Ongoing Gaps in Scientific Research to Facilitate ARO Policy in Healthcare

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Outline

- Funding sources and commitment to funding
- Gaps in funding/research
  - Training/education/infrastructure
  - Surveillance
  - Infection control
  - Antimicrobial stewardship
  - Diagnostics

NDM-1 Around the World

Rolain, J.M., et al. Soc Clin Microbiol Infect Dis 2010;16: 1699-701.

UK Funding commitments

Population 63.23 million

UK $4.2 billion between 2007-2010

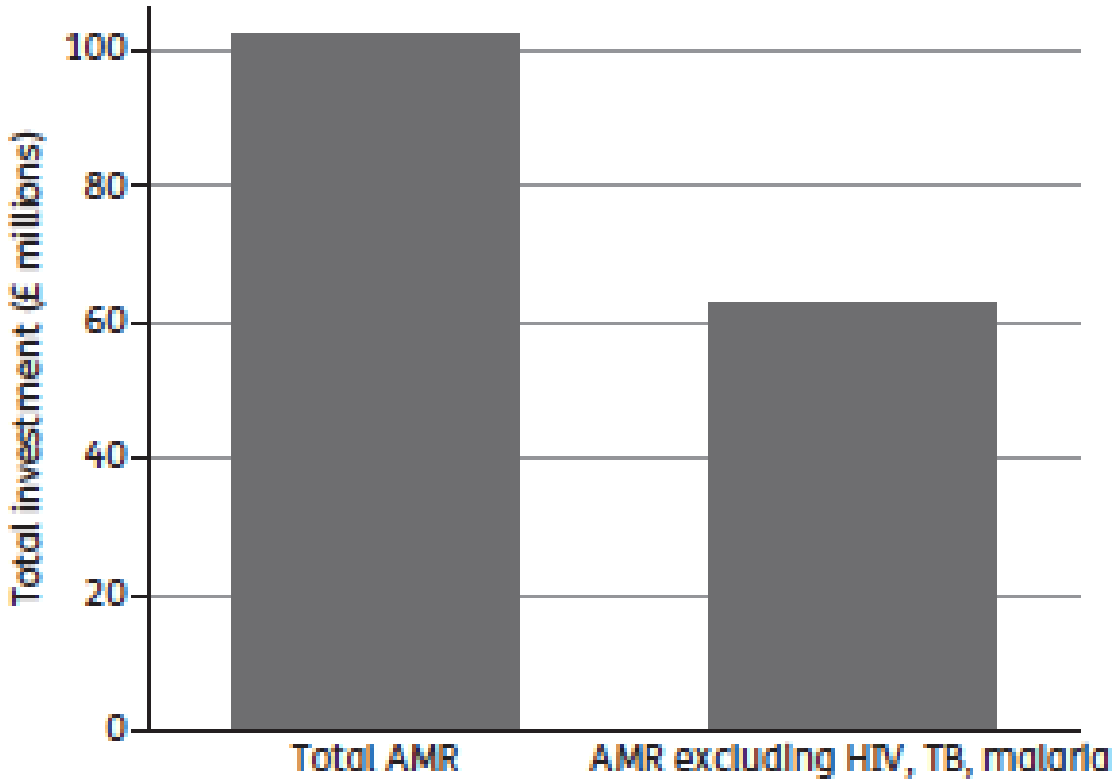


Table 1. Funding award projects

al resistance-related

e-related funding

Microbiological subject area	ment, (%)	median grant award, £
Bacteriology	0.2)	112152
Parasitology	7.4)	222912
Virology	7.2)	120926
Mycology	.5)	91761
Prion		—
Not specified	4.2)	115120
Overall	.9)	119685

Head et al JAC 2014: 69; 548

Funding commitments

Population 318 million

US $398 million on antimicrobial resistant and HAIs in 2009

Table 1 Number of NIAID Grants and Amounts by Search Term and Year

Search Term	Fiscal Year (FY)	Total Amount ($)	Total Number of Grants	Amount per Grant ($)
Antibiotic Resistance	2007	67,860,927	199	341,010
	2008	72,972,153	223	327,229
	2009	101,623,126	282	360,366
Antimicrobial Resistance	2007	6,817,017	24	284,042
	2008	136,111,065	241	564,776
	2009	138,905,976	242	573,992
Hospital-Associated Infection	2007	105,574,441	183	576,910
	2008	118,117,691	176	671,123
	2009	158,118,571	216	732,030
Combined	2007	180,252,385	406	443,971
	2008	327,200,909	640	511,251
	2009	398,647,673	740	538,713
Approximate NIAID budget	2007	4,366,000,000		
	2008	4,561,000,000		
	2009	4,569,000,000		

