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## skin and soft tissue infections in primary healthcare in Denmark: a 12-year population-based study

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1 1 *Staphylococcus aureus* skin and soft tissue infections in primary healthcare in

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4 2 Denmark: a 12-year population-based study

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1 1 **Abstract**

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5 3 A rise in community-onset *Staphylococcus aureus* infections has been observed in European countries. To ascertain  
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7 4 secular trends of *S. aureus* infections in primary healthcare in Denmark, we conducted this register-based study in  
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9 5 North Denmark Region, 1997-2008. We identified all skin and mucosa specimens obtained by general practitioners and  
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11 6 all prescriptions for the preferred oral anti-staphylococcal antibiotic, dicloxacillin. Repeat observations within a 12-  
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13 7 month period were excluded prior to calculation of age and gender standardised incidence rates per 100.000 person-  
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15 8 years.

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17 9 We included 108,758 specimens of which 42,778 (39%) yielded *S. aureus*. The annual incidence rate of specimens  
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19 10 doubled during the study period reaching 2,399 in 2008. The overall rate of *S. aureus* isolates increased 2-fold to a  
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21 11 stable rate at about 850, but for isolates from children and for impetigo specimens the increase was steeper with a peak  
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23 12 in 2002. 156,462 dicloxacillin prescriptions had been redeemed and the annual prescription rate increased 2.5-fold,  
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25 13 peaking at 3,714 in 2007.

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27 14 In conclusion, annual rates of specimens, *S. aureus* infections and dicloxacillin prescriptions more than doubled in  
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29 15 primary healthcare during the 12-year period.

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31 16 A major impetigo epidemic and calls for antibiotic stewardship with increased utilisation of specimens were  
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33 17 contributing factors.

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37 19 **Key words**

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39 20  
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41 21 *Staphylococcus aureus*, skin and soft tissue infection, impetigo, wound, community, epidemiology.

1 1 **Introduction**

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5 3 Community-onset *Staphylococcus aureus* infections have attracted increasing attention in recent years. One important  
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7 4 reason is the spread of methicillin-resistant *S. aureus* (MRSA) outside hospitals and healthcare facilities, especially in  
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9 5 the United States [1]. Community-onset MRSA infections are also recognized in Europe but the overall prevalence  
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11 6 remains low [2-3]. Another possible reason is the increasing incidence of impetigo that has been observed in several  
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13 7 Western European countries during the last decade [4-7]. This rise has been linked to the epidemic European fusidic  
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15 8 acid resistant impetigo clone (EEFIC), which belongs to clonal complex (CC) 121 and is characterised by low level  
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17 9 resistance to fusidic acid [8-10].  
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A recent registry-based study from the United Kingdom reported an increasing rate of hospital admissions for  
community-onset infections typically caused by *S. aureus* and a rise of anti-staphylococcal antibiotic prescriptions in  
primary care settings [11]. The standardised admission rate rose 3-fold for pyogenic skin infections and 6-fold for  
impetigo from 1989-1990 to 2003-2004. Similarly, flucloxacillin prescriptions increased 1.8-fold and fusidic acid  
prescriptions 2.5-fold during 1991-2006. Limitations to this study are lack of culture data and the fact that only a  
fraction of community-onset *S. aureus* infections lead to hospital admission. Nevertheless, the study highlights the need  
for better estimates of the burden and time trends of staphylococcal infections in the community.

Apart from antibiotic resistance surveys, we are not aware of longitudinal studies based on bacteriological specimens  
taken by general practitioners (GPs). Therefore, we conducted this population-based study of specimens obtained by  
GPs and practising specialists as well as prescriptions of dicloxacillin which is the preferred oral anti-staphylococcal  
beta-lactam in Denmark. Our aim was to describe the temporal trends of community-onset *S. aureus* infections in  
Denmark, 1997-2008.

1 1 **Materials and methods**

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5 3 **Setting**

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8 The study was conducted in North Denmark region within the boundaries of the former North Jutland County. We

9 5 obtained data for the years 1996-2008; during this period the catchment population was close to 495,000 inhabitants

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11 6 (approximately 9% of the Danish population). The primary care sector included approximately 320 GPs and practising

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13 7 specialists.

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15 8 All Danish residents have free access to tax-supported healthcare provided by GPs and public hospitals. A unique

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17 9 personal identification number is provided at birth or immigration by the Central Person Registry and is used for all

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19 10 healthcare contacts and health administrative databases.

