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Outbreaks of infection with methicillin-resistant *Staphylococcus aureus* on neonatal and burns units of a new hospital

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SUMMARY

Multiple introductions of methicillin-resistant *Staphylococcus aureus* (MRSA) strains occurred to a new hospital in Hong Kong. Two years of clinical microbiological surveillance of the resulting outbreaks was combined with laboratory investigation by phage and antibiogram typing, and plasmid profiling. The outbreaks on the special care baby (SCBU) and burns (BU) units were studied in detail, and colonization of staff and contamination of the environment were investigated. MRSA were spread by the hands of staff on the SCBU, where long-term colonization of dermatitis was important, but were probably transmitted on the BU by a combination of the airborne, transient hand-borne and environmental routes. Simple control measures to restrict hand-borne spread on the SCBU were highly effective, but control was not successful on the BU.

INTRODUCTION

> ... the harvest of disease is reaped in hospitals far removed from that in which it was sown and by different medical hands.
>
> Hutchinson, 1959 [1].

Hutchinson made these remarks about neonatal and maternal infections with the 'hospital staphylococcus', but they are equally applicable today to cross infection with methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA were first described shortly after the introduction of methicillin to clinical practice [2]. During the next decade large, sporadic outbreaks occurred particularly in Europe [3]. Fewer problems were reported in the 1970s, a period described by Shanson as the 'decade of "complacency"' [4], but outbreaks have increased in frequency worldwide since the late 1970s. East Asia has not escaped [5] and there have been reports of international cross infection from the region [6, 7]. In Hong Kong hospitals almost a third of *S. aureus* isolates are resistant to methicillin and these strains cause invasive infections as well as innocuous colonization [5, 8, 9].

Casewell [10] has reviewed recent epidemics of multiply resistant staphylococcal infection in the West, drawing parallels between the requirements for control of

these outbreaks today and those applied to the 'hospital staphylococcus' in the 1950s and 1960s. Eradication of MRSA, particularly 'epidemic strains', from hospitals generally requires a prompt response and dedicated isolation facilities [11]. Effective general guidelines for control of MRSA have been published [12, 13] but these may not be applicable in detail to individual units, or to less medically advanced countries where the selective response proposed by Spicer [14] may be more appropriate.

The Prince of Wales Hospital (PWH) is a new regional and teaching centre of 1400 beds serving the new town of Shatin in the eastern New Territories of Hong Kong. Phased opening began in May 1984 with many patients taken over from the care of other hospitals. The PWH became fully operational in September 1985 with over 2500 discharges and deaths per month [5]. The hospital includes a full range of specialist services, but has cramped wards, few single rooms, no areas with controlled ventilation and no dedicated isolation unit. MRSA were first detected in August 1984, and organisms and epidemiological information have been collected prospectively since then.

We have compared the origin and progression of MRSA outbreaks on the special care baby unit (SCBU) and the burns unit (BU) during the first 2 years of the hospital's operation. We describe the results of staff and environmental screening, and assess the impact of infection control procedures.

METHODS

Microbiology

Staphylococcal isolates were tested for coagulase (tube method) and DNAase production, and considered to be resistant to methicillin if a heavy inoculum on unsupplemented Mueller–Hinton agar incubated for 18 h at 30 °C produced no inhibition zone around a 10 μg methicillin disk (Oxoid, Basingstoke, England) [15]. All MRSA were saved on nutrient agar slopes at room temperature. Antimicrobial susceptibilities were determined by agar dilution as described previously [16]. Plasmid DNA was extracted according to the method of Dunkle and Sippel [17] and was electrophoresed in a 0·9% agarose gel as described previously [5]. Selected isolates were typed with standard and experimental phages by the Staphylococcus Reference Laboratory, Central Public Health Laboratory, Colindale, London, UK.