No duplicate grants in each search term

Kwon et al ARIC 2012;1:5

NIH Funding

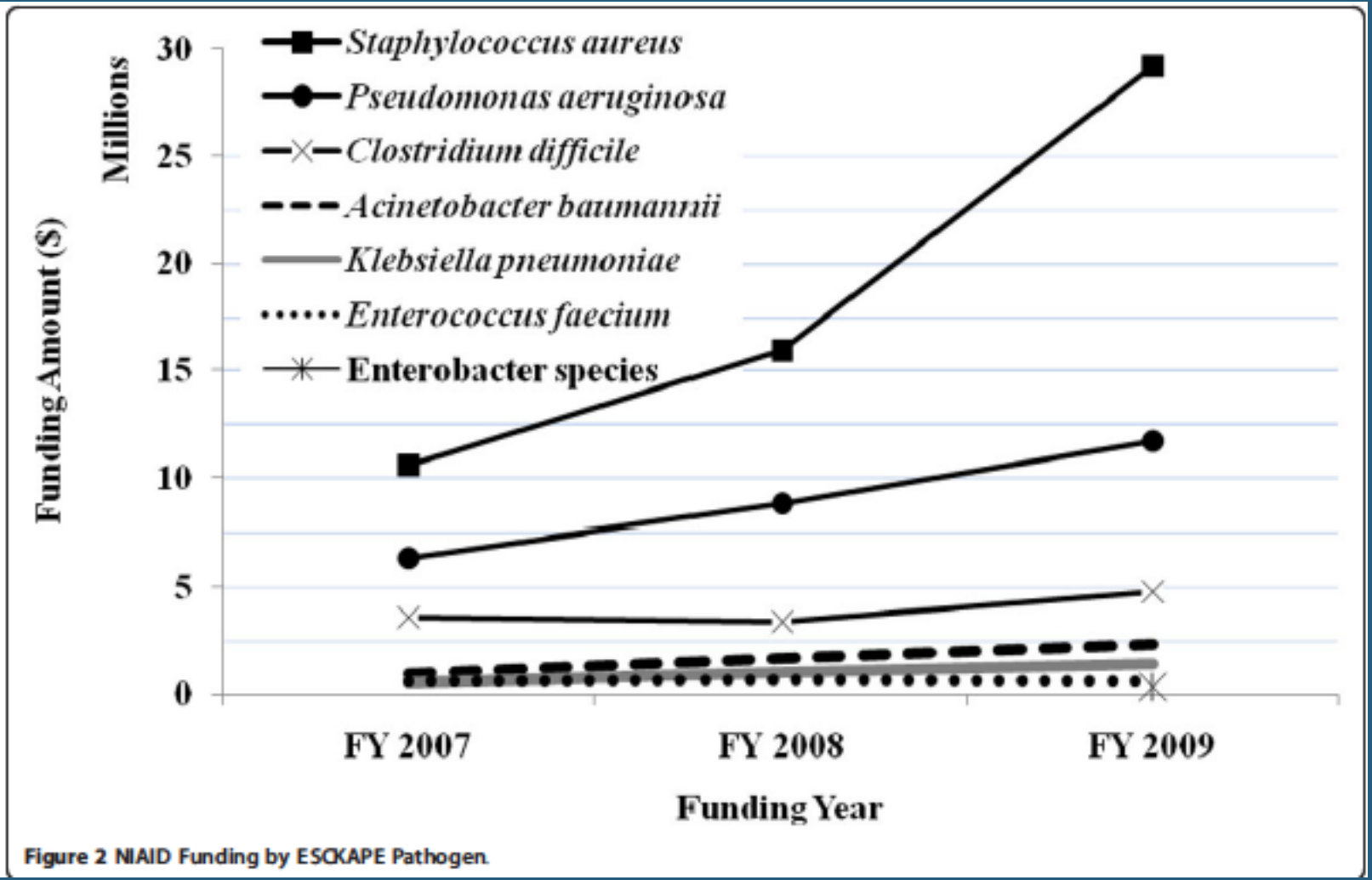


Figure 2 NIAID Funding by ESCKAPE Pathogen.

Kwon et al ARIC 2012;1:5

Canadian/EU Funding

- Population 34.8 million
- $15.3 million for Antimicrobial Resistance
- UK and Canadian partnership $4 million plus £2 million

- Population 505.7 million
- € 223.7 million Innovative Medicines Initiative (New Drugs for Bad Bugs)

Needs and Consideration

Wide variations in funding ratios (back of the napkin)

- UK $1.66/person
- US $1.25/person
- Canada $0.94/person
- EU $0.65/person

Develop a measure to benchmark funding and assure adequate funds are available

Assure that funding is allocated for pragmatic translational studies

Increase funding to support needs based on frequency and impact

Engage in international partnerships as the EU to maximize use of funds, increase generalizability and assure adequate outcomes are achieved

What Level of Evidence is Needed?

- "The RTC is generally considered to have the highest credibility with regard to assessing causality however in a hospital …the intervention often cannot be randomized for one or more reasons: 1) ethical considerations, 2) inability to randomize patients , 3) an inability to randomize locations or a 4) need to intervene quickly…the clinical and ethical necessity makes it difficult or impossible to undertake the lengthy process of implementing a RTC."

