continuance of injections caused a decrease in haemoglobin values as well as in red-cell counts.

Injection of serum from normal *bled* mice into normal mice caused reticulocytosis, and continued injections produced polycythaemia.

Erythropoietin produces reticulocytosis when injected into normal mice, but not in nephritic mice. The erythropoietic principle produced in the kidney, however, brings about reticulocytosis when injected into nephritic mice, but not in normal mice. From these findings it has been possible to test serum from mice as well as from human beings with regard to two different erythropoietic principles.

The titre of erythropoietin as well as that of the erythropoietic principle produced in the kidney generally increases in the anaemic patient, if the anaemia is not to be ascribed to lack of one of these principles.

No rise in the titre of the erythropoietic principle produced in the kidney has been found in anaemic patients suffering from chronic nephritis. This indicates that the lack of the erythropoietic principles produced in the kidney may be the cause of the anaemia accompanying nephritis in man.

No rise in the titre of the erythropoietic principle produced in the kidney has been found in anaemic patients suffering from chronic infection (ulcerative colitis, rheumatic arthritis). This finding has led to the conclusion that some, if not all, of the anaemias seen in chronic infections may be caused by the absence of the erythropoietic principle of the kidney.

Totally nephrectomized *bled* mice are able to increase their erythropoietin titre. This observation shows that erythropoietin is produced outside the kidney. No rise in the erythropoietin titre was found in a patient suffering from chronic hepatitis. This indicates that the erythropoietin is produced in the liver.

[ADDENDUM.—Since this paper was written sera from another five anaemic patients have been tested.

Serum from one patient suffering from pernicious anaemia gave, as expected, good reticulocyte response in normal as well as in nephritic mice (no lack of the two erythropoietic principles discussed in this paper). Serum from one patient suffering from chronic glomerulonephritis and sera from two patients suffering from chronic rheumatic infection gave good reticulocyte response in normal but no response in nephritic mice (lack of erythropoietic factor produced in the kidney). Serum from one patient suffering from chronic hepatitis gave no reticulocyte response in normal but good reticulocyte response in nephritic mice (lack of erythropoietin).

These results show complete agreement with the tests described in the paper above.]

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NASAL STAPHYLOCOCCI AND SEPSIS IN HOSPITAL PATIENTS

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The noses of healthy individuals probably form by far the largest breeding-ground for the pathogenic staphylococci, and it is known that staphylococci from the nose can be responsible for septic lesions in the same individual. This has been shown for recurrent furunculosis (Valentine and Hall-Smith, 1952), for recurrent styes (Roodyn, 1954), and for minor industrial wounds (Williams and Miles, 1949). Studies of the incidence of cross-infection in one surgical ward at St. Bartholomew's Hospital have been in progress for the past three years, and a preliminary analysis (cited by Williams, 1958) suggested that nasal carriers of *Staphylococcus aureus* suffered wound infection more often than non-carriers. This analysis was therefore extended to the records from other wards.

Materials and Methods

The results described in this paper are derived from studies in three male surgical wards (A, B, and C) and one male medical ward (D). The analyses in the first half of the paper, on the nasal carrier state of 602 hospital patients, are based almost entirely on the records from ward A, while the analyses in the second half of the paper relating nasal carriage to sepsis are derived from the 1,358 patients in all four wards.

Ward A had 25 beds; we have already described the nursing regimen (Shooter *et al.*, 1958). Ward B was of the same shape and size as ward A and the nursing practices were similar. Ward C was similar physically, but differed in that no attempt was made to isolate patients with septic lesions. Ward D had 26 beds; again patients with sepsis were not isolated. Studies were carried out during the following periods. A: September, 1956, to May, 1957, and December, 1957, to September, 1958; B: May, 1958, to April, 1959; C: January to April, 1959; and D: October, 1958 to April, 1959.

Clinical records were kept of all wounds in the surgical wards. The term "septic" was used to denote the presence of visible pus. In both surgical and medical wards a note was made of the occurrence of other septic lesions—for example, boils, otitis media, chest and urinary infections, and enteritis. In this paper only septic lesions from which *Staph. aureus* was isolated are considered.