Patient epidemiology

In this study each distinct type of MRSA isolated from each patient was counted only once and is referred to as a 'patient-isolate'. On the SCBU the nose, throat, umbilicus, ear and rectum were screened on admission. On the BU, burns and anterior nares were swabbed on admission and twice weekly thereafter. All other isolates came from specimens taken for clinical diagnostic reasons. Infection Control Nurses collected information about affected patients from laboratory records and ward visits. The data were entered to a microcomputer database and entries were verified and updated by laboratory medical staff. One of us (M.F.) reviewed the case notes after discharge of the first 199 affected patients. Culture results, previous hospital stays within the past 3 months, antibiotic treatment,

percentage of body area burned, dates and wards of transfer within the PWH and dates of discharge were recorded. Statistical analysis was by the Wilcoxson Rank Sum Test (2-tailed).

Screening for MRSA

Cotton tipped swabs moistened with sterile peptone water were used for screening nurses and medical staff. Anterior nares were sampled by rotating the swab firmly three times in each nostril. To sample hands the swab was rubbed over both palms, between all fingers, then over each fingertip. Swabs were transferred to bijoux bottles containing 2 ml broth (Nutrient broth no. 1, Oxoid) containing 5% sodium chloride and 10 mg/l methicillin. The bijoux bottles were incubated at 37 °C for 48 h before subculture to blood and cysteine-lactose-electrolyte-deficient (CLED) agars which were incubated at 37 °C for 48 h. The selective broth supported multiplication of inocula of about 10 colony-forming units of both HK1 and HK2 strains of MRSA (therefore sampling bias in favour of strains showing greater methicillin resistance in salt media in the presence of methicillin is unlikely). Air sampling was performed by exposing 9 cm blood agar settle plates on the floor of busy ward areas for 2 h, and similar plates were used for contact-sampling of surfaces.

Control measures

Recommended control measures for most areas of the hospital generally followed those of the joint Hospital Infection Society and British Society of Antimicrobial Chemotherapy working party [13], but full compliance was impossible because of limited isolation facilities and inadequate funding. In the early summer of 1985 it became clear that the areas with the highest incidence of MRSA transmission were the BU and SCBU and that serious sepsis as well as colonization was occurring [5], therefore it was decided to concentrate efforts on these areas [14].

Control measures on the BU. The BU consists of 12 beds in six double rooms with shared washing facilities. All staff on the ward were screened at least once and environmental specimens were taken in May and July 1985. From May 1985, patients were segregated in single rooms with closed doors where possible, but the Infection Control Nurses supervised cohorting of colonized patients when the ward was more than half full. Regular cleaning of the ward with phenolic disinfectants was encouraged, and the Infection Control Team held teaching seminars for all ward staff. Staff removed outer clothing and donned cotton gowns before entering the unit. Gowns were laundered daily. Before entering patient rooms, staff put on paper masks and added another cotton gown, supplies of which were kept separately for each patient. Disposable gloves were worn if the patient or his bedlinen was to be touched, and handwashing with chlorhexidine gluconate soap between each patient was encouraged.

Control measures on the SCBU. Opening with 15 cots in May 1984, 52 cots were available on the SCBU by October 1984. When the SCBU was fully operational in July 1985 there were 104 cots available in two wards subdivided into high and low dependency areas, with extensive sharing of staff and equipment. At this time there were about 400 live births per month at the PWH.

The SCBU environment was screened in late July 1985, and all staff were screened on four occasions between July and December 1985. There was a shortage of trained nursing staff, and cohorting of colonized staff or patients was not possible. Hand hygiene was taught during seminars from the Infection Control Team and regular visits from the Infection Control Nurses. From the beginning of August 1985, pump dispensers of chlorhexidine hand lotion (1% chlorhexidine digluconate in isopropyl and ethyl alcohols with skin conditioners; 'Hexol', Sigma Pharmaceuticals PTR Ltd, Victoria, Australia) were made available within each room in the SCBU and staff were encouraged to apply it between every patient contact.

