Antibiotic Stewardship to Control MRSA: is it possible?

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Much attention is given to the rising carbapenemase problem across the globe but MRSA continues to be a major burden with few countries successful in its control. One exception is the UK where hospital strains were so prevalent at the turn of the century that their control became an important campaign factor in the government elections in 2005. At that time, major public concern about the dangers of hospital -acquired MRSA led to a national hand hygiene campaign, government funding for admission screening and improvements to hospital hygiene standards[1,2]. The general attitude to MRSA at that time was that it was a hygiene / infection, prevention & control (IPC) issue. Several high profile UK publications suggested some reduction in MRSA rates after these measures were introduced but also suggested that much of the decline was due to natural strain variation[3]. In the USA too, IPC measures and universal chlorhexidine decontamination (particularly targeting ICU patients) were introduced with some success.[4, 5, 6,] (Figure 1)

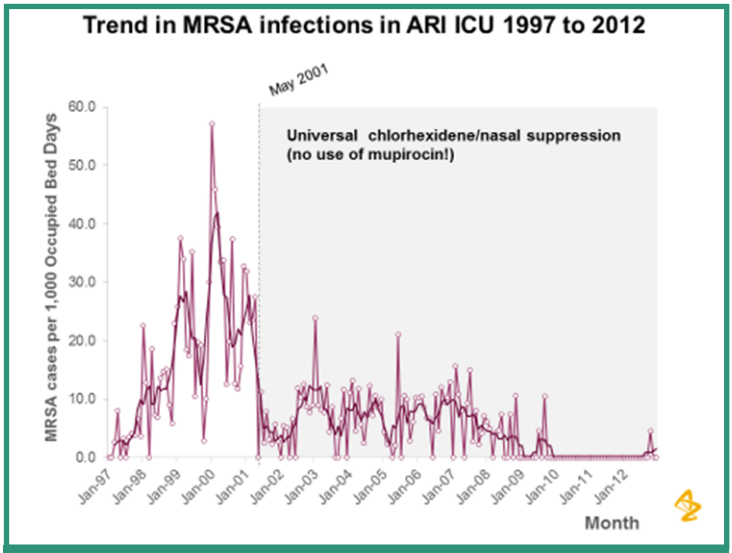

Figure 1

The real success in MRSA control in the UK came after the introduction of antibiotic restriction policies to control a nation-wide epidemic of *C. difficile*, predominately epidemic strains 001 and 027[7, 8]. These were unusually antibiotic resistant strains, resistant not only to the cephalosporins (as are all strains of *C. difficile*) but also to the quinolones and macrolides. Earlier work from our centre in Scotland demonstrated it was these antibiotic classes that were driving the MRSA epidemic which was caused by E15 and 16 and which were resistant to these agents[9]. At that time, there was no opportunity to strictly control these heavily used antibiotics. In order to address the *C. difficile* epidemic, the government restricted cephalosporins and quinolones, which resulted in a > 50% drop in usage. The macrolides, clindamycin and co-amoxiclav were also variably restricted. Small reductions in MRSA rates due to hand hygiene campaigns and screening were rapidly magnified and the epidemic strains were controlled in 2009 – 10 (Figure 2). To date, these strains have not been replaced in hospitals or the community, despite the cessation of routine universal admission screening which has been replaced by risk assessment based screening. Hand hygiene is however, strictly audited. Cephalosporin restriction is being maintained although the use of other restricted agents has increased, often to pre-restriction levels of use (Figure 3).

Most of the data that enables us to be very confident of the reasons for the successful control of MRSA in North-East Scotland comes from more than 20 years' worth of antibiotic resistance / use data. The same phenomena may be evident elsewhere in the UK, but other antibiotic resistance / use databases are less complete. Our early ICU intervention [Fig 1] with chlorhexidine bathing commenced in 2001 and was successful in controlling E16, which had its epicentre in the ICU. This was soon replaced however, by E15 in the rest of the hospital. Recently we stopped ICU chlorhexidine bathing (unless patients screen positive for MRSA) as we have seen a build-up of QAC genes linked to AMR on mobile elements in epidemic strain of *S. epidermidis*, which is a worrying feature[10].