In all the wards nasal swabs were taken from the patients on admission or as soon after as convenient. Thereafter they were taken weekly. Swabs from noses and lesions were cultivated on blood-agar, and colonies resembling staphylococci were tested for coagulase production. All coagulase-positive strains were tested for phage-type by the routine described by Anderson and Williams (1956). No more than one colony from one culture was tested unless there were obvious colonial differences. In this paper the term "*Staph. aureus*" or just "staphylococci" is used to describe coagulase-positive strains.

Carrier Rates

Altogether 38% of the 602 patients admitted to ward A carried *Staph. aureus* in their nose during the first week after admission to hospital; 13% of them carried staphylococci resistant to penicillin. There was a steady increase in the general carrier rate for staphylococci and in the rate of resistant strains in patients swabbed during their stay in hospital, so that of the patients swabbed after eight weeks in hospital some 70% carried *Staph. aureus* in the nose and half carried penicillin-resistant strains (Table I). It is clear from Table I

TABLE I.—Nasal Carrier Rates for *Staph. aureus* During Stay in Ward

Week	No. Patients	No. (and %) Carrying <i>Staph. aureus</i>		
		Penicillin-resistant	Penicillin-sensitive	Total
1	602	80 (13)	150 (25)	230 (38)
2	399	81 (20)	95 (24)	176 (44)
3	221	67 (30)	48 (22)	115 (52)
4	132	48 (36)	28 (21)	76 (58)
5	86	34 (40)	15 (17)	49 (57)
6	47	18 (38)	9 (19)	27 (57)
7	34	15 (44)	6 (18)	21 (62)
8	25	13 (52)	4 (16)	17 (68)
9	19	10 (53)	4 (21)	14 (74)
10	11	6	1	7
11	9	4	2	6
12	6	3	—	3
13	4	1	—	1
14	4	2	—	2

that the greater part of the increase in carrier rate could be accounted for simply by acquisition of penicillin-resistant staphylococci in the ward. Of the patients who were non-carriers on admission 30% had acquired resistant staphylococci by the third week in hospital, compared with only 18% of those who carried sensitive strains on admission (Table II).

TABLE II.—Acquisition of Penicillin-resistant *Staphylococci* in the Nose

Carrier State in First Week	No. of Patients	Cumulative Percentage* Acquiring Resistant Strains on or Before Week			
		2	3	4	5
No <i>Staph. aureus</i> ..	372	16	30	46	54
Penicillin-sensitive <i>Staph. aureus</i> ..	151	10	18	25	25

* Percentage calculated on life-table basis to give the proportion of original entrants who would be expected to have become carriers in the specified weeks, based on the experience of the patients then still in the ward.

Almost half of the 173 patients who had two or more positive nasal cultures showed a change in the drug sensitivity or in the phage type of the staphylococcus they carried. Of 30 patients whose staphylococci showed a change in penicillin sensitivity, only 3 appeared to have retained a staphylococcus of unchanged phage-type; 24 showed definite differences in the phage-pattern, 2 had untypable strains, and in 1 one of the strains was not tested for phage-type.

There were 353 patients who had two or more nasal swabs and who were not carrying penicillin-resistant strains in the first week (Table III); 98 acquired a

TABLE III.—Acquisition of Penicillin-resistant *Staphylococci* in the Nose in Relation to Antibiotic Treatment

Carrier State in First Week	No.	Patients Acquiring Penicillin-resistant Strains in Ward		Patients Not Acquiring Penicillin-resistant Strain	
		Total	No. Given Antibiotic	Total	No. Given Antibiotic
No <i>Staph. aureus</i> ..	250	77	52 (42)*	173	63
Penicillin-sensitive <i>Staph. aureus</i> ..	103	21	12 (12)	82	38
Total ..	353	98	64 (54)	255	101

* In parentheses, number given antibiotic before acquisition of the resistant staphylococcus.

penicillin-resistant staphylococcus in their nose, in 54 cases after having had antibiotic treatment. Altogether 165 patients had antibiotic treatment, and 64 of them acquired a resistant strain.

The number of patients carrying tetracycline-resistant staphylococci in any one ward was rather small; to study them we have therefore used the material from wards A, B, and C. Altogether 39 patients acquired tetracycline-resistant staphylococci in their noses, but only 7 of them had had tetracycline treatment; 11 other patients were treated with tetracycline but were not observed to become nasal carriers of resistant strains. Of 14 patients who carried a sensitive strain when first swabbed and later acquired a tetracycline-resistant staphylococcus all but two also showed a clear change in phage-type. In one there was a change of doubtful significance, and in a second there was no change in type but other carriers of resistant strains of the type were present in the ward at the time.