RESULTS

Course of the hospital outbreak

After the first introductions of MRSA to the PWH in August 1984, there were between 1 and 3 patient-isolates per month until February 1985 when there was a progressive rise to a mean of about 25 per month, which is about 1% of admissions [5]. A total of 373 patients was colonized or infected with MRSA during the hospital's first 2 years of operation; 9021 patients were transferred to the PWH directly from other hospitals or nursing homes. Only 14 MRSA isolates came from patients attending the outpatient clinic, all of whom had been previously hospitalized. During this period 27% of total discharges and deaths on the BU and 3·8% on the SCBU were affected.

Thirty-one (16%) of the first 199 affected patients at the PWH had been inpatients at other hospitals within the previous 3 months and 74 (37%) had received antibiotics before MRSA was detected. Only one of the first 22 MRSA from the BU came from a patient who had been in another hospital within the previous 3 months, but 12 (55%) affected patients had received topical or systemic antibiotics prior to detection of MRSA. The mean percentage burned area of the 22 patients was 16% (range 2–60%). Eight (17%) of the first 48 patient-isolates from affected babies in the SCBU had been born by caesarean section (a rate similar to that for caesarean births in the hospital as a whole), 8 (17%) had been transferred to PWH from other hospitals and 14 (29%) had received antibiotics prior to the isolation of MRSA.

The plasmid profiles of consecutive epidemiologically linked isolates from the same ward, of repeat isolates from the same patient, and of the same isolates retested after up to 18 months of laboratory storage were stable. MRSA of plasmid type HK1 contained a large plasmid of 18–25 MDa and one of 2·8 MDa [5]. A few similar isolates, containing extra smaller plasmids or lacking the large plasmid, were allocated to types HK1A to J. HK1 commonly was lysed by the standard phages 29, 77, 84 and 85, and an experimental phage, and was usually resistant to gentamicin and either erythromycin and tetracycline or sometimes chloramphenicol. HK2 contained a large plasmid of 17–27 MDa with a trio of small plasmids of about 1·7, 1·6 and 1·35 MDa. Subtypes of type 2, HK2A to F, lacked one or two of these plasmids. HK2 was not usually phage typable and was consistently resistant to gentamicin, erythromycin, tetracycline and chloramphenicol, and sometimes to trimethoprim. Organisms were found with a

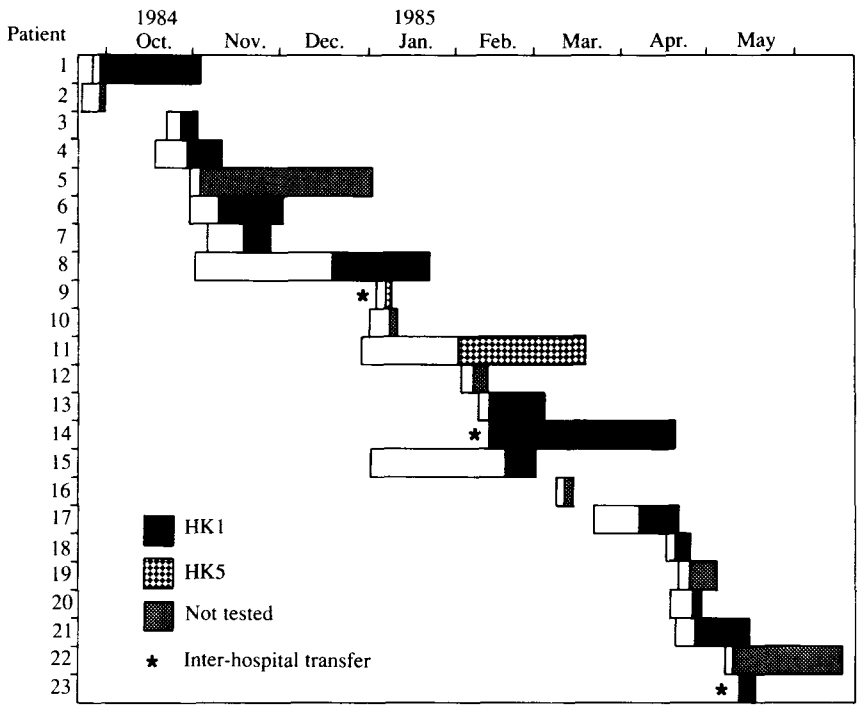

Fig. 1. MRSA outbreak on SCBU: September 1984 to June 1985 (cases 1–23).