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23 12 **Microbiological data**

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26 The Department of Clinical Microbiology, Aalborg Hospital, provided diagnostic bacteriology to all GPs and practising

27 14 specialists in the study area. Point of care tests undertaken by GPs did not include skin specimens. Specimens were

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29 15 obtained with charcoal-coated cotton wool swabs and transported in Stuart's medium (SSI Diagnostika, Hillerød,

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31 16 Denmark). Information on specimen type was given on a request form; further information on type of lesion (e.g.

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33 17 impetigo) and anatomic region were voluntary.

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35 18 Specimens were processed by standard culture techniques including 5% horse blood agar (SSI Diagnostika). In 2005 a

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37 19 chromogenic agar medium selective for *S. aureus* was introduced (chromID *S. aureus*, bioMérieux, Marcy l'Etoile,

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39 20 France). *S. aureus* was identified by clumping factor (StaphPlus, bioMérieux) or coagulation of horse citrate plasma.

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41 21 From 2003 onwards, most *S. aureus* isolates were tested for susceptibility to fusidic acid by tablet diffusion

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43 22 (Neosensitabs, Rosco, Taastrup, Denmark) on Mueller-Hinton II agar (SSI Diagnostika). A break-point of

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45 23 susceptibility >32 mm was confirmed by graphical analysis of recorded diameters [12,13].

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47 24 Information on specimens was retrieved from the laboratory information system (ADBakt; Autonik, Sköldinge,

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49 25 Sweden). We included specimens from the following sites/lesions: skin, abscess, pus, wound, impetigo, conjunctiva,

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51 26 urethra, vulva or anus, and specimens without specification. We excluded all specimens that indicated previous hospital

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53 27 contact (e.g., incisional wound, tracheostomy, and catheter exit site) and surveillance specimens from the nasal

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55 28 vestibule. Specimens from the respiratory tract including the external auditory meatus were excluded as we could not

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57 29 determine whether *S. aureus* might represent a colonising flora.

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1 1 Prescription data  
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3 2 In Denmark, antibiotics are available on prescription only and redeemed prescriptions are reimbursed according to  
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5 3 changeable administrative rules. Reimbursement had effect during the entire study period for oral prescriptions of the  
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7 4 isoxazolympenicillins dicloxacillin and flucloxacillin (Anatomical Therapeutic Chemical classification J01CF01).  
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9 5 Reimbursed prescriptions redeemed at pharmacies within the study area have been recorded in a  
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11 6 pharmacoepidemiological register since 1991 [14]. We retrieved information on all prescriptions of dicloxacillin and  
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13 7 flucloxacillin, but only the former is included in the study as consumption of the latter was negligible.  
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## 17 9 Definitions and statistical analyses 18

19 10 We defined an incident observation as a person with a specimen, *S. aureus* isolate or dicloxacillin prescription and no  
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21 11 similar record during the preceding 12-month period.  
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23 12 Repeat observations within a 12-month period were excluded because we wanted to reduce the impact of recurrent  
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25 13 infections.  
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27 14 We present annual incidence rates of specimens, *S. aureus* isolates and redeemed dicloxacillin prescriptions per  
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29 15 100,000 person-years at risk (pyr) for the period 1997-2008. Data from 1996 ensured incident observations from 1997.  
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31 16 The rate of specimens and *S. aureus* isolates were stratified into 4 age groups and 5 specimen groups. Age groups were  
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33 17 0-14 (children), 15-64, 65-79 and 80+ years (oldest old). Specimen groups were abscess/pus, wound, impetigo, skin  
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35 18 (including unspecified site), and mucosa (including conjunctiva, genital area and anus). We calculated the rates by  
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37 19 dividing the annual number of patients with a given observation by the number of inhabitants in the study area in the  
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39 20 beginning of that same year. To compare the rates among different years, we standardized the rates to the age and sex  
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41 21 distribution of the population in the region in 1997, using direct standardisation. Population statistics for the years  
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43 22 1997-2006 was obtained from Statistics Denmark [15]. Data from 2007 and 2008 were unavailable due to a reform of  
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45 23 the local government in 2007. Therefore, we used 2006 data instead.  
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47 24 To estimate presence of the EEFIC which is distinctive by its low-level resistance to fusidic acid [8-10], we calculated  
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49 25 the annual prevalence proportion of fusidic acid resistance overall and per specimen group.  
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53 27 STATA 9.2 for Windows (Stata Corp., College Station, TX) was used for data analyses. Data were obtained from  
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55 28 regional registries which are generally available to researchers and their use does not require informed consent.  
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57 29 Therefore, permission from the Danish Scientific Ethical Committee was not required for this study.  
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1 1 **Results**