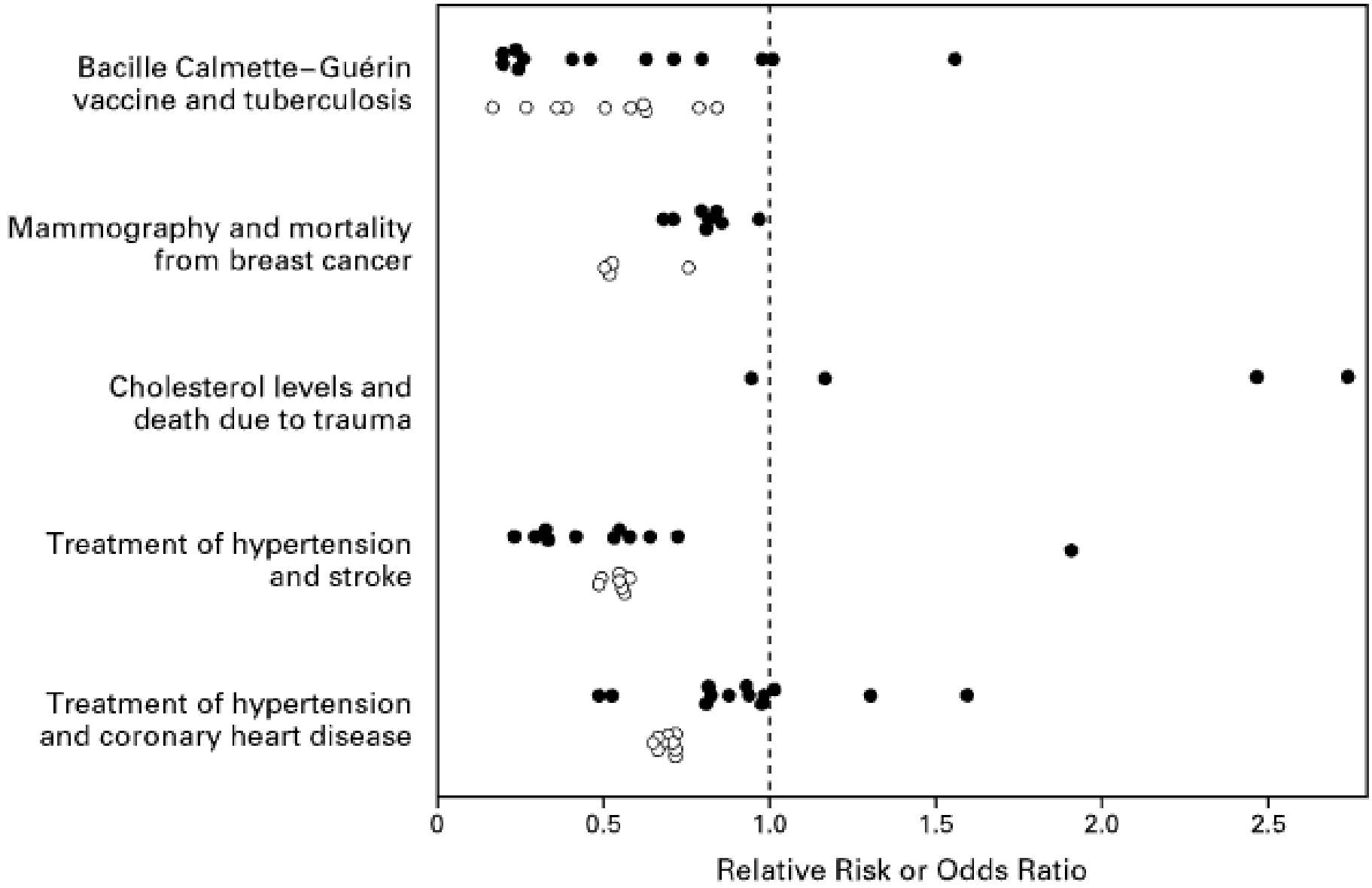
Harris et al. CID 2004:38;1586-91

TABLE 2. TOTAL NUMBER OF SUBJECTS AND SUMMARY ESTIMATES FOR THE EFFECT OF FIVE INTERVENTIONS ACCORDING TO THE TYPE OF RESEARCH DESIGN.

CLINICAL TOPIC	TYPE OF STUDY	META-ANALYSIS*	TOTAL NO. OF SUBJECTS	SUMMARY ESTIMATE (95% CI)†
Bacille Calmette–Guérin vaccine and tuberculosis	13 Randomized, controlled	Colditz et al.[14]	359,922	0.49 (0.34–0.70)
	10 Case–control	Colditz et al.[14]	6,511	0.50 (0.39–0.65)
Mammography and mortality from breast cancer	8 Randomized, controlled	Kerlikowske et al.[15]	429,043	0.79 (0.71–0.88)
	4 Case–control	Kerlikowske et al.[15]	132,456	0.61 (0.49–0.77)
Cholesterol levels and death due to trauma	6 Randomized, controlled	Cummings and Psaty[16]	36,910	1.42 (0.94–2.15)
	14 Cohort	Jacobs et al.[17]	9,377	1.40 (1.14–1.66)
Treatment of hypertension and stroke	14 Randomized, controlled	Collins et al.[18]	36,894	0.58 (0.50–0.67)
	7 Cohort	MacMahon et al.[13]	405,511	0.62 (0.60–0.65)
Treatment of hypertension and coronary heart disease	14 Randomized, controlled	Collins et al.[18]	36,894	0.86 (0.78–0.96)
	9 Cohort	MacMahon et al.[13]	418,343	0.77 (0.75–0.80)

*Meta-analyses that included either randomized, controlled trials or observational studies are cited.

†CI denotes confidence interval.