Sepsis

Altogether we had records of 1,358 patients, 722 of whom had surgical operations. Seventy-six (5.6%) of the patients developed some infective lesion due to staphylococci during their stay in hospital; 60 (4.4%) had some lesion other than wound sepsis; and 34 (4.7%) of those having operations developed post-operative wound sepsis. Eighteen patients had both wound sepsis and some other staphylococcal lesion.

Post-operative Wound Sepsis

The incidence of staphylococcal wound sepsis was lower in patients who never yielded staphylococci from the nose during their stay in hospital than it was in patients who were found to be carriers (Table IV). Of the 342 patients who were not nasal carriers at any examination, only 7 (2%) developed staphylococcal wound sepsis, as compared with 27 (7.1%) of the 380 patients who were carriers.

There were 104 patients who were not carrying *Staph. aureus* when swabbed during the first week after their admission to the ward but who became carriers later. Their incidence of post-operative sepsis (6.7%) was very similar to that of the 276 patients who were carriers in the first week. Of the 276 patients who carried *Staph. aureus* at their first swabbing, 89 showed a change of phage-type of their nasal staphylococcus while in the ward; 6 of the 89 (6.7%) developed wound sepsis, in 4 cases with a staphylococcus of the same type as that acquired in the ward.

Altogether 18 of the 27 nasal carriers who developed post-operative sepsis yielded a staphylococcus from their wound of the type they harboured in their nose.

TABLE IV.—Wound Sepsis in Relation to Nasal Carrier State

Nasal Carriage of <i>Staph. aureus</i>	No. of Patients having Surgical Operations	Developing Wound Sepsis Due to Staphylococci					
		Of Type Present in Nose		Different in Type from those in Nose		Total	
		No.	%	No.	%	No.	%
a: Never	342	—		7	2.0	7	2.0
b: Not carrier at first swabbing; acquired <i>Staph. aureus</i> later	104	7	6.7	0		7	6.7
c: Carrier at first swabbing	276	7	2.5	3.3		20	7.3
d: Carrier at first swabbing; acquired new type in ward	89	4	4.5	9			
e: Total, carriers at some time	380	18	4.7	9	2.4	27	7.1
f: Grand total	722	18	2.5	16	2.3	34	4.7

Note.—The cases of sepsis entered in rows c and d are respectively those due to staphylococci of the type found at first swabbing and those acquired in the ward.

In only three cases was the nasal staphylococcus not isolated until after the development of wound sepsis; in one case it was first isolated from nose and lesion on the same day. It is worth noting that of the 18 patients, 11 (61%) had become nasal carriers of the relevant staphylococcus during their stay in the ward.

The incidence of infection due to staphylococci different from those carried in the nose is presumably a measure of cross-infection direct to the wound, and one might expect that this would be independent of the nasal carrier state. In fact, 7 (2%) of 342 wounds in non-carriers developed sepsis, and 9 (2.4%) of 380 wounds in carriers developed sepsis due to staphylococci of a different type from that carried in the nose (Table IV).

It was of interest to seek evidence of differences in the "virulence" of the staphylococci in the noses and wounds of these patients. We can do this if we assume that, when the same staphylococcus was isolated from nose and wound, the wound was infected from the nose, and, further, that the nasal carriers were, on average, all equally at risk of acquiring wound sepsis

TABLE V.—Wound Sepsis in Relation to Nasal Carriage of Drug-resistant or "Virulent" Staphylococci

	No. of Patients having Surgical Operations	Percentage Developing Wound Sepsis with Staphylococci			
		Same Type as Nose	Different from Nose		Total
			Not Res. or VT 3	Res. or VT 4	
a: Never carriers	342	—	—	—	2.0*
Some-time carriers:					
b: Penicillin-sensitive strains only	172	4.1	2.9	1.2	8.2
c: Penicillin-resistant strains	206†	5.3	—	1.0	6.3
d: Tetracycline-sensitive strains only	334	3.3	2.4	0.3	6.0
e: Tetracycline-resistant strains	46	15.2	0	0	15.2
f: Non-"virulent" types only	354	2.5	0.3	2.3	5.1
g: "Virulent" types	26	34.6	0	0	34.6

Note.—In columns 3 and 4 "Res." refers to penicillin-resistance in rows b and c and to tetracycline-resistance in rows d and e; VT=virulent types, referring to rows f and g.