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5 3 Incidence of specimens and *S. aureus* isolates

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7 4 During the study period, we identified 143,887 specimens of which 108,758 were incident specimens. A total of 42,778  
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9 5 (39%) of the incident specimens were positive for *S. aureus*. Numbers of observations per 4-year period appear from  
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11 6 Table 1. There was an approximately 2-fold increase in rates of specimens and *S. aureus* isolates between 1997 and  
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13 7 2008 (Figure 1). The rate of *S. aureus* isolates paralleled the increase observed for specimens until 2002 and remained  
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15 8 stable thereafter. In 2008 the incidence rates of specimens peaked at 2,399 and the rate of *S. aureus* isolates peaked in  
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17 9 2006 at 889 per 100,000 pyr.

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19 10 During the study period there was a steady increase in the incidence rate of *S. aureus* isolates among adults with the  
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21 11 highest rate observed for the oldest old (Figure 2a). For children the overall increase was steeper and peaked at 1,740  
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23 12 per 100,000 pyr in 2002. Analysis of incidence rates by specimen group showed a similar peak for impetigo specimens  
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25 13 (Figure 2b). A subanalysis of patients with impetigo showed that this rise predominantly was caused by infections  
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27 14 among children (Figure 2c). Specimens from wounds accounted for the highest annual incidence rates of *S. aureus*  
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29 15 isolates (Figure 2b), with a particularly high and steady increase among the oldest old (Figure 2d). Rates of *S. aureus*  
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31 16 isolates from other specimen types remained stable during the entire study period (Figure 2b). Incidence rates and time  
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33 17 trends were similar for males and females.

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37 19 Fusidic acid susceptibility

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39 20 Almost 50% of *S. aureus* isolates from impetigo patients were resistant to fusidic acid during 2003-2005, i.e. more than  
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41 21 twice the prevalence proportion for isolates from other specimen groups (Figure 3). From 2006 there was a  
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43 22 considerable fall in the prevalence of fusidic acid resistance among isolates from impetigo specimens.

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47 24 Dicloxacillin prescriptions

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49 25 We identified 246,400 dicloxacillin prescriptions of which 156,642 were incident. The incidence rate of prescriptions  
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51 26 more than doubled during the study period reaching ~3,600 per 100,000 pyr in 2008 (Figure 1). In adults, the increase  
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53 27 was unremitting and reached almost 7,000 per 100,000 pyr among the oldest old. In children, the time pattern was  
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55 28 similar to that seen for *S. aureus* isolates from impetigo specimens. Notably, the peak incidence of prescriptions  
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57 29 (~3,800 per 100,000 pyr) was almost 5-fold the incidence rate of *S. aureus* isolates.

