ITS, details on interventions
- Relative absence plausible alternative explanations
- Provide testable hypotheses for future planned studies

Conclusions of HTA MRSA Systematic Review (2003)

- Evidence that concerted efforts can reduce MRSA even in endemic settings
- Little evidence to suggest that current guidelines applied in many countries are ineffective.
- Isolation measures combined with other interventions should continue to be applied until further research establishes otherwise.
- Future research should concentrate on prospective planned studies with pre-defined comparisons, with systematic assessment and adjustment for confounders.

HTA MRSA Systematic Review

Modeling

Scenario 1: No isolation

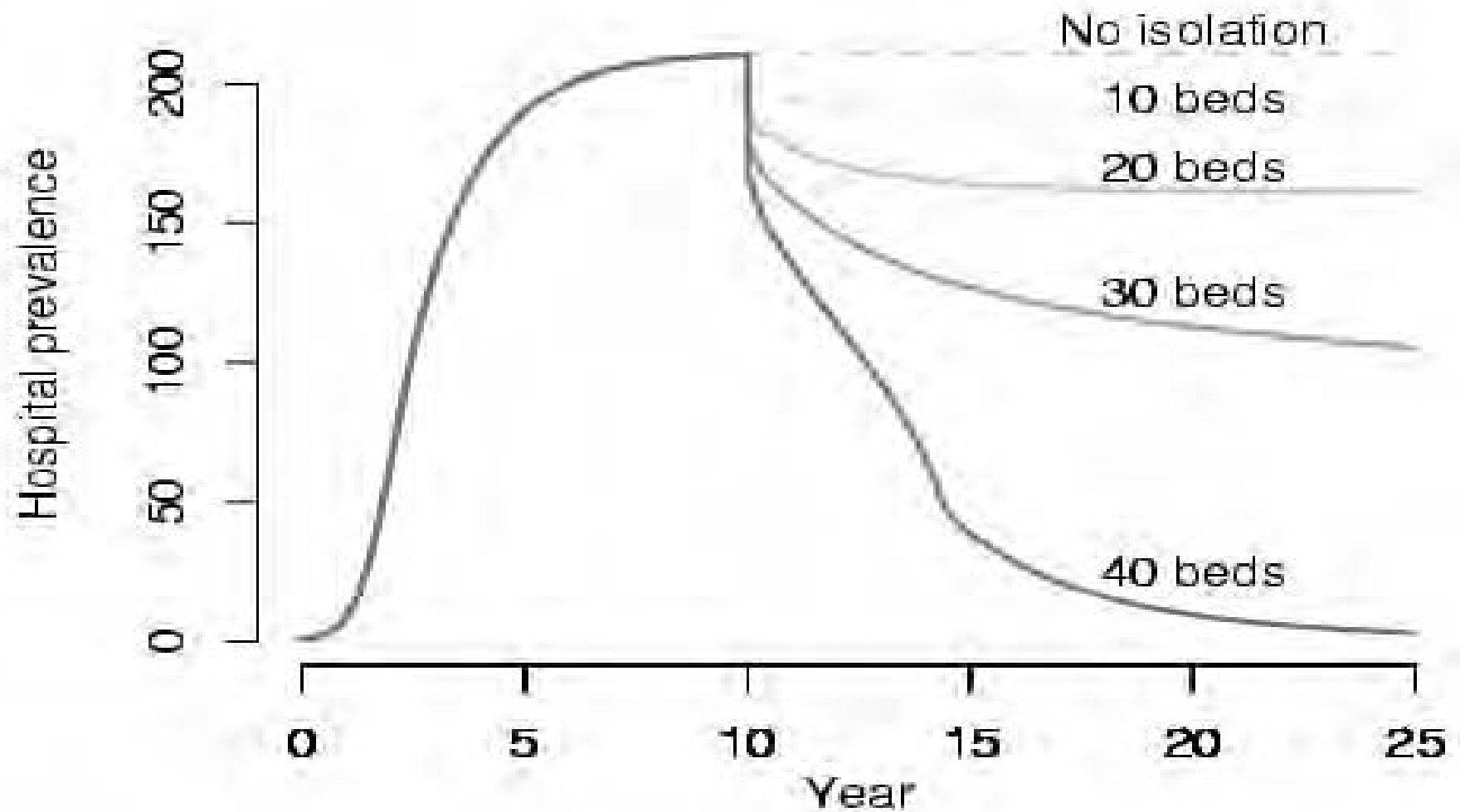
The results indicates that costs can be expected to be very sensitive to:

the attributable length of stay
(increasingly so for higher transmissibilities)

the proportion of patients who become infected
(the virulence/patient vulnerability).

Cooper et al, *Proc Nat Acad Sciences* 2004: **6**: 10223-10228





Isolation ward is introduced after ten years. $\phi=0.04$, $R_0=1.3$.

Conclusions of Mathematic Modeling of introductions of MRSA to a hospital

- Increasing the detection rate reduces the endemic prevalence
- Effectiveness of intervention can depend critically on timing (the earlier the better)
- Isolation policies that do not scale with the MRSA reservoir are vulnerable to failure
- The ability of the MRSA strain to persist in the patients and to transfer between them can be key factors in the long-term dynamics

Cooper et al, *Proc Nat Acad Sciences* 2004: **6**: 10223-10228



Conclusions (continued)

- Isolation policies can result in cost savings over ten years
 - prevent endemic levels from becoming established.
 - reduce the endemic prevalence to lower levels.
- Valid over a wide range of transmissibilities and virulence levels
- **Surprisingly insensitive to capital costs.**
- UNLESS extended periods with large number of unused isolation beds, when reduced isolation ward staffing will be more cost-effective
- Or low infections without control measures.