Epidemiology of *Staphylococcus aureus* bacteremia in Denmark from 1957 to 1990

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Objective: To investigate the changes in epidemiology of *Staphylococcus aureus* (SA) bacteremia in Denmark over a 30-year period, where the population has remained stable.

Methods: Bacteriologic and clinical data were generated on 17 712 SA strains from virtually all SA bacteremia cases in Denmark from 1957 to 1990 submitted to our laboratory for phage typing. The data were related to information about population, hospital activity and blood-culturing activity during that period.

Results: SA bacteremia cases increased from 3 to 20/100 000 inhabitants per year, with the largest increases in incidence rates for the <1-year and >50-year age groups. While blood-culturing activity increased three-fold during the period, the rate of SA bacteremias actually decreased relative to the number of blood cultures taken. The increase in SA bacteremia cases was mainly due to increases in nosocomial infections for all age groups and was related to the increasing admission rates to Danish hospitals. Major shifts in antibiotic resistance patterns and phage types took place during the period, i.e. a marked reduction in multiresistant (including methicillin-resistant) strains, but could not explain the change in the epidemiology of the infections.

Conclusions: The data indicate that increases in SA bacteremia rates correlated significantly with increasing numbers of admissions to hospitals. The main increase in SA bacteremia rates was represented by nosocomial infection, although increasing blood-culturing activity during the period may have contributed.

Key words: *Staphylococcus aureus*, bacteremia, epidemiology, blood culture

INTRODUCTION

Staphylococcus aureus (SA) has remained one of the most important pathogens encountered in the clinical microbiology laboratory, as exemplified by the frequency of its isolation in blood cultures from patients of all age groups. SA has constantly been reported among the top three pathogens in this respect [1–7]. The severity of the disease that SA can cause is illustrated by reviews of SA bacteremia in the pre-antibiotic era, where the case-mortality rate was over 80% [8]. SA bacteremia associated with endocarditis, pneumonia or meningitis still carries a high mortality in spite of treatment with antibiotics active against the infecting staphylococci in vitro [9–11]. Methicillin-resistant SA strains (MRSAs) have emerged as pathogens which are causing increasing concern among all specialities involved in infection control, and these bacteria caused considerable problems during the 1960s and the 1970s in several European countries and in Australia [12,13]. The incidence of MRSAs among SA bacteremia strains was higher than 40% during the peak of the epidemic experienced in Denmark in the late 1960s [14,15]. The serious consequences experienced from the spread of these bacteria in the Danish hospitals prompted the need for typing systems, reliable susceptibility testing and registration of cases, which was centralized in the Staphylococcus Laboratory at the Statens Serum

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Institut, the central institution for diagnosis and control of infections in Denmark.

The continuing registration of bacteriologic and clinical data concerning SA bacteremias from all over Denmark since 1957 has made it possible to study various aspects of these infections. The purpose of the present study is to illustrate the changing epidemiology of SA bacteremia in Denmark during the last three decades and provide data on nationwide incidence rates in different age groups.

MATERIALS AND METHODS

The Staphylococcus Laboratory receives more than 25 000 SA isolates for phage typing from various human sources from all over Denmark every year. Among these strains are virtually all blood culture isolates, now over 1000 cases per year. Clinical information is obtained in all cases, and the data, including age, sex, complicating disease, focus of infection and mortality, are stored in a computerized database. The bacteriologic data include the phage type [12,16,17] and the antibiotic susceptibility as reported from the referring laboratory and retested by a tablet diffusion assay [18] or a disk pre-diffusion method [19] at the Staphylococcus Laboratory. All bacteremia strains have been stored in the lyophilized state or at −80°C since 1957.

The present study comprises the bacteriologic and clinical data generated from 17 712 strains from the same number of episodes from the period 1957–1990, both years included. An SA bacteremia case was defined as the finding in a blood culture of one clinically significant strain of SA, i.e. in the presence of signs of infection such as fever, chills, focal symptoms of inflammation, elevated leukocyte count, and left shift in differential leukocyte count. Contaminants were defined as SA bacteria isolated from blood cultures in small numbers (e.g. in one of three cultures from a blood specimen) with no signs of relevant illness. All cases of suspected/proven contamination with SA were excluded from the database.