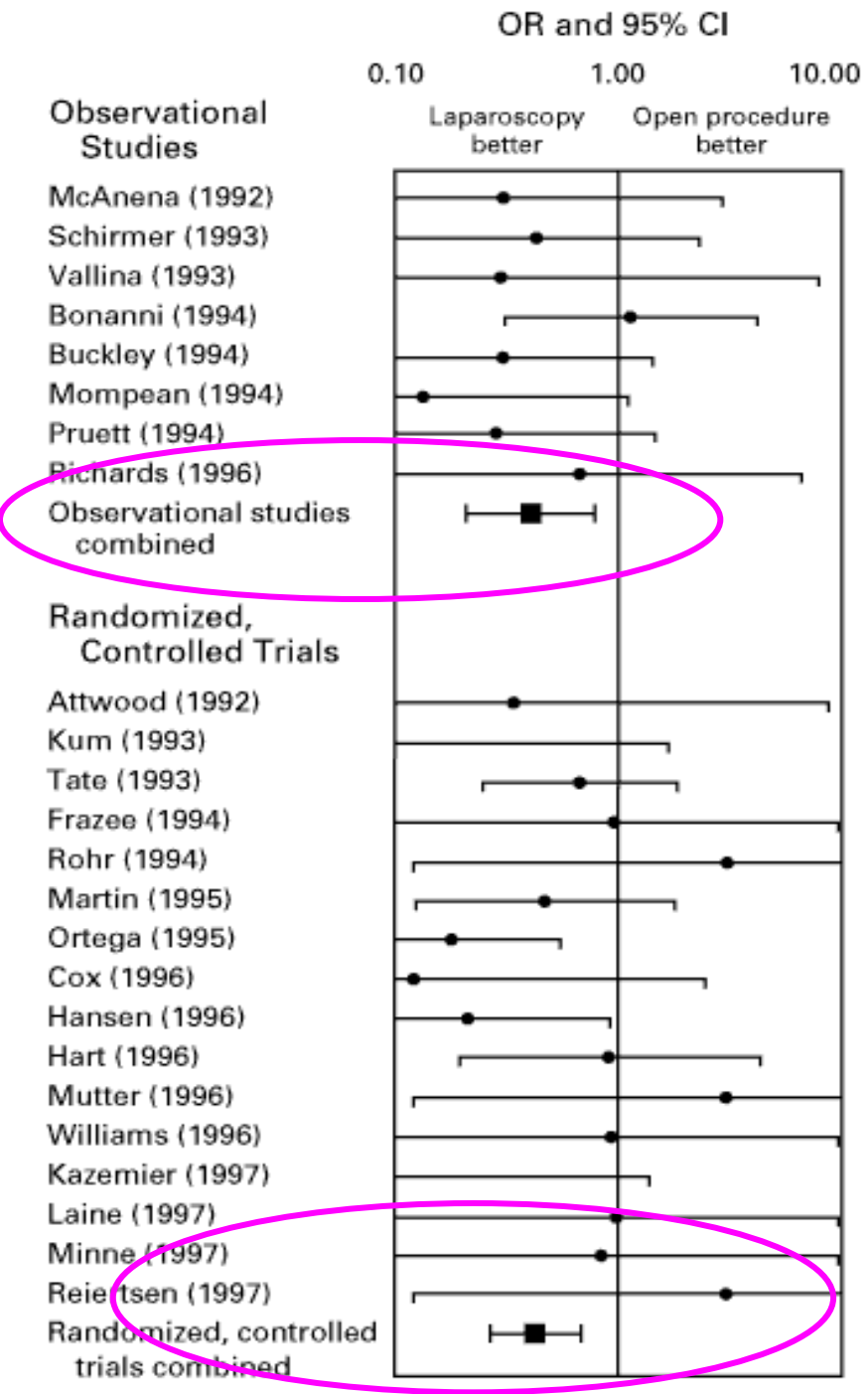


Cancato et al. NEJM 2000;342:1887

Consistency in findings

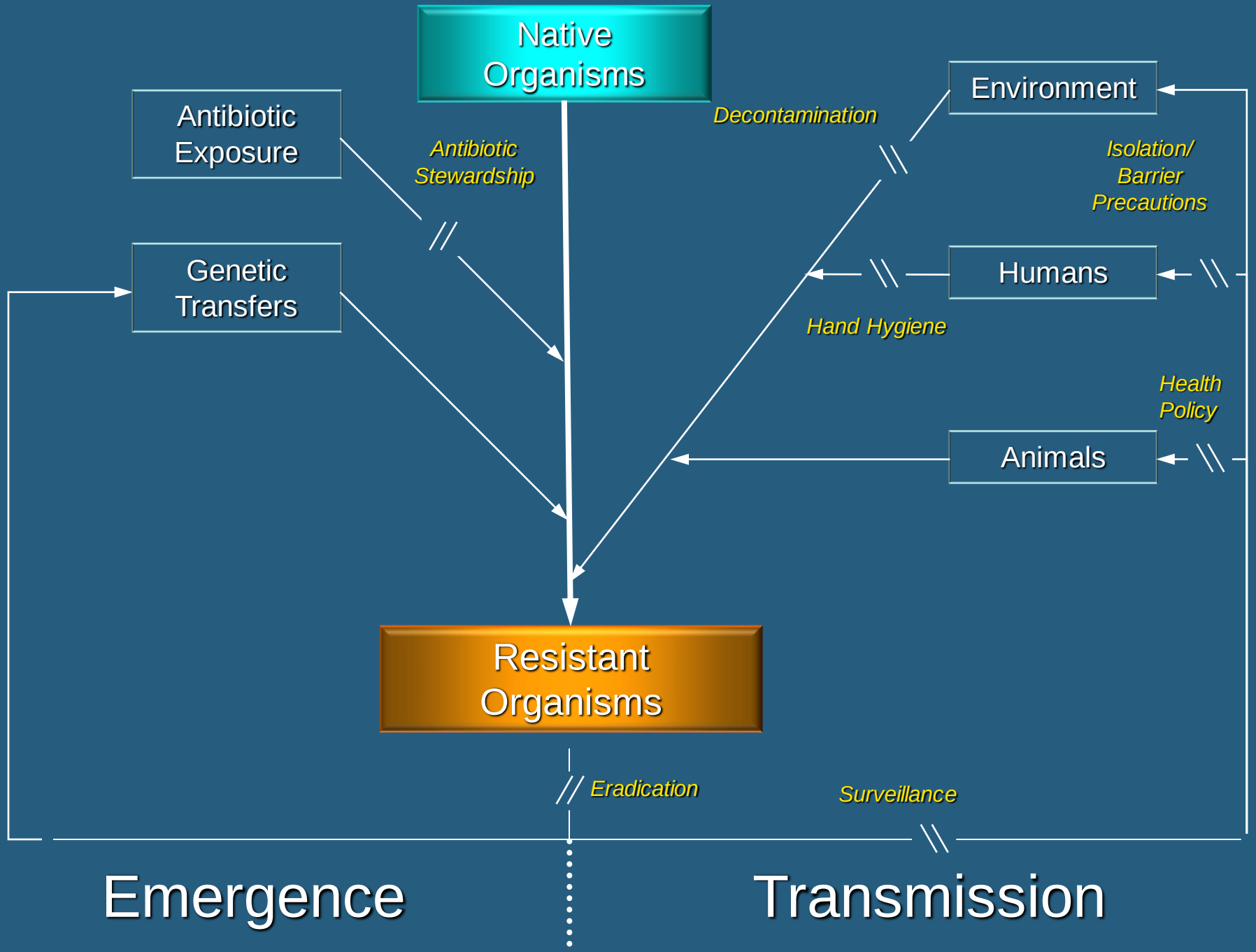
- A Index Medicus and Cochrane (1985-98) identified observational studies that compared 2 or more treatments and compared these to RCT and observational studies Summary estimates and 95% CI were calculated.
- 136 reports of 19 subjects were evaluated.
  - In 2 /19 analysis did the treatment effect lie outside the 95%CI when compared to the combined magnitude identified in the RTC.
- The authors conclude that there is LITTLE evidence that the estimates of treatment in well-designed observational studies (CC or cohort) systematically overestimate the magnitude of effect or are qualitatively different when compared to RTC.