1 **Discussion**

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5 We have documented a continuous rise in the rate of specimens obtained in primary healthcare with a doubling from  
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7 1997 to 2008. There was a parallel increase of *S. aureus* isolates up to 2002, thereafter the incidence remained fairly  
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9 stable. The largest source of *S. aureus* isolates was wound specimens with the highest incidence rates observed among  
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11 the oldest old. A remarkable finding was the steep increase in impetigo among children from 1997 to 2003, followed by  
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13 a rapid decline. The similar trends in the proportion of fusidic acid resistant isolates indicate a prominent role of the  
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15 EEFIC in this impetigo epidemic as shown in other European countries [8-10]. Dicloxacillin prescriptions followed the  
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17 trend for specimens but at a higher rate.  
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21 Strengths of the current study include access to data on microbiological specimens and prescriptions and the  
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23 population-based design that allowed calculation of age and sex adjusted incidence rates. However, this study has  
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25 limitations and most important is the possibility for surveillance bias. We had little information on GPs decision to  
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27 obtain specimens and no Danish guideline specifies the indications for obtaining specimens from skin and soft tissue  
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29 infections. In an effort to reduce surveillance bias we excluded repetitious observations and surveillance specimens.  
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31 Specimens that indicated hospital or healthcare contact were also excluded but we had no information on previous  
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33 hospital admissions. Nosocomial infections may therefore have affected the rates of specimens and *S. aureus* isolates,  
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35 especially among the elderly. Likewise, dicloxacillin prescriptions from hospital and outpatient clinics may have been  
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37 included because the prescriber's code was often unavailable. Based on available data, we estimated that less than 15%  
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39 of prescriptions were related to hospital or ambulatory care. Also, awareness of the EEFIC may have caused a shift  
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41 from fusidic acid to dicloxacillin, which could have contributed to the steady rise in consumption of dicloxacillin.  
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43 Fusidic acid is mostly used in a topical formulation that is not reimbursed. Therefore, we lack data on consumption of  
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45 this drug from the regional database.  
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49 Another concern is the validity of the clinical information on the request form. This information was given on a  
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51 voluntary basis and may also have been coded erroneously in the laboratory. We consider the source information  
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53 reliable for impetigo and abscess/pus. In contrast, information may be less valid for skin and wound specimens; these  
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55 may include eczematous lesions for which a GP might obtain specimens in order to rule out infection rather than to  
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57 confirm an infectious aetiology.  
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1 1 Our findings are consistent with information available from other countries. Fleming et al. [16] examined the trends in  
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3 2 incidence and treatment of skin infections presenting to GPs in England and Wales. From 1999 to 2005, they reported a  
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5 3 slight decrease in the incidence of skin infections while the number of flucloxacillin prescriptions increased. The study  
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7 4 examined several different skin infections, but it is noteworthy that wound infections were not included. In our study  
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9 5 wound specimens was the most important source of *S. aureus* isolates with a particularly high and steadily increasing  
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11 6 rate among the oldest old. The increasing age of the population makes this a worrisome finding [17]. Hospital  
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13 7 admission rates for skin infections have also been found to be increasing in the US [18] and the UK [11]. No Danish  
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15 8 studies have addressed this issue, which warrants further attention, preferably with inclusion of microbiological data.  
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19 10 The increasing rates of specimens and *S. aureus* isolates in the first half of our study period were driven by an impetigo  
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21 11 epidemic. Similar epidemics of childhood impetigo caused by the EEFIC have been reported from Norway and Sweden  
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23 12 [4-6]. These epidemics culminated in 2002 and waned until the end of the study periods, 2004 and 2005 respectively.  
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25 13 Increasing incidence of impetigo patients presenting to GPs has also been reported from the Netherlands [19]. Thus,  
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27 14 physicians may have become more inclined to obtain specimens in the beginning of the period because of the  
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29 15 contagiousness and virulence of the EEFIC [8-10]. In another Danish county, an outbreak of bullous impetigo led to a  
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31 16 10-fold increase in the number *S. aureus* positive specimens obtained by GPs during 1999-2003 [20]. Local attention to  
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33 17 the outbreak led to a further increase in the number of specimens. Causes for the rapid decline in *S. aureus* isolates  
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35 18 from impetigo specimens after 2003 are unclear. In Sweden, the decline in fusidic acid resistant *S. aureus* isolated from  
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37 19 children was preceded by a decline in sales of fusidic acid ointments [5]. Since we lacked data on fusidic acid  
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39 20 consumption, we could not explore this topic.  
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42 21  
43 22 Reasons for the continued rise in the specimen rate after 2003 are also unclear. Attention to community-onset MRSA  
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45 23 infections in the medical press and news media may have contributed [21]. In the 1990's, a cluster of community-onset  
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47 24 MRSA infections was diagnosed in North Denmark Region [22]. Since then, the incidence of community-onset MRSA  
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49 25 has been slowly rising in the entire country [3]. As a consequence, national surveillance of MRSA was enforced in  
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51 26 2006. This is likely to have heightened the awareness of staphylococcal infections among GPs during the last years of  
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53 27 the study. Furthermore, Danish GPs are well informed about antibiotic resistance and antibiotic stewardship through  
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55 28 multiple channels including the annual physician's desk reference (Medicinfortegnelsen) [23], the Institute for Rational  
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1 1 Pharmacotherapy [24] and the weekly newsletter EPI-NEWS from Statens Serum Institut [21-22]. Therefore, we are  
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3 2 inclined to see the continuous rise in the rates of specimens as a response to this information.  
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7 4 In conclusion, we have identified a major increase in community-onset staphylococcal infections in the first half of the  
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9 5 study period and a steady level thereafter, despite decreasing rates of impetigo. The age groups most affected were  
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11 6 children and the oldest old. Staphylococcal skin and soft tissue infections are an important public health concern  
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13 7 because of its burden on primary healthcare, the potential association with deep-seated or generalised infections, and  
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15 8 high consumption of antibiotics.  
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9 5 **Conflict of interest**