The cases were assigned to the categories community acquired and hospital acquired by consideration of clinical data, including the time of onset of illness.

Data concerning the blood-culturing activity in Denmark during the period were obtained from the departments of clinical microbiology all over the country, including the universities in Copenhagen and Aarhus and the Statens Serum Institut. Reliable data were available from 1965 to 1990. Since different blood culture systems had been used, both the number of cultures (sets of two or three cultures per blood specimen) and the estimated volume of blood cultured were calculated. During the first period of 20–25 years, the common blood culture system all over Denmark was drawing blood into a tube via an airtight rubber stopper. After arrival at the laboratory, the blood was distributed by pipettes into 12 containers of beef broth, semi-solid serum broth or thioglycollate broth. In recent times most laboratories have changed to bottle systems, where the blood is directly inoculated into the bottle. While the older system was slower, the same volume of blood was drawn for culture as in the modern systems. The different systems were therefore considered equally sensitive with regard to SA bacteremia. No appreciable changes in the diagnosis of SA have taken place during the 30-year timespan. Population data, including the annual number of inhabitants in 10-year age groups from 1957, were obtained from the National Bureau of Statistics (Danmarks Statistik). Hospital activity data, including the annual number of hospital admissions and number of bed-days from 1965, were obtained from relevant publications from the Danish National Health Board (Sundhedsstyrelsen). Admission rates and bed-days included all Danish hospitals and clinical departments except for psychiatric departments or institutions.

Statistical methods

The relation of different counts or rates to time was calculated by least-squares linear regression with P-values <0.05 (two-tailed) considered significant. Comparison of slopes of regression lines was performed by analysis of co-variance (F-test). The incidence rate was calculated as the number of SA bacteremias (by age group) per year divided by the number of inhabitants for the same year and same age group.

RESULTS

Figure 1 illustrates the changes in the Danish population and hospital activity data since 1965. The Danish population has remained very constant at approximately 5 million inhabitants/year. The hospital admission rate, in contrast, increased steadily from *c.* 600 000/year in 1965 to almost 1.1 million in 1990. The mean number of bed-days in Danish hospitals peaked at more than 9 days in 1978, decreasing to about 7.5 days in 1990. Figure 2 depicts the actual number of cases per year as well as the incidence rate (no. of cases/100 000 inhabitants/year) of SA bacteremia in Denmark from 1957 to 1990. There has been a steady increase in both rates, with an almost 10-fold increase during the 33-year period. In the 5 years after 1990, more than 1000 cases/year of SA bacteremia from all over Denmark were reported.

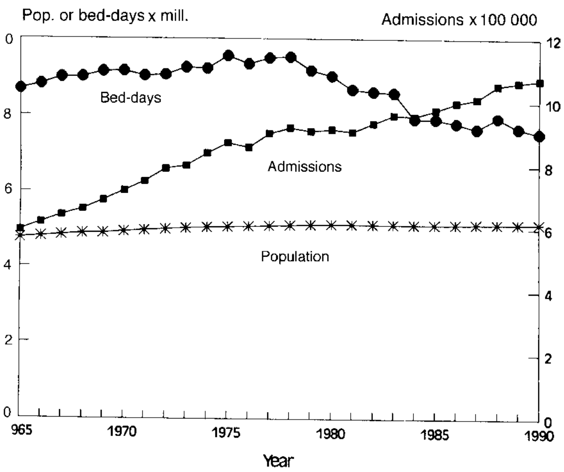

Figure 1 Annual rates for number of inhabitants (population) (left ordinate), number of admissions to hospitals (right ordinate), and average number of bed-days in all hospitals (left ordinate) from 1965 to 1990 in Denmark.