variety of other plasmid profiles and were designated arbitrarily to types HK3, HK3A to C, HK4 and HK5, which were associated with a great variety of phage reactions and antibiotic resistance patterns. Because of variations in antibiotic sensitivity patterns and the delay inherant in referring organisms abroad, antibiograms and phage reactions were less useful for solving epidemiological problems during the outbreak than plasmid typing. We are now performing additional genetic and phenotypic tests that may further discriminate between or group the arbitrary types.

Outbreak on the SCBU

This outbreak (see Fig. 1) began at the end of September 1984, 5 months after the unit opened, with two isolates (one type HK1, one died before typing) from babies born at PWH. Therefore we assume the organisms were acquired from another carrier baby who was not detected, from a staff member or possibly from a maternal carrier. Three infants colonized early in the outbreak (numbers 1, 3 and 7 in Fig. 1) were transferred to other post-natal wards. Shortly after transfer of two of these cases, outbreaks of type HK1 began on their new wards. Baby 7 transferred to postnatal ward 7E where type HK1 strains subsequently replaced type HK3 organisms that had been prevalent before. Infant 9 was transferred to the SCBU from another Hong Kong hospital probably carrying a distinct strain of plasmid type HK5 and phage type 6 which was apparently acquired by infant 11 but did not spread further. No strains of type HK2 were seen on the SCBU during the study period.

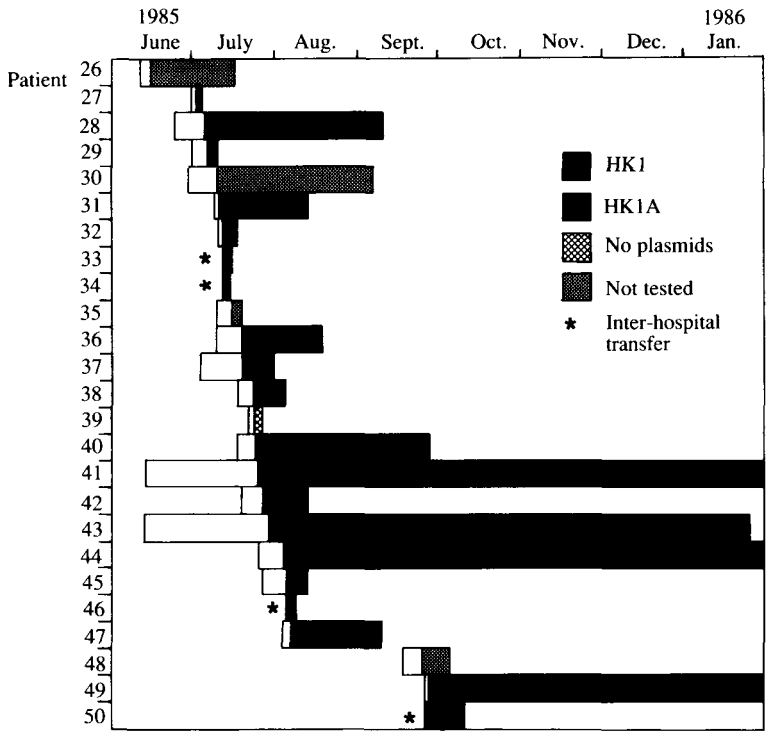

Fig. 2. MRSA outbreak on SCBU: June 1985 to January 1986 (cases 26–50).