Benson et al. NEJM 2000;342:1878



Infection After Laparoscopic as Compared with Open Appendectomy Consistency in findings

Benson et al. NEJM 2000;342:1878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Genetic Transfers
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Animals
Resistant Organisms
Antibiotic Stewardship
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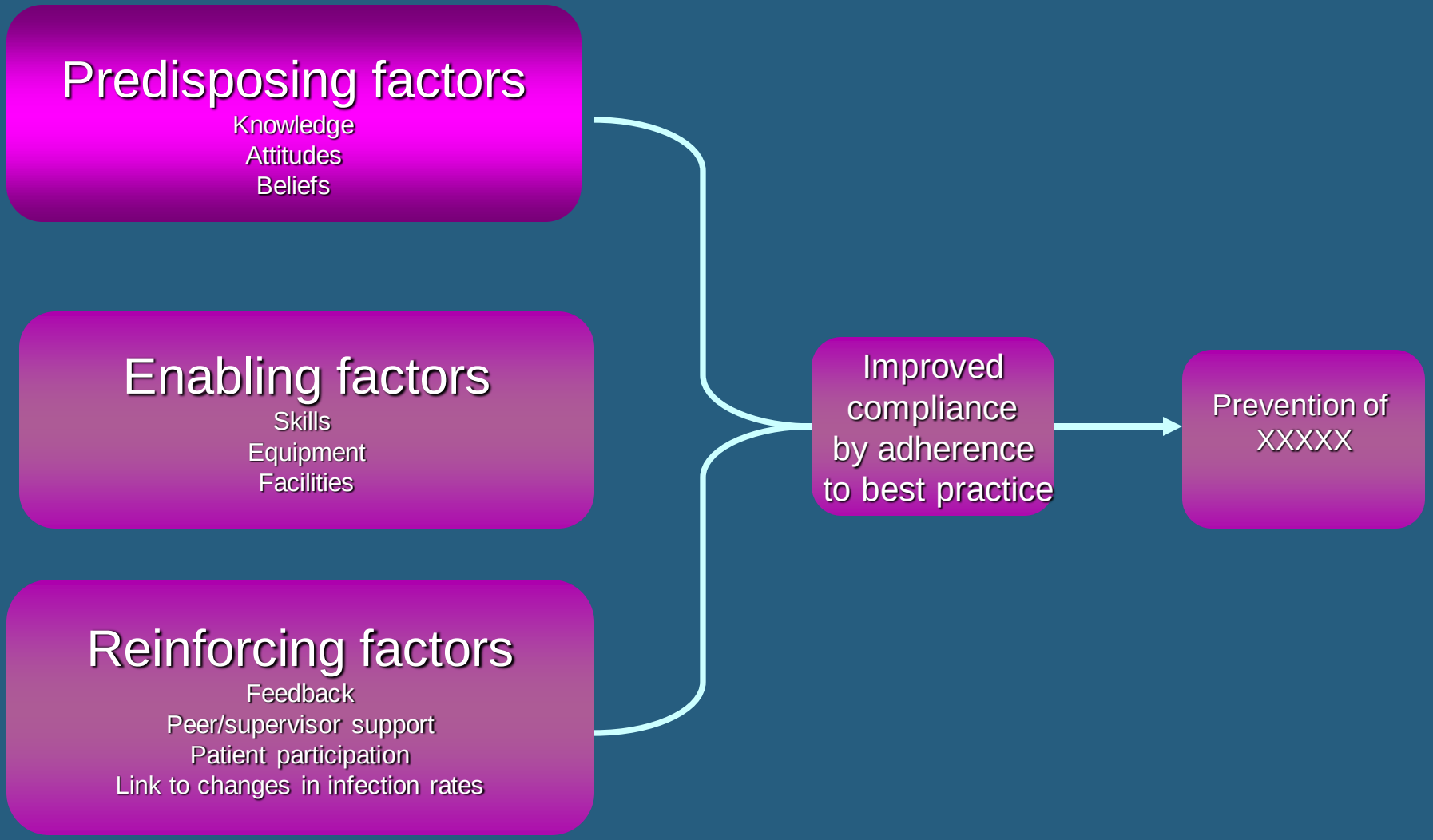
Hand Hygiene
Health Policy
Eradication
Surveillance
Emergence
Transmission