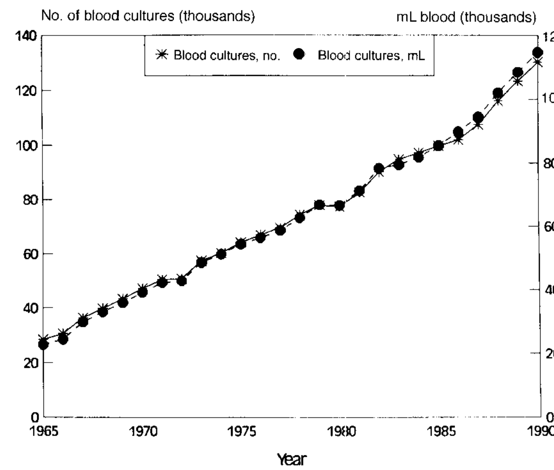

Figure 3 Total number of blood cultures (left ordinate) and corresponding volume of blood cultured (right ordinate) in Denmark from 1965 to 1990.

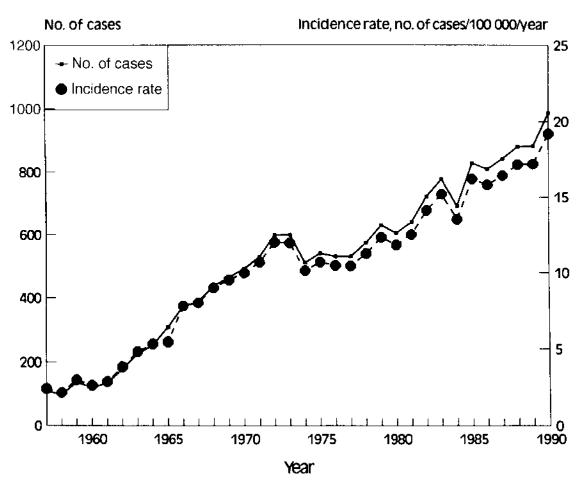

Figure 2 Total annual number of SA bacteremia cases (left ordinate) and incidence rate (right ordinate) from 1957 to 1990 in Denmark.

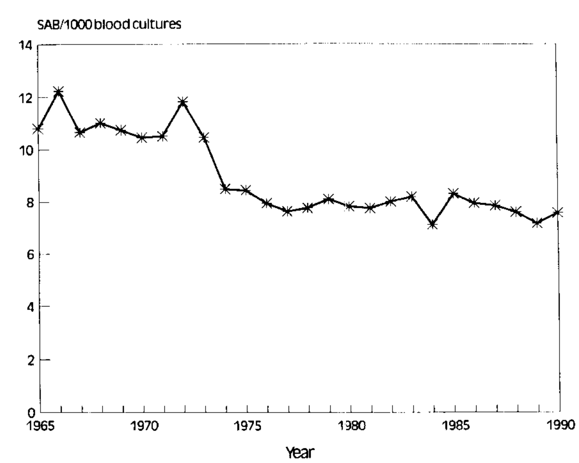

Figure 4 Relative rate of SA bacteremias (SAB) to total number of blood cultures taken in Denmark from 1965 to 1990.

A possible explanation for this major increase in SA bacteremias could be the escalation in blood-culturing activities known to have taken place during the period in question. The blood-culturing activity in Denmark from 1965 to 1990 is illustrated in Figure 3. The curves are almost identical whether number of blood cultures or volume of blood cultured is calculated. The figure shows that the number of blood cultures increased four-fold from 1965 (*c.* 30 000 cultures/year) to 1990 (*c.* 130 000 cultures/year). Significant correlation was present for the rate of blood cultures/1000 admissions with year from 1965 to 1990 (blood cultures/1000 admissions=7.17 × year − 409.9; R=0.993, P<0.000001) as well as for the two other parameters (blood cultures/100 000 inhabitants=2.56 × year − 114.3; R=0.989, P<0.000001, and blood cultures/100 000 beddays=51.97 × year − 3158; R=0.977, P<0.0001, respectively). Figure 4 shows the number of SA bacteremias per 1000 blood cultures performed, by year from 1965 to 1990. There was a negative linear correlation for this rate versus time, which was highly significant, i.e. SA bacteremia/1000 blood cultures=