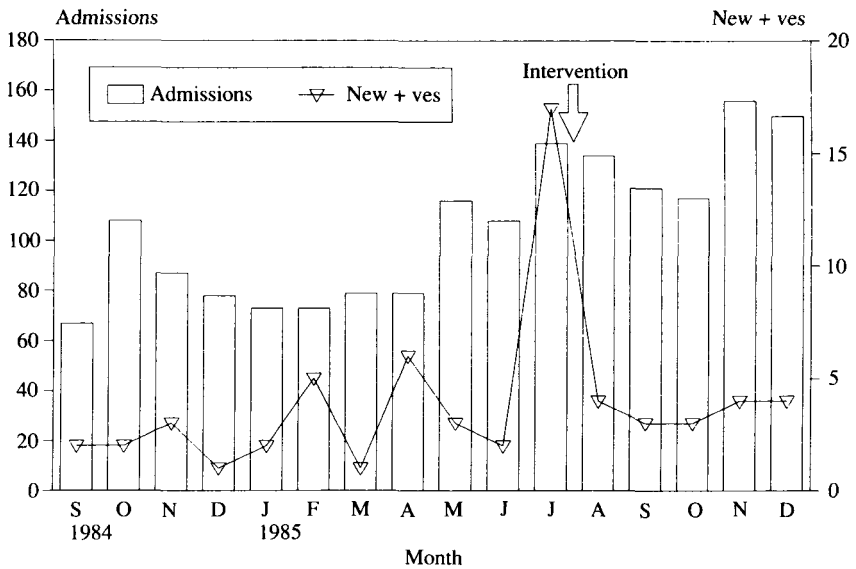

Fig. 3. Monthly admissions and new MRSA-positive cases on SCBU (September 1984 to December 1985).

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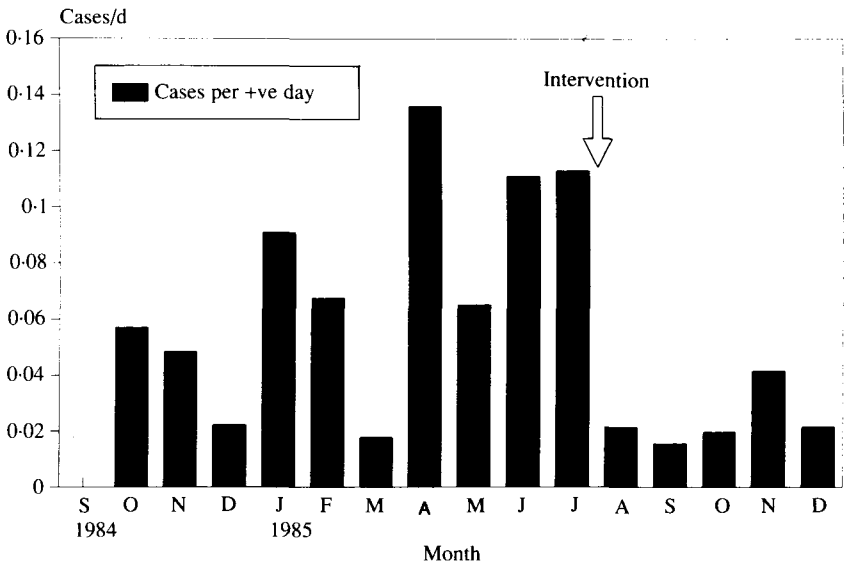

Fig. 4. MRSA transmission rate on SCBU corrected for pressure driving transmission. (Vertical axis = number of new MRSA acquisitions divided by total number of days spent by MRSA positive babies during each month.)

New isolations continued at a rate of just below three per month until July 1985 when a marked increase was seen, and several long-stay babies became colonized (babies 41, 43, 44 and 49, Fig. 2). Figure 3 shows the number of admissions to the SCBU per month from September 1984 to December 1985 and the corresponding numbers of new patient-isolates. The acquisition rate fell after intervention in August 1985. Figure 4 illustrates for each month the number of new acquisitions divided by the total number of days spent on the unit by babies who were known to be MRSA positive during that month. The means of these rates for periods of 10 months before (0·0729) and 5 months after (0.0241) intervention are significantly different ($P = 0·013$). Thus encouragement of optimal hand hygiene, and removal from work of members of staff with only long-term colonization, were highly effective at reducing transmission. This occurred despite the presence of long-stay, MRSA positive neonates, and without therapy or cohorting of staff with transient nasal colonization, and in the face of increasing numbers of admissions. Eradication was not achieved, and isolations of type HK1 (with occasional strains of type HK1A or HK1G) continued throughout 1986 and 1987 at a similar relatively low rate.