* For 7 patients, never carriers, with wound sepsis, the wound staphylococci were penicillin-resistant in 4 cases, tetracycline-resistant in 3, and "virulent" types in 2.

† 1 patient carrying 2 strains—one resistant and one sensitive to penicillin—omitted.

from the staphylococci carried in their nose. As a first step we may compare the experience of patients who were nasal carriers at their first swabbing (and probably in most cases on admission to the ward) with those who became carriers subsequently. There was no more than a slight suggestion that the strains appearing in the nose during the patient's stay in the ward were in general more likely to produce sepsis than those carried at the first swabbing: the "self-infection" rates were 6.7% and 4.5% for the former and 2.5% for the latter group (Table IV, rows b, c, and d).

We next took penicillin-resistance as an indicator of the "hospital" staphylococci (Table V). There was again no more than a very slight suggestion that these strains may have been more virulent than the penicillin-sensitive strains: 5.3% of the 206 nasal carriers of penicillin-resistant staphylococci had wound sepsis due to the type found in their nose, compared with 4.1% of the carriers of sensitive strains.

When the same analysis was carried out for carriers of tetracycline-resistant staphylococci a substantial difference was observed: 7 (15.2%) of the 46 patients who, at any time, had tetracycline-resistant strains in their nose developed wound sepsis with the nasal strain, as compared with 11 (3.3%) of the 334 patients who carried only sensitive strains in their nose.

In a previous paper (Shooter *et al.*, 1958) we suggested that some phage-types of staphylococci were particularly "virulent" and liable both to spread through the ward and to produce septic lesions. During the period of the present survey there were 10 phage-types that produced two or more septic lesions within a short period. These were: 47/53/75/77+; 75/77+; 75/77; 80; 6/42E/47/75v.w.; 187; 52/52A/80; 3C/71+; 79; 52/80. We have provisionally taken these as our local "virulent types" and analysed the comparative experience of patients who did or did not become nasal carriers of one or other of these types (Table V, rows f and g). Of 26 patients who at one time or another carried one of the "virulent" types in their nose, 9 (34.6%) developed post-operative wound sepsis due to a strain of the type carried in the nose.

On the other hand, only 9 (2.5%) of the 354 patients who carried other types developed wound sepsis with their nasal staphylococcus.

The virulent types were responsible for 2 of the 7 cross-infections in non-carriers and 2 of the 9 in carriers. The similarity of these proportions suggests that the colonization of the nose may have been important in conducing to the virulence. It could, however, merely be that nasal carriage offered an opportunity for the staphylococci to get into the wound, either directly or from the skin, in the operating theatre. But in fact only 2 of all 27 cases of wound sepsis gave an indication of arising from theatre infection, and in neither case was the staphylococcus one of the virulent types.

Other Septic Lesions

Table VI and VII also present a similar analysis of septic lesions other than post-operative wound sepsis in relation to nasal carrier state. Not only the trends but

the actual rates of infection are remarkably similar to those for wound sepsis. Altogether 4.5% of the 1,319 patients had some septic lesion. The rate in carriers was 6.9% and in non-carriers 2.1%. Twenty-eight (62%) of the 47 infections in carriers were due to staphylococci of the type present in the nose. The incidence of direct cross-infection estimated in the same way as for the wounds was 2.1% in the non-carriers and 2.8% in the nasal carriers. The 37 carriers of virulent types had a 35.1% incidence of apparent self-infection, compared with 2.3% in the 650 other carriers.

The "other septic lesions" included 12 cases in which the patient was admitted with the septic lesion; 4 of these patients carried the same type of staphylococcus in nose and lesion on admission. Altogether 6 of the patients developed their nasal carriage after the appearance of sepsis.

Discussion

In considering the aetiology of post-operative sepsis and other hospital infections, the bacteriologist is apt to think in bacteriological terms and to seek to explain the incidence of infection by reference to the sources from which the patient could have become infected. The clinician, on the other hand, is inclined to think of clinical reasons why some patients become septic and others not.