A Framework to Improve Practice: Implications for Guidelines



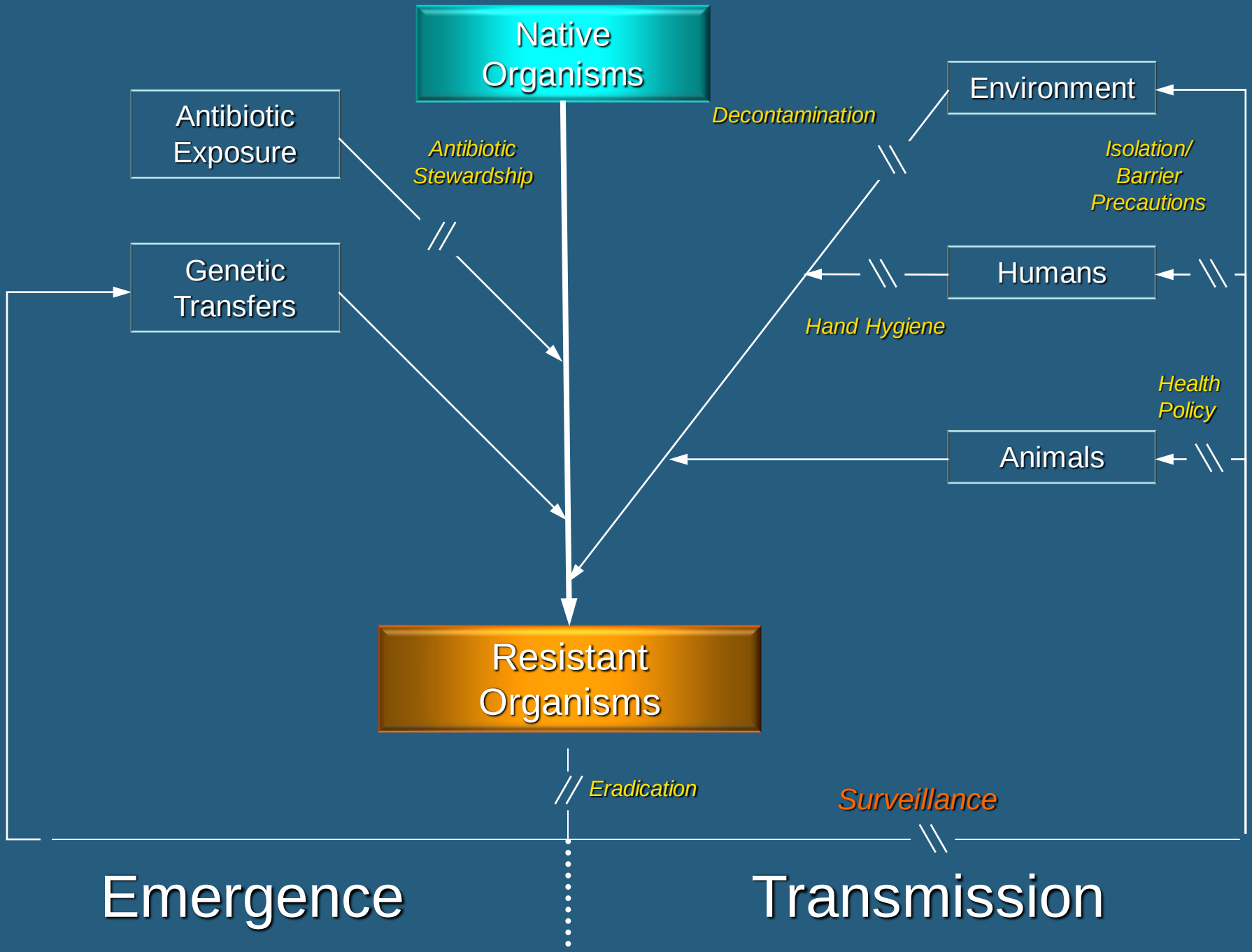
Needs and Consideration

- Provide career development awards targeting antimicrobial resistance including infectious diseases, medical microbiology and epidemiology
- Is there are need for formal training in infection prevention and antimicrobial stewardship
- What expertise and what are the resource needs for
  - Medical microbiology
  - Field epidemiology
  - Infection prevention and antimicrobial stewardship
  - human factors training and skills
- What planning (models) need to be developed to determine the facility and capacity needs in

Needs and Consideration

Education gaps

- What is the best strategy to education healthcare personnel and the general public about antimicrobial resistance?
- What tools will enhance knowledge, beliefs and attitudes about the risks/impact and outcomes of antimicrobial resistance?
  - Patient centered
  - Healthcare provider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Surveillance

- What type of surveillance system is needed to identify trends, emerging resistance and provides the robustness to provide population specific information?
- How can you capitalize on the new interest in big data to develop an integrated, comprehensive surveillance system within the province, across Canada and with international partners?
- What elements need to be in a surveillance system to meet the public health needs (to drive policy)? Ie human and animal

Surveillance

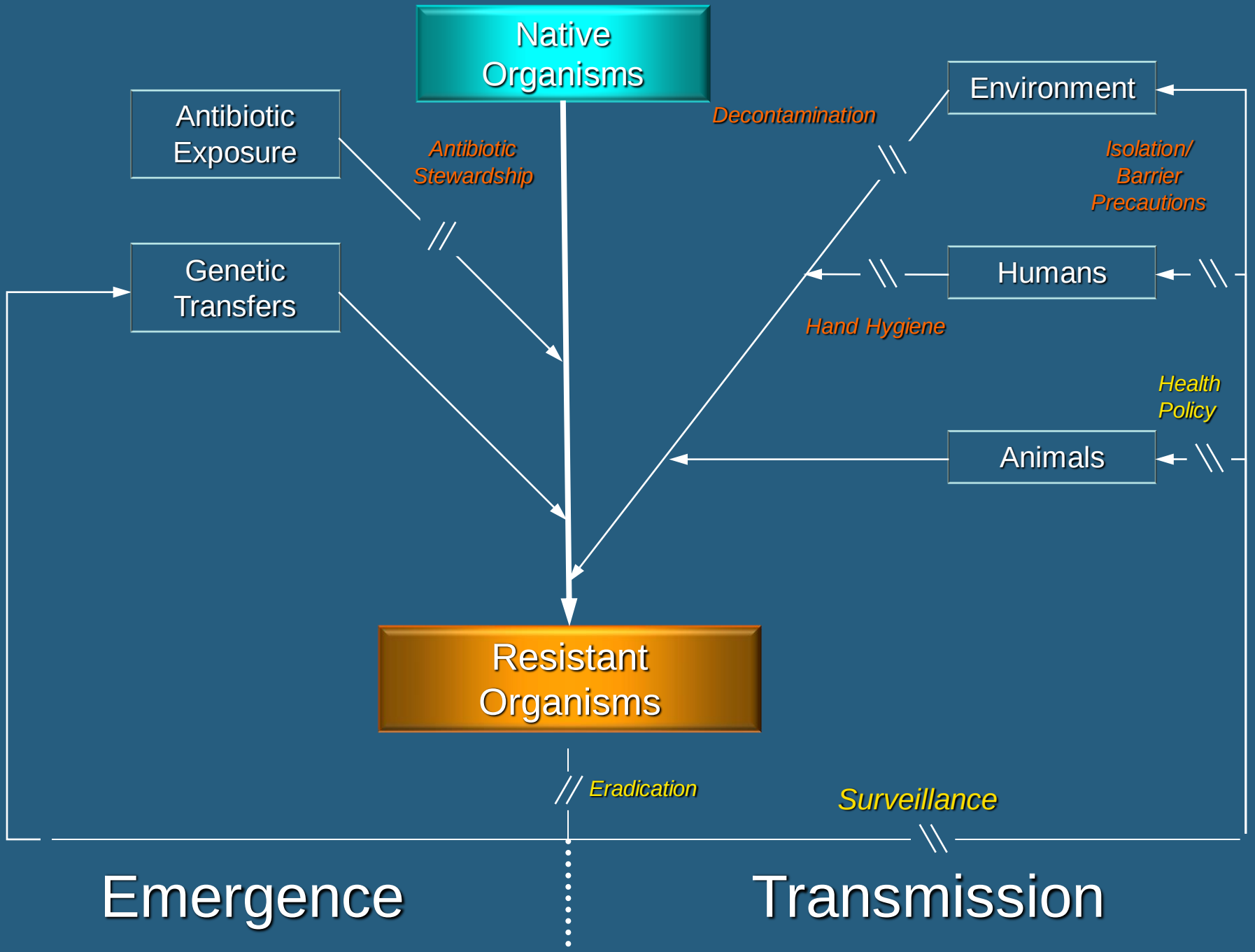
- What patients should be included in surveillance (risk assessment)?
- What strategies should be used to determine the prevalence including provincial and national of AROs?
- What sites should be used to screen
  - What is enough? number of body sites and number of rectal screens for gut AROs)
  - Are some sites more important than others (e.g. more associated with clinical outcomes)?