$-0.178 \times \text{year} + 362.47$; $R = -0.86$, $P < 0.0001$. This decrease in the relative number of SA bacteremias in spite of increasing blood-culturing activity shows that the increase in SA bacteremias cannot be explained by increasing blood-culturing activity. However, the four-fold increase in numbers of blood-cultures taken was higher than the less than two-fold decrease in the rate of SA bacteremias/1000 blood cultures, suggesting that the number of cultures did in fact artifactually increase the bacteremia rate. Although the ratio of SA bacteremias/admissions showed a significantly positive correlation with time (SA bacteremias/1000 admissions$=0.091 \times \text{year} - 172.6$, $R=0.727$, $P<0.0001$), the rate of SA bacteremias/1000 admissions increased slowly from 0.5 to 0.9 in the 25 years from 1965 to 1990, indicating that the increasing incidence of SA bacteremia could be related to the increasing admission rate. There was a poor linear correlation of annual rate of SA bacteremia with the annual mean number of bed-days in Danish hospitals (data not shown).

The SA bacteremia data were further broken down according to gender. The overall male/female ratio was almost constant during the whole period and averaged 1.2 (data not shown).

Figure 5A–D shows the age-related incidence rates of SA bacteremias in Denmark from 1957 to 1990. There was a large increase in the rates for the <1-year age group (Figure 5A), increasing six- to seven-fold in