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13 7 The authors declare that they have no conflict of interest

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1 **Figure Captions**

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**Fig. 1** The incidence rates of specimens and *S. aureus* isolates from primary healthcare as well as prescriptions of dicloxacillin redeemed at local pharmacies, North Denmark region, 1997-2008

**Fig. 2** Incidence rates of *S. aureus* isolates from primary healthcare in North Denmark region, 1997-2008. **a** According to age group. **b** According to specimen type. **c** From impetigo specimens according to age group. **d** From wound specimens according to age group

**Fig. 3** Prevalence proportion of fusidic acid resistant *S. aureus* isolates according to specimen type in primary healthcare in North Denmark region, 2003-2008

Figure

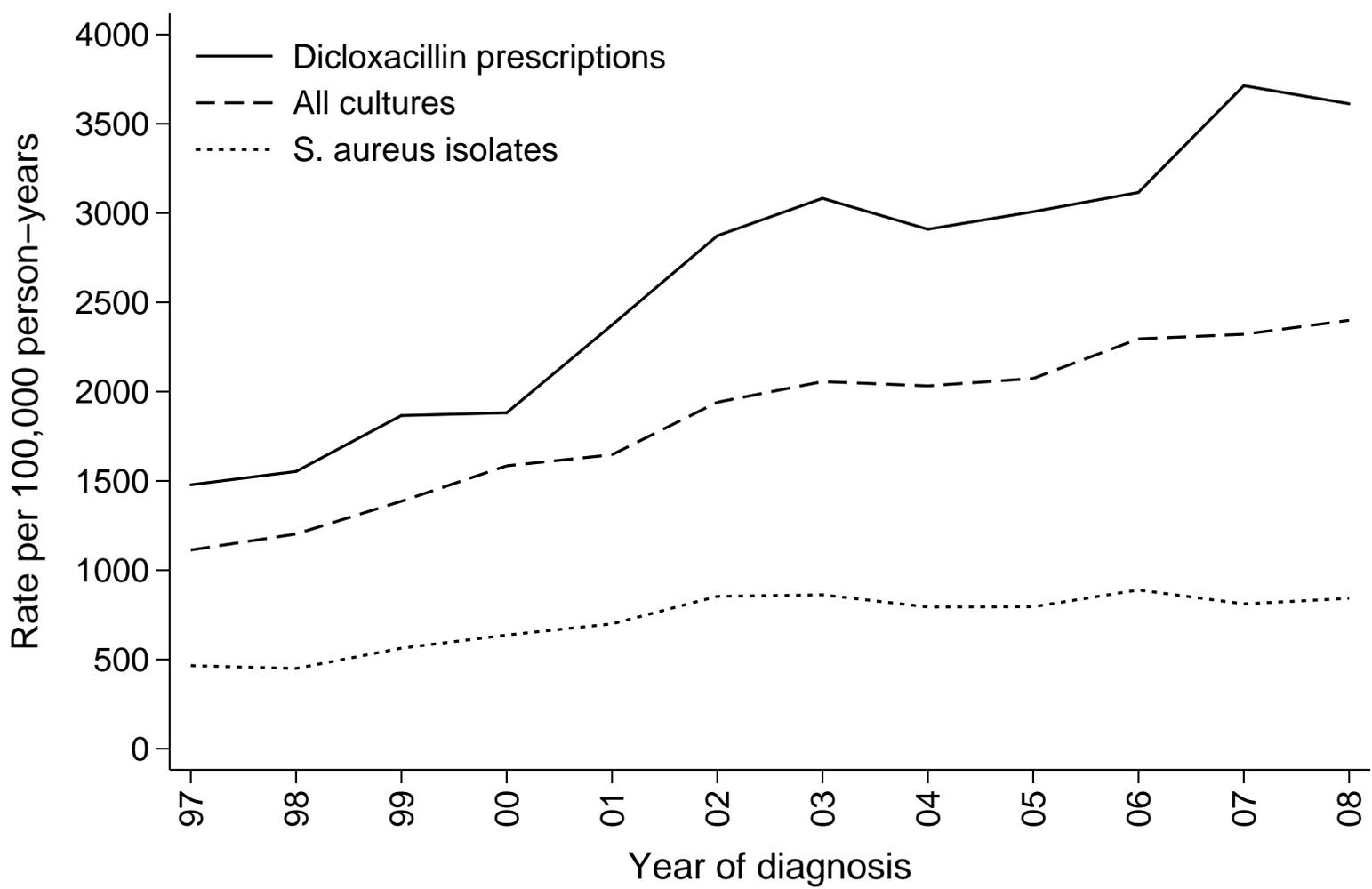


Figure 2

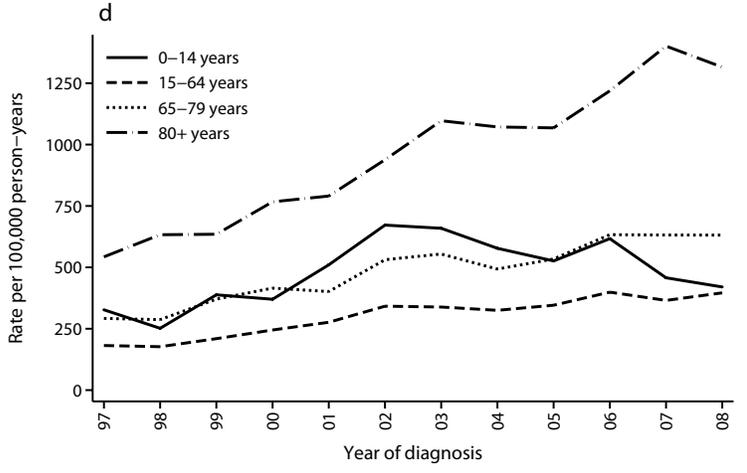
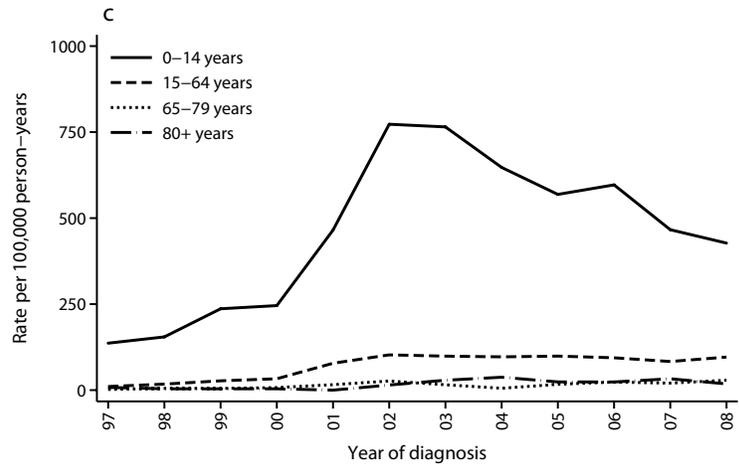
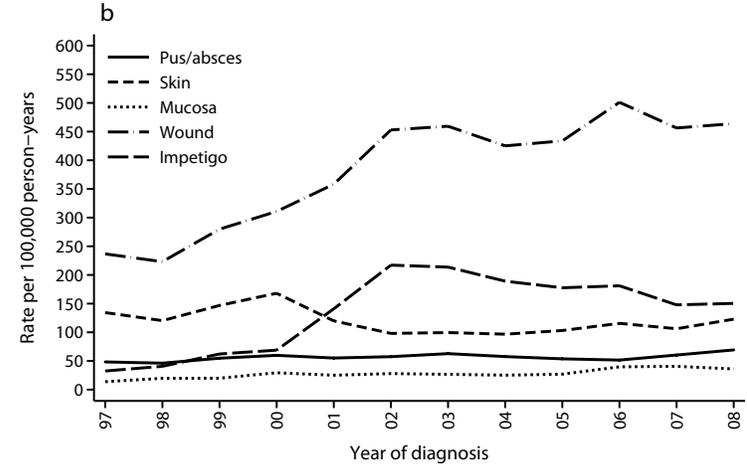
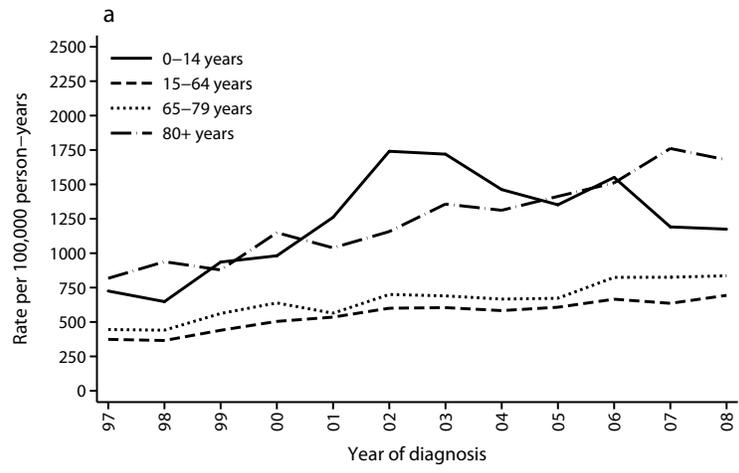
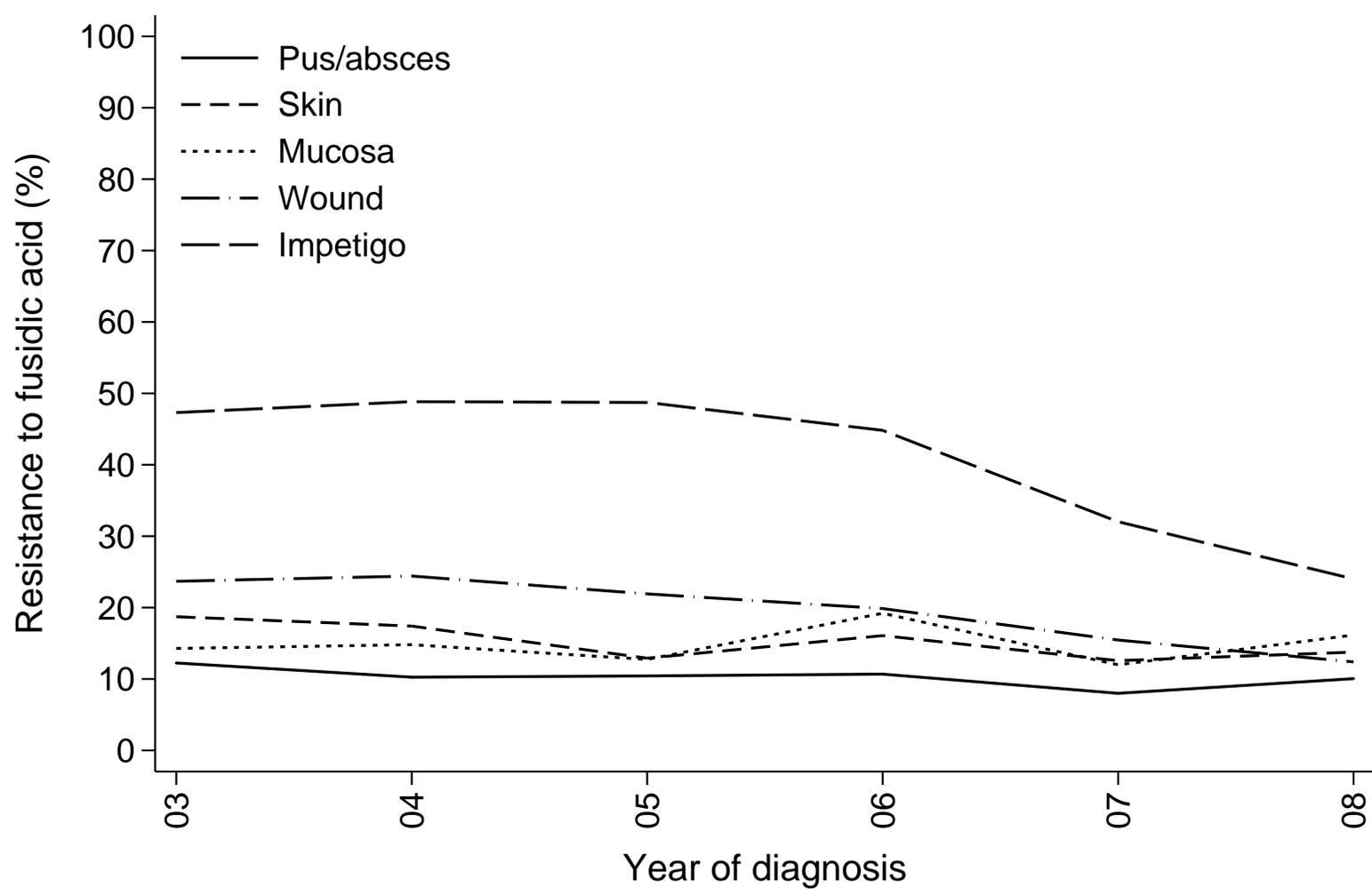