A true understanding of the aetiology of septic complications in hospital patients can be achieved only by a combination of bacteriological and clinical analysis. But we may be reasonably certain that the sepsis would not develop if there were no pathogenic bacteria available, and it is therefore worth plotting the potential sources of infection in the ward. This paper is thus, quite frankly, a bacteriological contribution in which we have tried to show how much of the infection in the patients could have been derived from their own noses, and to what extent this nasal carriage was acquired in the ward.

The figures that we present for the acquisition of hospital staphylococci in the nose of hospital patients serve as a reminder of facts already known. They also offer some confirmation to the observation of Knight, White, and Martin (1958) on the importance of systemic antibiotic treatment in fostering the acquisition of resistant staphylococci in the nose. From the figures of Table III it can be seen that some 64 of the 165 patients given antibiotic treatment acquired penicillin-resistant staphylococci in their nose compared with only 34 of the remaining 188 who were given no such treatment.

It is, however, rather the importance of the acquisition of hospital staphylococci to the individual that we wish to stress. The patients who were or became nasal carriers of staphylococci had three times as much staphylococcal sepsis as those who were never carriers. And, altogether, 18 of the 27 patients with wound sepsis and 27 of 58 patients with other septic lesions (not all different individuals from those with wound sepsis) harboured the same phage-type of staphylococcus in their septic lesion and their nose. Since we found nearly 40 different types of staphylococci in septic lesions, and probably upwards of 200 different types in noses, this frequency of concurrence is clearly enormously greater than would be expected by chance. It appears, therefore, that self-infection is important in the aetiology of the septic lesions.

TABLE VI.—Sepsis Elsewhere Than in Wound in Relation to Nasal Carrier State

Nasal Carriage of <i>Staph. aureus</i>	No. of Patients	Developing Sepsis					
		Of Type Present in Nose		Different in Type from those in Nose		Total	
		No.	%	No.	%	No.	%
a: Never	632	—		13	2.1	13	2.1
b: Not carrier at first swabbing acquired <i>Staph. aureus</i> later	172	11	6.4	8	4.6	19	11.0
c: Carrier at first swabbing	515	16	10.5	11	2.1	28	5.5
d: Carrier at first swabbing acquired new type in ward	111	1	0.9				
e: Total, carriers at some time	687	28	4.1	19	2.8	47	6.9
f: Grand total	1,319*	28	2.1	32	2.4	60	4.5

Note.—The cases of sepsis entered in rows c and d are respectively those due to staphylococci of the type found at first swabbing and those acquired in the ward.

* An additional 39 patients, none developing sepsis, had no nasal swabs taken.

TABLE VII.—Sepsis Elsewhere Than in Wound in Relation to Nasal Carriage of Drug-resistant or "Virulent" Staphylococci

	No. of Patients	Percentage Developing Sepsis with Staphylococci			
		Same Type as Nose	Different from Nose		Total
			Not Res. or VT 3	Res. or VT 4	
a: Never carriers	632	—	—	—	2.1*
b: Some time carriers: Penicillin-sensitive strains only	330	0.6	1.2	1.2	3.0
c: Penicillin-resistant strains	351†	7.4	1.4	1.7	10.0
d: Tetracycline-sensitive strains only	615	2.9	1.6	0.8	5.3
e: Tetracycline-resistant strains	66†	16.7	0	6.1	21.2
f: Non-"virulent" types only	650	2.3	1.5	1.2	5.1
g: "Virulent" types	37	35.1	0	2.7	37.8

Note.—In columns 3 and 4 "res." refers to penicillin-resistance in rows b and c and to tetracycline-resistance in rows d and e; VT=virulent types, referring to rows f and g.

* For 13 patients, never carriers, with sepsis, the staphylococci were penicillin-resistant in 6 cases, tetracycline-resistant in 3, and virulent types in 2.

† For 6 patients, none developing sepsis, the sensitivity of the nasal staphylococci was not known.