Outbreak on the BU

Two months after the BU opened, the first isolates of MRSA of type HK1 were made from three patients admitted directly from home (Fig. 5). Patients 2 and 3 carrying type HK1 strains were transferred to an orthopaedic ward against the wishes of the Infection Control Team and, soon after, another patient on the orthopaedic ward acquired MRSA of type HK1. Patient 4 carrying a distinct strain of type HK5, phage type 6/42E/81, was transferred from the orthopaedic ward to the BU, but no transmission of HK5 was seen on the BU.

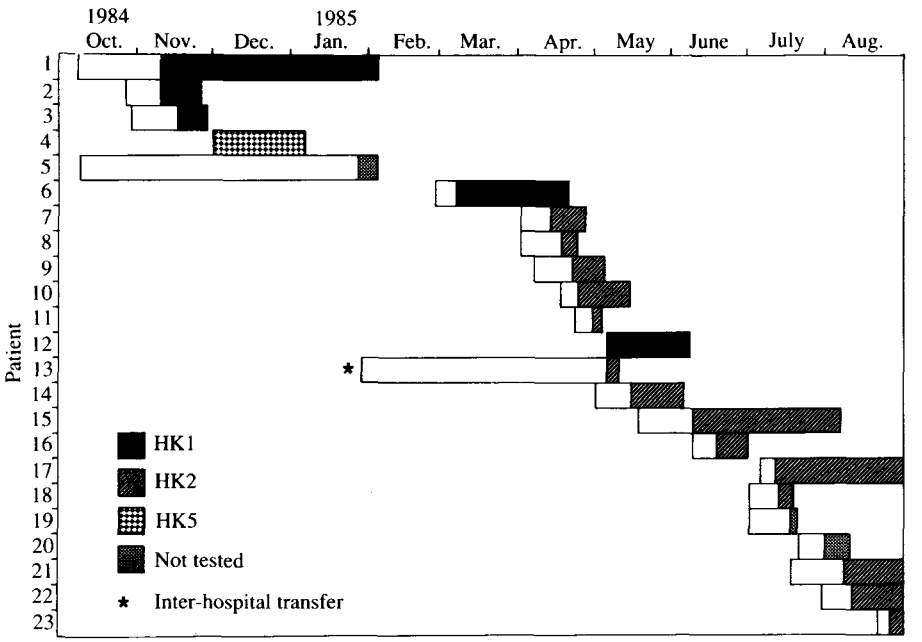

Fig. 5. MRSA outbreak on Burns Unit: November 1984 to August 1985.

For the first 6 months there was a low rate of transmission of MRSA within the BU with a mean of 1·2 new cases per month. The introduction of type HK2 (first isolated from a patient admitted directly from home in April 1985) allied to a steadily increasing workload was followed by a marked acceleration in the isolation rate of MRSA on the BU, and by a replacement of type HK1 strains with HK2. Thus, of the 24 strains investigated after April 1985, 23 were type HK2; the other strain was of type HK1 (case 12 in Fig. 5) isolated from a patient transferred to the BU from a paediatric surgical ward within PWH where two babies carrying HK1 had recently been admitted from the SCBU.

Control measures instigated on the BU in July 1985 had no demonstrable effect on the rate of transmission of MRSA.