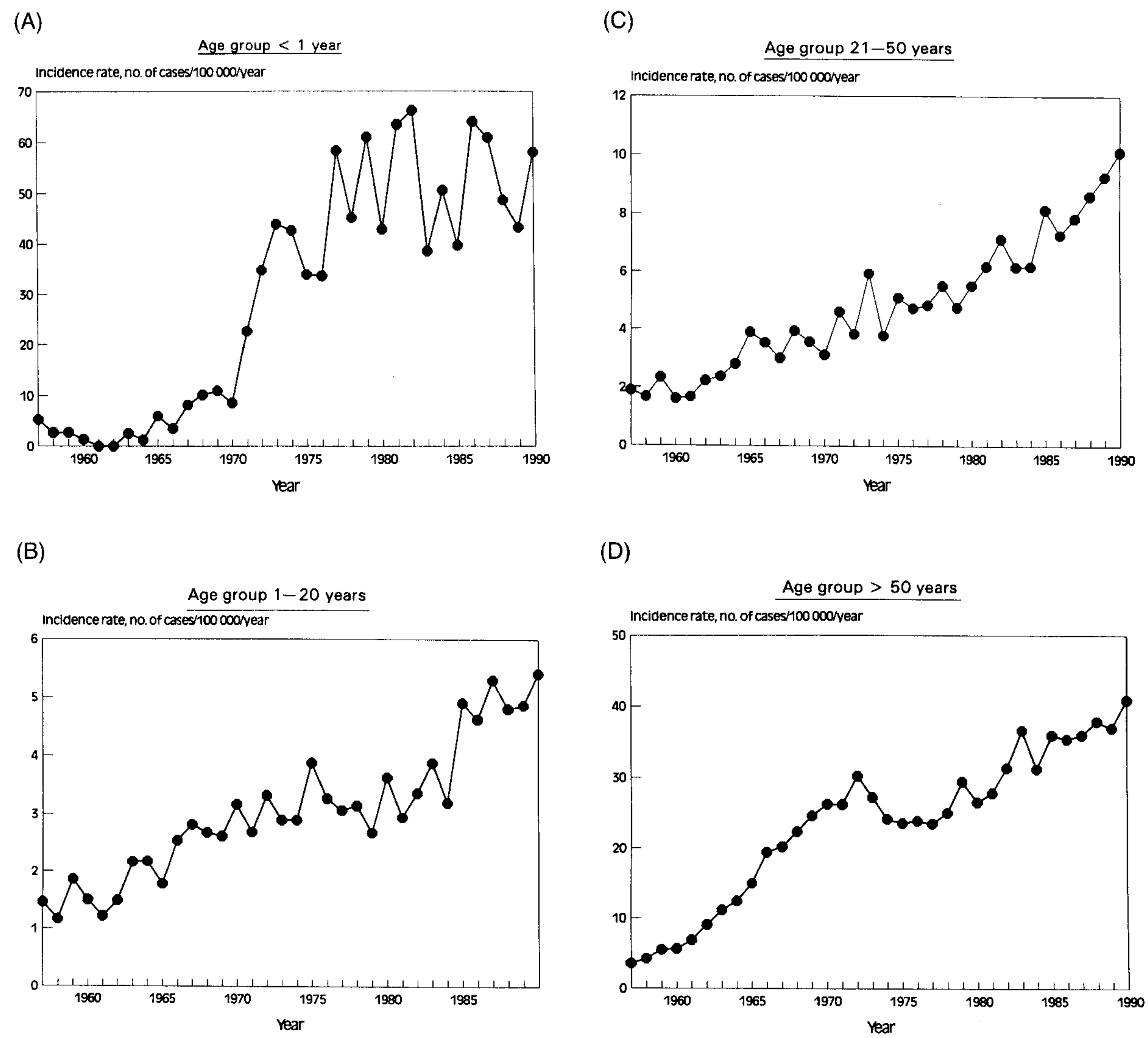

Figure 5 Age-related incidence rate of SA bacteremia from 1957 to 1990 in Denmark for the following age groups: (A) age group <1 year; (B) age group between 1 and 20 years; (C) age group between 21 and 50 years; (D) age group >50 years. Please note the different *y*-axis scales in the four figures.

the 5-year span from 1970 to 1975, thereafter leveling off at an incidence rate of 40–65 cases/100 000. There were more constant or steady increases in the rates for the three older age groups. The incidence rates were lowest in the 1–20-year age group (Figure 5B: 2–5/100 000), with only a three-fold increase in the annual or incidence rates during the 33-year period, while the increases in the rates were four- to five-fold in the 21–50-year age group (Figure 5C) and 10-fold in the >50 age group, respectively (Figure 5D). Apart from the earlier years until 1962–63, the relative proportions of the age groups of SA bacteremia cases remained constant during the period, as shown in Figure 6.

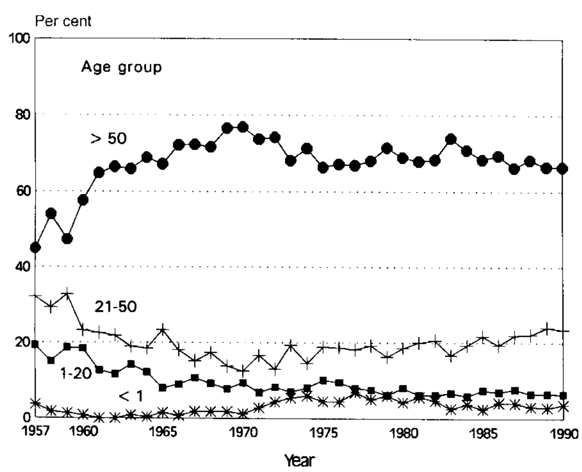

Figure 6 Relative proportion (in per cent) of the four age group: <1 year, 1–20 years, 21–50 years and >50 years, respectively, among all SA bacteremia cases for each year from 1957 to 1990 in Denmark.

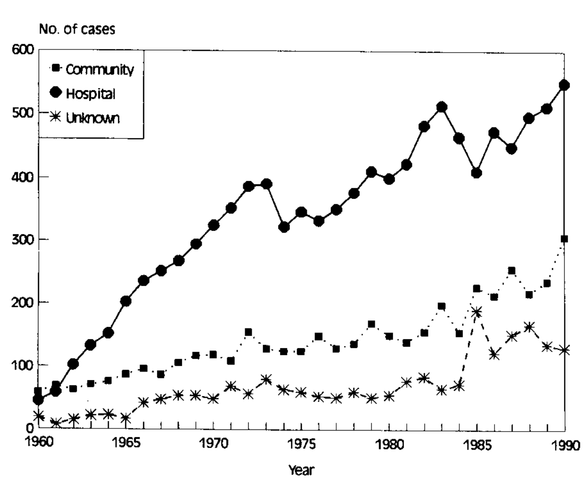

Figure 7 Total Danish SA bacteremia cases according to origin of infection, i.e. community acquired, hospital acquired or unknown, from 1960 to 1990.