It is, however, possible either that the lesion infects the nose or that both are infected separately from some other source. The first is unlikely, because in only very few patients were the staphylococci not found in the nose until after the development of sepsis, though, with the relatively long intervals necessarily elapsing between swabbings, exact timing is impossible. The second is possible because there was almost always some other patient infected with the same type elsewhere in the ward, though there were rarely many. In only 4 of the 10 incidents of cross-infection was the spreading type found in any large numbers in the air. But to explain the differing experience of nasal carriers and non-carriers one would have to postulate some general staphylococcal "diathesis" which made those who became nasal carriers also more likely to become infected in their wound or elsewhere. In this case one would hardly expect the nose and lesion to show the same type of staphylococcus with such frequency.

It seems more reasonable to regard the nose as being often the source of the sepsis. The incidence of sepsis due to staphylococci not carried in the nose is then reasonably regarded as an index of the amount of cross-infection conveyed direct to the wound or other site. Cross-infection of this sort was hardly more common in carriers than in non-carriers—a fact that seems to argue against any general proneness in the carriers.

The analysis also offers some further support for the idea that some staphylococci are more virulent than others. We did not suffer any extensive outbreaks of cross-infection, but, though nearly 40 different types produced sepsis, only 10 types were responsible for two or more cases of sepsis—that is, produced evident cross-infection—and these did so at widely scattered times. Over 30% of the patients who became nasal carriers of one or other of these strains also developed some septic lesion, compared with 5% of those carrying other strains.

The use of phage-type as a guide to virulence has the disadvantage that it takes time to get the typing done, and that there are clearly a great number of types that can sometimes produce epidemics (see Williams, 1959). For several years tetracycline-resistance has been used in some wards at St. Bartholomew's Hospital as a presumptive guide to virulence. In the present study only 6 of the 10 virulent types were tetracycline-resistant, but it needs to be remembered that we took the production of only two cases of sepsis as an indication of "virulence." Because of this, and because not all tetracycline-resistant strains were virulent, the incidence of sepsis in the carriers of tetracycline-resistant strains (15%) was not so high as in carriers of the locally "virulent" types. Nevertheless the excess of this rate over that for all carriers is a clear vindication of the policy of regarding the tetracycline-resistant strains as potentially dangerous.

The tentative picture that seems to emerge from this survey is this: in about half the cases of sepsis the staphylococci in the lesion could have been derived from the patient's own nose, and in half of these possible self-infections the nasal strain had certainly been acquired in the ward. The latter proportion is probably really greater than this because a rather large number of patients were not swabbed until after they had been in the ward several days. About 40% of the cases of sepsis, both in wounds and elsewhere, were due to a small number of apparently more virulent types of

staphylococci, and almost all the patients infected with these types had them in their nose as well as in their lesion.

These results suggest that the role of the nose as a source of self-infection is not confined to the relatively trivial septic lesions studied in the past, a conclusion amply confirmed by Weinstein (1959) in an analysis of sepsis in 125 patients undergoing thoracic surgery. The results also suggest that the incidence of sepsis ought to be reduced by the elimination or prevention of the nasal carriage of staphylococci. This might be achieved by measures designed to protect susceptible patients from exposure to those already infected (whether they have septic lesions or are symptomless carriers) or by topical application of antibiotics to the nose. Gillespie (1958) has already reported favourably on the latter method, though Weinstein (1959), in a very different situation, seemed to have no success.

Summary

Of 602 patients swabbed within a few days of admission to a male surgical ward, 38% carried *Staphylococcus aureus* in their nose, and 13% carried penicillin-resistant strains. Of 25 swabbed after eight weeks in the ward 68% were carriers and 52% had resistant strains.

Patients who were non-carriers on admission acquired resistant strains in the ward more readily than those initially carrying sensitive strains. 64 of 165 patients treated with antibiotics acquired penicillin-resistant strains in their noses; 39 patients acquired tetracycline-resistant strains in their noses.

The incidence of post-operative staphylococcal wound sepsis was 2% in 342 patients who were never nasal carriers of staphylococci and 7.1% in the 380 who carried at some time. In about half the cases the sepsis was due to a staphylococcus of the same type as was found in the nose. Of patients who were nasal carriers of one or other of 10 apparently more virulent types, 35% had wound sepsis, in all cases due to the nasal type of staphylococcus.

Of a total of 1,319 patients 4.5% developed sepsis elsewhere than in a wound. The relation to nasal carriage was very similar to that of wound sepsis.

The results suggest that the incidence of sepsis might be reduced if acquisition of staphylococci in the nose could be prevented.

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