European Federation of Pharmaceutical Industries and Associations

Development of Drugs for Eradication of Carriage

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Eradication of carriage: Context

- Nasal/gut:
  - *S. aureus, N. meningitidis, H. pylori, C. difficile,* gut flora (SDD)
- Existing country labeling:
  - nasal mupirocin: *S. aureus/*MRSA
  - oral ciprofloxacin/rifampicin: *N. meningitidis*
  - oral clarithromycin/amoxicillin/metronidazole: *H. pylori*

- Regulatory focus going forward on proven clinical benefit over and above successful eradication (draft guideline 4.2.1.5.4)
- Appropriate usage paramount in 'prophylaxis' setting

What is eradication?

- Reducing the bacterial load based on pre and post-therapy matched cultures
  - key focus: short-term highest risk periods or intermittent use in people with ongoing risk (dialysis)
  - not total eradication / not proven PCR negativity
  - makes most biological sense and is what has been linked with reduced infection rates
  - transient phenomenon - know that re-colonisation can occur

Issues: *S. aureus* nasal eradication

- Premise: *S. aureus* nasal carriage is an important risk factor for infection due to *S. aureus* [1,2]

- Limited debate but conclusions from data in literature variable
- Targeting patient population and/or intervention
  - surgical, dialysis, other high risk groups
- Estimating placebo infection rates
- Impact of evolving clinical & infection control practice on infection rates
- Impact on surgical site infections only *vs*. all nosocomial infections
- Applicability of rapid diagnostic testing for early carrier identification
- Defining those at greatest risk & the unmet medical need

1. Munoz *et al*. J Hosp Inf 2008; 68: 25-31
2. Kluytmans *et al*. Infection 2005; 33: 3-8

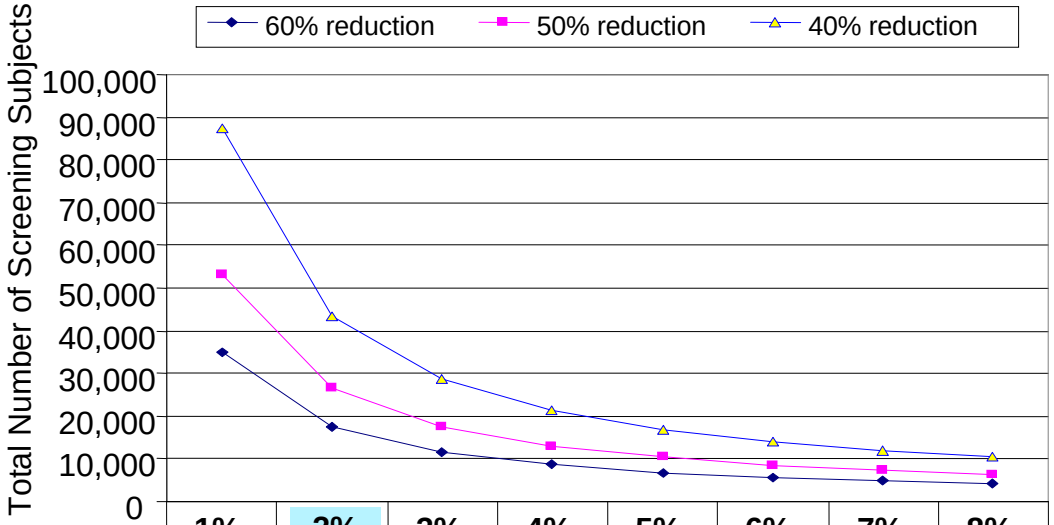
S. aureus nasal eradication

Sample size for clinical benefit are in the thousands

Scenario:

- 25% screened = nasal *S.aureus* carriers
- 2% placebo infection rate post-op
- objective: 50% reduction of infections
- 90% power, two-sided type-1 error 5%

→ 26,400 subjects required



	1%	2%	3%	4%	5%	6%	7%	8%
60% reduction	35,064	17,408	11,528	8,584	6,816	5,640	4,800	4,168
50% reduction	53,200	26,400	17,472	13,008	10,328	8,544	7,264	6,304
40% reduction	87,328	43,320	28,656	21,320	16,920	13,984	11,888	10,320

Post-surgery infection rate in placebo group

Impact: *S. aureus* nasal eradication

- Accurately defining sample size problematic, but very likely that study subject numbers to prove clinical benefit in a highly defined population unmanageable

  → will be no new agent for *S. aureus* nasal eradication

- As exogenous infection rates drop pre-op *S. aureus* colonisation is more relevant in serious, albeit increasingly rare, post-op infections
- Control of *S. aureus* remains a challenge

Summary

- Fully support appropriate antibiotic use
  - preserve existing drugs, but, new drugs are needed (e.g. mupirocin resistance, emerging retapamulin resistance)
- Nosocomial infections not solved by ‘best practice’ infection control alone
- Insistence on demonstration of clear clinical benefit → unmanageable subject numbers
- A need to rethink…. denying relevant microbiological endpoint is potentially depriving patients of new therapies

Proposal

- Can we validate well defined microbiological eradication to develop a surrogate variable as reliable predictor of clinical benefit?

- How can industry work with academia and EMA to explore and define what it would take?

  - biological plausibility
  - prognostic value from existing epidemiology for the clinical outcome
  - clinical trial data