Surveillance/Laboratory

- What laboratory techniques are appropriate in healthcare facilities and what techniques should be deployed regionally?
- What microbiologic capabilities are needed to characterize new strains and who should have these capabilities?
- Should there be an organism repository, what types of testing should be done to monitor for emerging resistance across a large number of organisms?

Surveillance Outputs

- How effective is screening and what contextual factors affect screening?
  - Organism specific?
  - Population specific?
  - Age specific/gender specific considerations
- What metrics should be used to assess
  - screening and process measures?
  - Population based antimicrobial use?
  - Use in agriculture/animal husbandry
- What is the correct measurement to assess and analyze the impact of interventions?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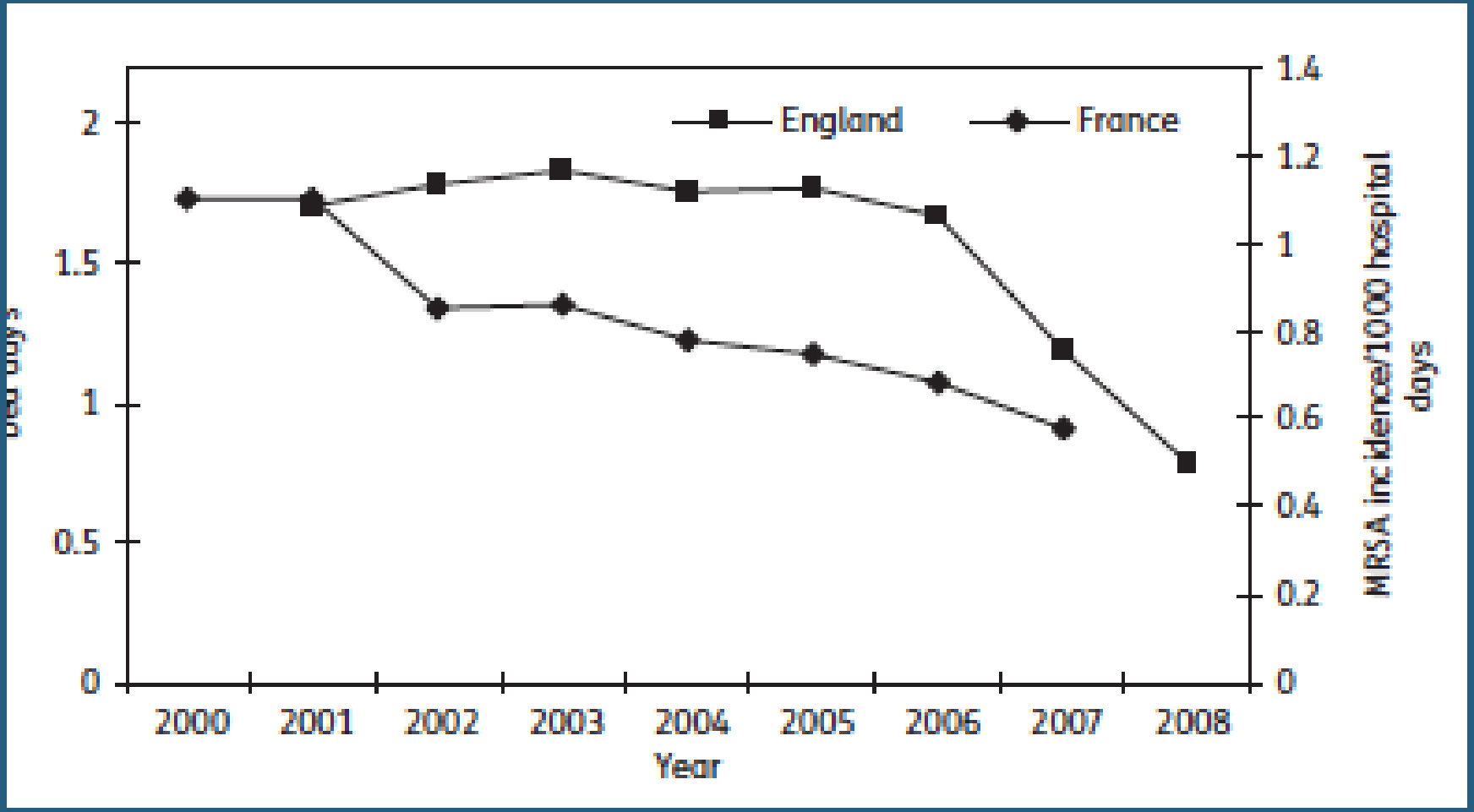
Prevention Strategies

- What “standard” and “non” standard measures are most important? Where do we get the most incremental benefit? Are these cost effective?
- Are there novel statistical techniques that can enhance the analysis?
- What are the unintended consequences of prevention strategies and can we determine if these outweigh the benefits?
- What are the best strategies to manipulate the microbiome?
- What are the consequences of manipulating the microbiome?