Analysis of antibiotic use data has allowed us to establish non-linear associations with resistance and the identification of thresholds of consumption, as originally postulated by APUA's founder, Stuart Levy[11]. It is apparent that there are no safe prescribing levels of cephalosporins in relation to MRSA. Reasonable levels of quinolone, macrolide and co-amoxiclav prescribing can be maintained even in the presence of resistant epidemic strains [7,12]. It is only when prescribing thresholds are exceeded that it is cost effective for carriage of the key resistant genes that give strains survival value. Thresholds were also identified for (a) bed occupancy (more than 80% was a tipping point for increased MRSA), (b) proportion of patients screened on admission, (c) number of MRSA patients admitted, (d) length of stay and

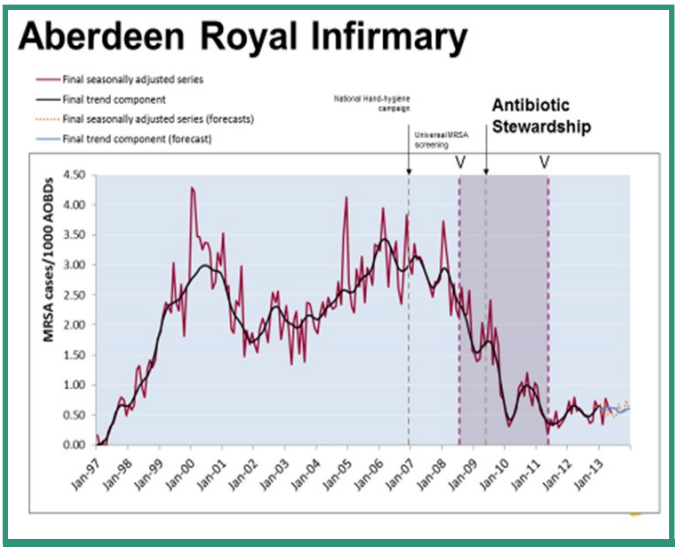

Figure 2

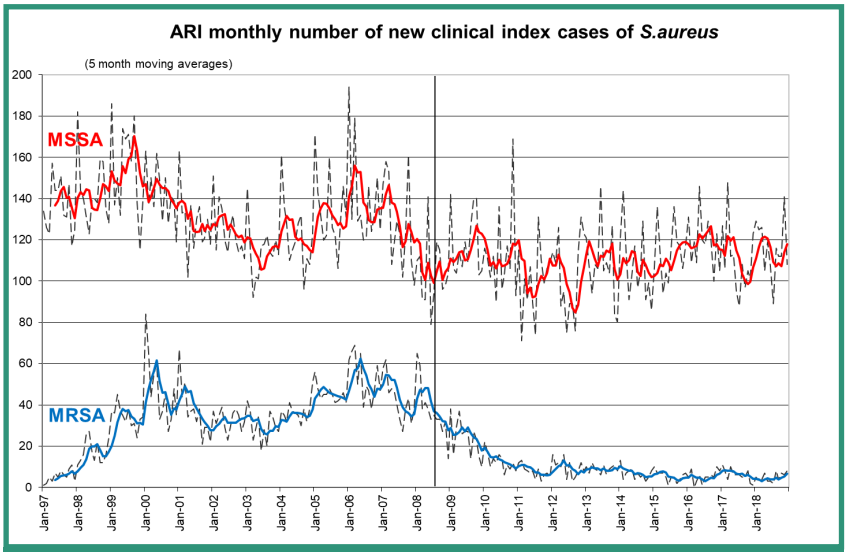

Figure 3

(e) levels of hand hygiene gel use. Antibiotic use thresholds vary with several factors e.g. susceptibility of patients (older patients require lower thresholds of antibiotic use to control epidemic strains of MRSA and *C. difficile*).

Success in MRSA control has not needed much resource; there was no use of molecular screening methods or expensive publicity campaigns. It simply requires government oversight and committed senior hospital management; co-ordination by existing IPC and AMS teams. Total antibiotic use was not reduced. Rather, substitution of key drug classes with gentamicin, cotrimoxazole, tetracyclines and narrow spectrum penicillins enabled more diversity in prescribing with limited increase in resistance to these agents. Additionally, there has been reduced mortality, not least from the control of MRSA bacteraemia. Given the well-known human and economic costs of MRSA[13, 14] why doesn't the world make more of an effort to control it? Control is not expensive. Moreover, epidemic strains of MRSA don't usually replace MSSA, but are an additional burden of infection. Outside Northern Europe, hospitals commonly cite MRSA rates of 50%, implying a doubling of *S. aureus* infections. This is certainly worth addressing!

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