One of the major reasons for the overall increase in SA bacteremia cases during the period is revealed in Figure 7, which shows the data for origin of infection for all cases, and in Figure 8, which illustrates the age-related origin of infection. For all cases (Figure 7), as well as for all age groups except the 1–20-year age group (Figure 8A–D), it is evident that the major reason for the increases in the annual rates of SA bacteremias was the increase in hospital-acquired cases, while the community-acquired cases have remained constant or have increased only slowly. The importance of hospital-acquired cases was most evident in the <1-year age group (Figure 8A) and the >50-year age group (Figure 8D), where hospital-acquired cases represented the majority of cases of SA bacteremias.

Major shifts in phage types of SA took place during the 33-year period (data not shown). Most marked was the epidemic during the 1960s and 1970s of strains of the 83A complex, which also carried the determinants for multiple antibiotic resistance, including methicillin resistance. After 1970, major increases were seen for strains of phage type 95, of the 94/96 complex and of group II. However, none of these shifts in phage-type patterns could explain the change in epidemiology of SA bacteremia in that period.

The major trends in antibiotic resistance of SA from bacteremia cases with regard to penicillin, methicillin, tetracycline, streptomycin and erythromycin during the 33-year period are illustrated in Figure 9. The methicillin and multiple resistance occurred mainly among strains of the 83A complex, as mentioned above. Multiple resistance faded out with the disappearance of the resistant strains of that phage-type pattern during the 1970s, and the last 20 years have seen a steady increase in penicillin resistance only, while MRSAs now constitute about 0.1% of SA strains. No difference between hospital-acquired and community-acquired infections has been found regarding antibiotic resistance patterns (data not shown).

DISCUSSION

We are unaware of any previous publication supplying information such as that provided in the present study regarding the epidemiology over more than three decades of virtually all SA bacteremias experienced in an entire population. The data in this study are interesting from several viewpoints. The period under scrutiny, from 1957 to 1990, has been a time of major developments in the healthcare system and in particular in the hospital sector, as illustrated by the steady