The War of the Roses Continues



Edgeworth JAC 2011:S41-7

The Risk of Wide Spread Antimicrobial (Mupirocin) Use

- MRSA outbreak among patients in a 625-bed public teaching hospital
- All patients found to be colonized or infected with MRSA were treated with Mupirocin and isolated. Other infection control measures not specified.
- Strains were evaluated for Mupirocin resistance

1990	2.7%;
1991	8.0%;
1992	61.5%;
1993	65%

Miller et al. 1996 ICHE;17:811-3

CHG/Mup Resistance in a NICU

- 32 hopsitalized dialysis patients and 66 hospitalizations
- CHG baths daily and 2% mupirocin to nares and exit site since 2008

Table 1. Distribution of mupirocin- and antiseptic-resistance genes by mupirocin MIC and organism type

Organism (no. of isolates)*	No. of patients†	Positive *ileS-2* (%)	Positive *smr* (%)	Positive *qacA/B* (%)
High-level mupirocin resistance (MIC ⩾512 μg ml^{-1})				
Meticillin-resistant CoNS (66)	19	66 (100)	28 (42.4)	52 (78.8)
Meticillin-sensitive CoNS (11)	9	11 (100)	1 (11.1)	6 (66.7)
MRSA (6)	3	6 (100)	2 (16.7)	6 (100)
MSSA (1)	1	1 (100)	0 (0)	0 (0)
Low-level mupirocin resistance (MIC 8–256 μg ml^{-1})				
Meticillin-resistant CoNS (10)	6	0 (0)	0 (0)	10 (100)
Meticillin-sensitive CoNS (1)	1	0 (0)	0 (0)	1 (100)
Mupirocin-susceptible (MIC <8 μg ml^{-1})				
Meticillin-resistant CoNS (9)	7	0 (0)	4 (44.4)	6 (66.7)
Meticillin-sensitive CoNS (25)	15	0 (0)	2 (8.0)	15 (60.0)
MRSA (5)	2	0 (0)	1 (20.0)	3 (60.0)
MSSA (6)	5	0 (0)	0 (0)	3 (50.0)

*CoNS, coagulase-negative staphylococci

Wee Teo et al J Med Microbiol 2013; 865-6

Costs and Cost Benefit

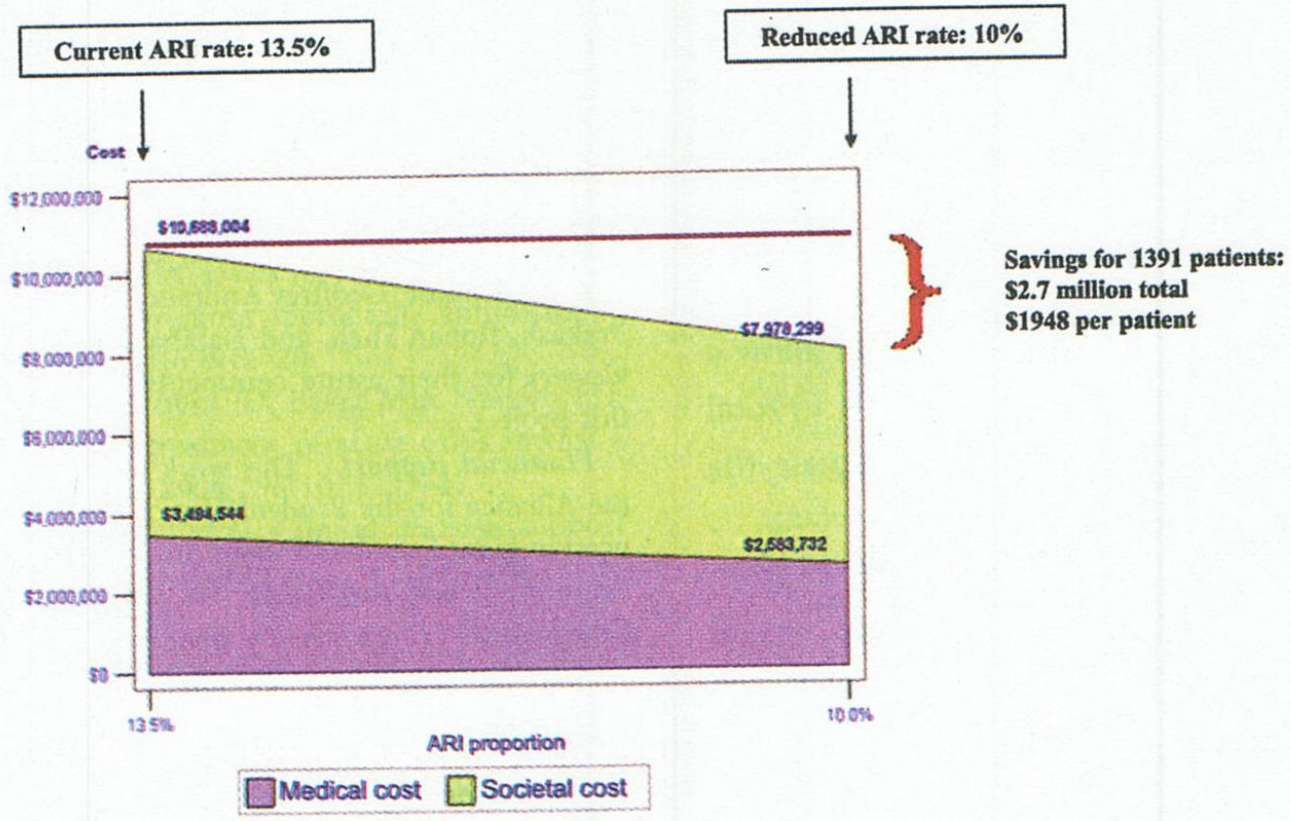


Figure 2. Projected cost savings if antimicrobial-resistant infection (ARI) rates were reduced from 13.5% to 10%.

Antimicrobial-Resistant Infection Costs- CID 2009: 1181.

Conclusions

- The ARO problem will require an international, national and provincial strategy. From a research point of view
- 1-grow the pipeline and keep it filled
- 2-use resources wisely and do not let the perfect be the enemy of the good
- Lack of consensus means the science has not been done and this requires resources!
- There are key questions in terms of surveillance, prevention strategies, laboratory diagnostics that need to be answered using a good education framework (to be defined) and cost effectively