Figure 3



**Table 1** Number of cultures from skin and mucosa and *Staphylococcus aureus* isolates obtained by general practitioners and practising specialists in North Denmark

	Number of cultures					Number of <i>S. aureus</i> isolates		
	Total (% <sup>c</sup> )	% <sup>d</sup>			Total (% <sup>c</sup> )	% <sup>d</sup>		
		1997-2000	2001-2004	2005-2008		1997-2000	2001-2004	2005-2008
Total	108,758	26,122 (24.0)	37,947 (34.9)	44,689 (41.1)	42,778 (39.3)	10,442 (24.4)	15,854 (37.1)	16,482 (38.5)
Age group (year)								
0-4	18,925 (17.4)	4,339 (22.9)	6,803 (36.0)	7,783 (41.1)	5,322 (12.4)	1,211 (22.8)	2,152 (40.4)	1,959 (36.8)
5-14	15,111 (13.9)	3,070 (20.3)	6,085 (40.3)	5,956 (39.4)	8,230 (19.2)	1,785 (21.7)	3,591 (43.6)	2,854 (34.7)
15-29	15,949 (14.7)	4,000 (25.1)	5,305 (33.3)	6,644 (41.7)	7,213 (16.9)	1,830 (25.4)	2,562 (35.5)	2,821 (39.1)
30-64	39,568 (36.4)	9,976 (25.2)	13,404 (33.9)	16,188 (40.9)	14,265 (33.4)	3,655 (25.6)	4,984 (34.9)	5,626 (39.4)
65-79	12,185 (11.2)	3,100 (25.4)	4,020 (33.0)	5,065 (41.6)	4,504 (10.5)	1,190 (26.4)	1,495 (33.2)	1,819 (40.4)
≥ 80	7,020 (6.5)	1,637 (23.3)	2,330 (33.2)	3,053 (43.5)	3,244 (7.6)	771 (23.8)	1,070 (33.0)	1,403 (43.3)
Sex								
Male	51,911 (47.7)	12,700 (24.5)	18,226 (35.1)	20,985 (40.1)	21,303 (49.8)	5,320 (25.0)	7,769 (36.5)	8,214 (38.6)
Female	56,847 (52.3)	13,422 (26.6)	19,721 (34.7)	23,704 (41.7)	21,475 (50.2)	5,122 (23.9)	8,085 (37.7)	8,268 (38.5)
Specimen types								
Abscess/pus	11,564 (10.6)	3,389 (29.3)	4,010 (34.7)	4,165 (36.0)	3,343 (7.8)	1,030 (30.8)	1,150 (34.4)	1,163 (34.8)
Skin <sup>a</sup>	19,693 (18.1)	6,893 (35.0)	5,879 (29.9)	6,921 (35.1)	7,051 (16.5)	2,806 (39.8)	2,039 (28.9)	2,206 (31.3)
Mucosa <sup>b</sup>	20,337 (18.7)	4,897 (24.1)	6,274 (30.9)	9,166 (45.1)	1,633 (3.8)	411 (25.2)	521 (31.9)	701 (42.9)
Wound	44,354 (40.8)	9,435 (21.3)	16,111 (36.3)	18,808 (42.4)	22,852 (53.4)	5,187 (22.7)	8,412 (36.8)	9,253 (40.5)
Impetigo	12,810 (11.8)	1,508 (11.8)	5,673 (44.3)	5,629 (43.9)	7,899 (18.5)	1,008 (12.8)	3,732 (47.3)	3,159 (40.0)

<sup>a</sup> Includes specimen without specification. <sup>b</sup> Includes conjunctiva, urethra, vulva and anus. <sup>c</sup> Percentage column. <sup>d</sup> Percentage rows.