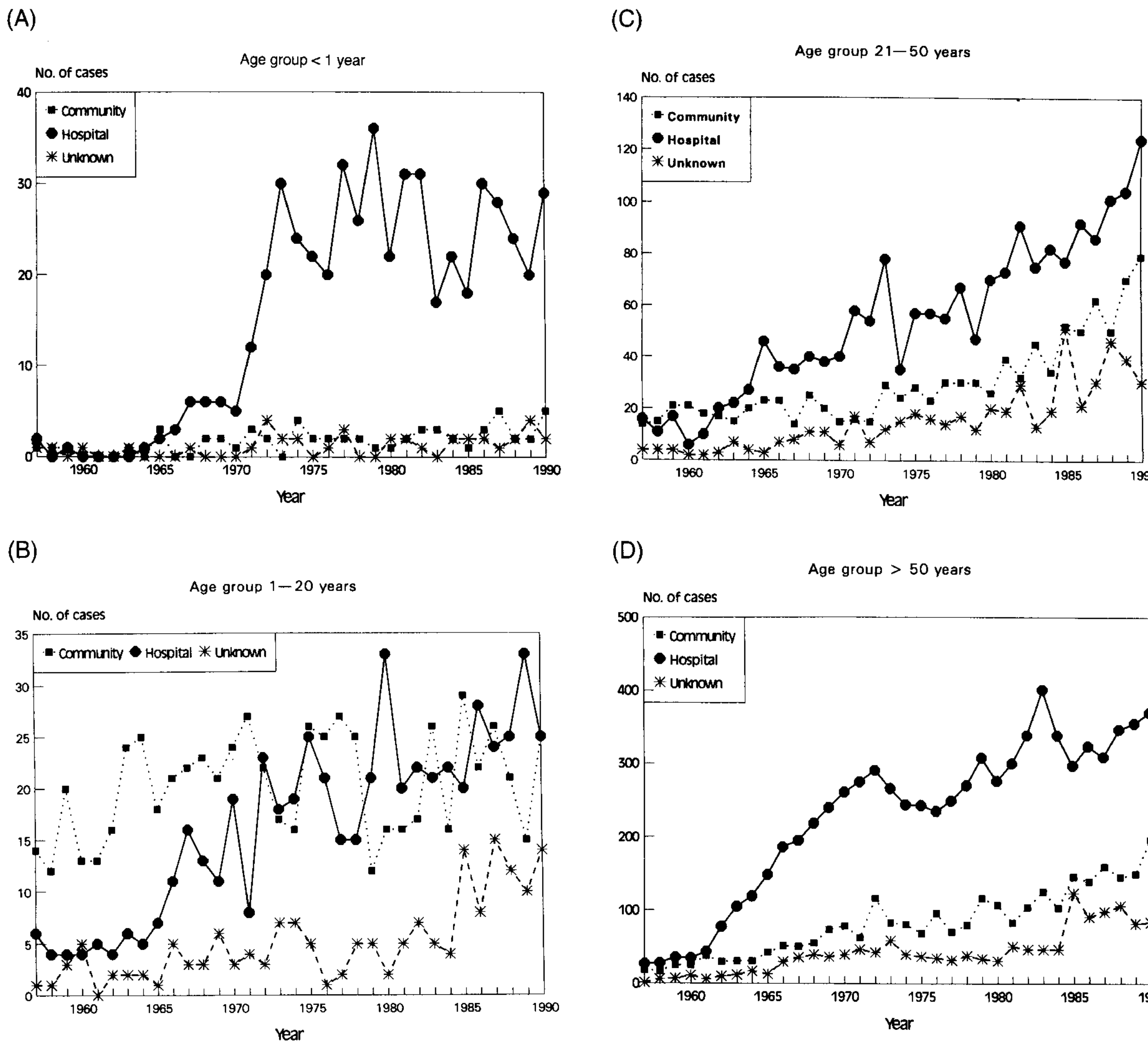

Figure 8 SA bacteremia cases according to age group and origin of infection. (A) age group <1 year; (B) age group 1–20 years; (C) age group 21–50 years; (D) age group >50 years. Please note the different *y*-axis scales in the four figures.

increase in admission rates to Danish hospitals during the whole period (Figure 1). This period saw major changes and improvements in a number of therapeutic areas, including surgery (e.g. transplantation, cardiac surgery), internal medicine, oncology, intensive care and pediatrics. The use of intravenous catheters was developed from the 1960s and onwards, and a number of other uses of implants and indwelling catheters were introduced later. An indicator of increased diagnostic activity in hospitals was the increasing number of blood cultures taken. The number of local clinical microbiology laboratories in Denmark increased from three in 1960 to 17 in 1990. The blood culture has become almost a standard ritual in any patient with fever, and in this respect it is interesting that the rate of SA bacteremias actually decreased relative to the number of blood cultures used. This indicates that the increase in SA bacteremias was not due to the increasing number of blood cultures being taken; rather, there might be an overuse of blood cultures. Regrettably, we have little information on the total rate of positive blood cultures during the period to substantiate this point.

Splitting the data into age groups showed that the very young and the older age groups (Figure 5) had experienced the major increases in staphylococcal infections. Since the relative proportions of age groups were constant during the period (Figure 6), the increasing rate of SA bacteremias in the various age groups must be connected with external factors. We have not been able to detect a particular reason for the

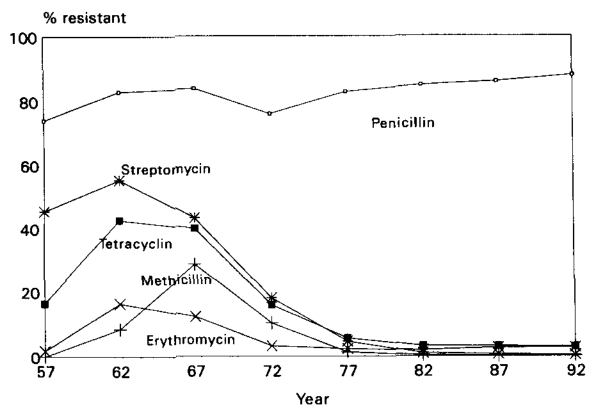

Figure 9 Distribution (in per cent of total) of SA bacteremia strains according to resistance to penicillin, methicillin, streptomycin, erythromycin and tetracycline.

rapid increase in the incidence rate of SA bacteremias during the 1970s for the <1-year age group. A previous detailed review of this group of patients revealed that the majority were below 1 month of age [20] and the focus of infection was often related to medical activity such as blood sampling by heel puncture, intravenous catheter access or operations. We have speculated that the reason for the increase was the more intensive and aggressive approach to investigation and treatment of neonates in maternity wards and the survival of smaller neonates [20].