Staff and environmental screening

Special care baby unit. Of 108 staff members screened on at least one occasion, 9 (all nurses) were positive. Seven of these nine were screened during shifts when they were working with babies known to be colonized. In five instances the carriage was nasal only and MRSA was not present on re-screening without treatment in 5–7 days. No attempt was made to clear carriage in these nurses. Screening in July 1985 revealed three nurses with persistent carriage in the anterior nares and on dermatitis of the hands. One other nurse had transient carriage at both sites with normal skin; immediately before screening she had been working with two colonized babies and she was negative in three screens over the next 2 months and continued to work without treatment. The other nurses were offered a clearance regimen, but one of these left the PWH before treatment and the other two moved on to other units within the hospital before post-treatment

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screening was completed. Subsequent screens did not reveal hand or persistent nasal carriage in any staff member. The only positive environmental sample of 50 sites sampled was the interior of the incubator of a neonate known to be carrying MRSA.

Burns unit. Of 22 BU staff screened at least once, MRSA was grown only from the hand swab of one physiotherapist who had been working with a colonized patient and had not washed her hands. Two subsequent screens from this subject were negative without treatment. No staff were noted to have dermatitis or other lesions. Samples from a nurse's gown, and settle plates from inside and outside colonized patient's rooms were positive for MRSA.

DISCUSSION

Typing methods useful for investigating outbreaks of MRSA include use of an extended set of phages [18] and a variety of electrophoretic techniques [19]. Plasmid profiling is the easiest and most rapid procedure but may not be ideal for long-term studies because of plasmid loss in some isolates [19]. We, however, found the method to be discriminatory, reproducible and to have a high typing capacity for MRSA in Hong Kong where other typing methods are not easily or rapidly available [5]. In the PWH, MRSA of our arbitrary type HK1 was the predominant isolate from the SCBU, whereas the majority of strains from the burns unit and orthopaedic wards were of type HK2 or 2A. A territory-wide survey in October 1985 confirmed these associations with similar units throughout Hong Kong hospitals [9]. The propensities of different plasmid types to spread on different wards are unexplained, but could be due to strain variations in survival after drying in the environment [20] or on the hands [21].

Transmission on the SCBU

Over 20 years ago, American workers studied transmission of *S. aureus* in a neonatal nursery and found acquisition from the hands of attendants to be much more common than airborne spread (see [22] and references quoted therein). Strict handwashing reduced the rate of transmission to a low level explicable by the airborne route alone. Although these experiments were performed with methicillin sensitive *S. aureus*, the results may well apply to MRSA strains on neonatal units today.

Michel and Priem in Holland described the first neonatal outbreak of MRSA [23], but more recently reports have appeared from special care baby units in several European countries and America [24–36]. Epidemiologically most of these outbreaks have been similar to that at the PWH, with single strains implicated and transfer of colonized neonates to local referral centres being the commonest route of introduction.

We found 5 of 108 SCBU staff to have dermatitis of the hands, probably resulting from frequent handwashing [37]. The lesions of four of these were found by broth enrichment culture to be colonized with MRSA. In contrast, although colonization of paronychias [28] and psoriasis [24] has been described, prolonged carriage of MRSA by neonatal unit staff has not usually been thought to be common or of major importance, but enrichment culture was not used in most

studies. The importance of optimal hand hygiene for controlling MRSA on the SCBU was recently emphasized by Reboli and co-workers [34]. Environmental contamination of special care baby units is very uncommon, but MRSA has been isolated from the air near colonized infants [27, 36] and faecal carriage may promote aerial dissemination [38].

Control measures on the SCBU

In common with our experience, others have found closure of neonatal units impossible because of the lack of alternative ventilation facilities [26, 28], and cohorting of colonized babies and staff has been found to cause considerable disruption [17, 24, 33]. Bathing with hexachlorophane was highly effective in neonatal outbreaks of the 'hospital staphylococcus' [39] and has been used in recent MRSA outbreaks [28, 33, 34]. However, worries over hexachlorophane's toxicity limit its use, and there is little experience with mupirocin in neonatal outbreaks. Increased staff workload promotes staphylococcal cross infection on neonatal units [40], therefore we did not recommend staff to apply topical antiseptics to babies at the PWH. The only modifications we made to routine practice were use of an alcoholic hand rub that does not dry the skin, and removal from duty of staff with long-term MRSA carriage. The result was a significant reduction in the rate of colonization of new babies without disruption of the work of the unit; MRSA were not eliminated, but there was little more we could do with the resources available.

Calculation of the 95% confidence interval of the measured infection rates [41] is not applicable to the results of intervention on the SCBU because there were only limited prior data to compare, and increasing numbers of babies were admitted. After removal of persistently colonized staff members, colonized neonates are presumably the most important source of staphylococci, therefore the allowance made for numbers and duration of stay of carrier infants on the SCBU per month (Fig. 4) should correct for the variable pressures driving staphylococcal transmission and hence provide a measure of the true effects of changes in infection control practice.

Transmission on the BU

Burned patients have been the primary source of MRSA outbreaks in many hospitals [42–49]. The largest outbreaks have apparently occurred in burns wards without single room isolation or controlled ventilation. Permanent eradication has proved expensive of resources and requires a well-designed burns unit which is closed until all colonized patients are discharged, terminal disinfection, and continuing vigilance for new potential carriers [6].

In contrast to the primacy of hand-borne transmission on neonatal units, dissemination of *S. aureus* between burned patients has been shown to occur both via direct contact with staff and by the airborne route [50]. Environmental contamination has also been implicated [6, 51], but its relative importance is unknown. The concentration of staphylococci settling from the air of patient's rooms depends on the size of their burns, and transmission may occur on staff clothing [52]. Although burns treated at the PWH were relatively small, ventilation of the unit was poor which may have increased the relative

contribution made by airborne spread, and nurses' gowns were contaminated.

There is contradictory published evidence of the importance of long-term MRSA carriage by burns unit staff [44, 45, 47, 48, 53–56], but our study and that of Baird [48] with broth enrichment and several others with direct plate inoculation [44, 45, 54–56] found infrequent carriage of MRSA in such staff. However, even one nurse with persistent hand carriage may infect many patients [44]. Prolonged nasal carriage of MRSA in staff members has been associated with colonized skin lesions [11, 57] and this may overcome the natural barriers to persistent replacement of an individual's native staphylococcal strains [57–59]. Few studies, however, have clearly distinguished between transient or prolonged nasal carriage, or recorded skin lesions, therefore it is difficult to assess the value of attempting clearance or removing nasally colonized staff from duty. It would be prudent to do so for staff with skin lesions.

Epidemic strains of MRSA are often assumed to have enhanced colonization abilities, but antibiotic resistance *per se* is not a marker for extreme transmissibility of staphylococci [60]. Thus, spread of resistant strains may be favoured if antibiotics are widely used [61] and sensitive ones may prevail if antibiotic usage is strictly controlled [62]. Two strains of MRSA predominated successively on the BU at the PWH and over half the colonized patients had received systemic or topical antibiotics before MRSA was detected. It may be possible to influence staphylococcal outbreaks on burns units by manipulation of antibiotic pressures. However, heavy environmental contamination by MRSA is the rule on burns units if they lack adequate isolation facilities, and it is likely to be the major source of persistence in the absence of prolonged staff carriage. We isolated MRSA from socially clean horizontal surfaces on the BU (despite regular cleaning with phenolic disinfectants) and from staff gowns (despite regular laundering), and demonstrated transmission out of patients' rooms. Presumably any reduction we were able to effect in hand-borne dissemination was overwhelmed by spread from the air and environment, and even rigid control of antibiotic usage would be unlikely to have influence under these conditions.

CONCLUSIONS

The epidemiology of MRSA transmission is not identical on all hospital units, therefore application of selected control measures to individual areas may be effective in some circumstances. A selective approach may be particularly valuable in the many parts of the world where MRSA are endemic and resources scarce. We found plasmid profiling to be useful in the investigation of locally important routes of transmission of MRSA in a hospital without easy access to phage or other typing methods. At the PWH this enabled simple, non-disruptive intervention to be used with success on the SCBU. By contrast, our failure to control the outbreak on the BU is to be expected on any unit where poor hospital design limits any possible influence of infection control measures.

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