Further proof of the role of hospitalization in the increase in the incidence of SA bacteremia comes from the fact that the great majority of cases were hospital acquired (Figures 7 and 8), in particular in the youngest and oldest age groups. The most frequent type of staphylococcal infection seen in the 1–20-year age group is hematogenous osteomyelitis, which usually develops outside hospital [21], explaining the high proportion of community-acquired infections in that age group (Figure 8B).

The total proportion of hospital-acquired SA bacteremias has remained around 60% since the mid-1970s (Figure 7). This change in SA bacteremia epidemiology was predicted by Jessen et al. [15], and correlates with published information about SA bacteremias in the western world during the 1970s and 1980s [22,26–29]. The rate of SA bacteremia as related to the admission rate reported from Denmark in the present study (0.54–0.92 SA bacteremias/1000 admissions from 1965 to 1990) is considerably lower than the rates reported from the USA, the UK, Spain and Sweden, i.e. 1.6–5.87 SA bacteremias/1000 admissions [3,27–30], but similar to rates reported from Israel [31], Holland [32] and Denmark [33], i.e. 0.55–0.8 SA bacteremias/1000 admissions. There could be several reasons for these differences in SA bacteremia/admission ratios; the most important is that the published data are usually from university or teaching hospitals [3,27–29] or from infectious disease departments [30], all of which may receive a higher proportion of cases with severe infections, while the data presented in this study were accumulated from all types of hospitals in the country. On the other hand, in a previous Danish study from a university hospital in Copenhagen [33], the SA bacteremia/admission ratio in 1979–80 was similar to that reported from all over Denmark in that year. Most of the cited studies report rates of hospital-acquired SA bacteremia similar to those reported in the present study [22–32]. Considerably lower rates of hospital-acquired SA bacteremia cases have been reported from the less developed world [34].

Actual SA bacteremia incidence rates based on population data as presented in this study are scarce. An incidence rate of 36 SA bacteremia cases/100 000 inhabitants could be deduced from a Swedish study of data from a 270 000 inhabitant county from 1980 to 1986 [35]. The corresponding annual incidence rates for that period in Denmark ranged from 11 to 16 SA bacteremia cases/100 000 inhabitants. A neonatal SA bacteremia incidence rate of 1.1/1000 live births from 1981 to 1985 was reported from the Karolinska hospital in Stockholm [36]. The incidence rate for the <1-year age group for the corresponding years from Denmark was 0.3–0.6 SA bacteremia cases/1000 (Figure 5A). Although major changes took place in the relative roles of different phage types of SA during the three decades from 1960 to 1990 in Denmark, and these changes correlated with changes in antibiotic susceptibility of the SA strains (Figure 9), they did not convincingly correlate with the general epidemiologic trends in SA bacteremia reported in this study. The changes in phage types have, to some extent, been related to changes in the use of antibiotics. The disappearance of methicillin-resistant SA during the 1970s, related to the decline in phage type 83A, is believed to be due to reduction in the use of broad-spectrum antibiotics such as tetracycline and streptomycin during that period and increased attention to infection control measures [14,37–41]. However, the increase in the rate of hospital-acquired cases of SA bacteremia continued, while multiresistant strains disappeared, whereas the contrary would have been expected. Furthermore, in the Danish experience, there have for a number of years been no differences in the phage types or antibiotic susceptibility between SA strains acquired in or outside hospitals [42]. These facts, together with the close relationship between admission rates and SA bacteremia rates, leads to the conclusion that the increase in SA bacteremia rates seen during the last 20 years is closely connected to the increase in hospital admissions and activity seen during these years which have increased the risk of infection with SA carried by the patient and probably present before admission to the hospital [43]. The increasing use of intravascular catheters as an explanation for increasing rates of SA bacteremia has been noted by others [20,22,23]. An increase in SA carriers among the patients might also explain the increased SA bacteremia rates reported. We have, however, no good data from the timespan studied to enable us to evaluate this possibility.

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