ORIGINAL ARTICLE

Nosocomial Infection and Antibiotic Use

A Second National Prevalence Study in Germany

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SUMMARY

Background: In 2011, seventeen years after the first national study on the prevalence of nosocomial infections and antibiotic use in German hospitals, a second national prevalence study was carried out according to the specifications of the European Centre for Disease Prevention and Control (ECDC).

Methods: The ECDC protocol, containing uniform surveillance definitions and ascertainment methods, was implemented. The only infections counted were those that were active or under treatment with antibiotics on the day of the study. In addition to the representative sample required by the ECDC, which consisted of 46 hospitals, further hospitals participated on a voluntary basis.

Results: Data on 41 539 patients in 132 hospitals were analyzed. The prevalence of infections that had arisen during the current hospital stay was 3.8% in the overall group and 3.4% in the representative sample of 9626 patients in 46 hospitals. The prevalence of all nosocomial infections, including those acquired before the current hospital stay and still present upon admission, was 5.1% in both the overall group and the representative sample. The prevalence of antibiotic use on the day of the study was 25.5% and 23.3% in the two groups, respectively.

Conclusion: The prevalence of nosocomial infection has not changed since 1994, but the prevalence of antibiotic use has increased. In interpreting these findings, one should bear in mind that confounders may have influenced them in different directions: The mean length of hospital stay is now shorter than in 1994, but the mean age of hospitalized patients is higher.

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Data on the frequency of nosocomial infections (NIs) and antibiotic use are important indicators of quality, and the increasing problem of antibiotic resistance has major consequences: It reduces infected patients' treatment options and results in additional morbidity, mortality, and costs (1–3). Rational antibiotic use can reduce selective pressure for the development of resistance to antibiotics (4). Prevalence studies provide an opportunity to gain an overview of the current situation regarding NIs and antibiotic use (5).

Since Germany's first national prevalence study on NIs and antibiotic use in representatively selected hospitals, in 1994 (NIDEP 1), no more have been conducted (6, 7). National prevalence studies have also been organized in many other European countries over the last 20 years, either once or several times (7). During the same period, the European Center for Disease Prevention and Control (ECDC) has developed a single Europe-wide protocol for conducting point prevalence studies (PPSs) and requested all European countries to conduct national PPSs on the prevalence of NIs and antibiotic use in 2011/12 (8). When this project was implemented in Germany, the National Reference Center for Surveillance of Nosocomial Infections was entrusted with gathering data for Germany and submitting them to the ECDC in anonymized form.

This national prevalence study had the following main aims:

- To estimate the prevalence of nosocomial infections (NIs) and antibiotic use in acute care hospitals in Germany
- To describe the types of infections and the pathogens that cause them
- To describe the antibiotics used and the indications for antibiotic use
- To forward the data to the ECDC.

Methods

The ECDC laid down a single protocol for conducting this research, and this was translated into German (9, 10). The ECDC also asked European countries to investigate a representative sample of patients. A random sample of hospitals based on bed counts was to provide a representative basis for study conduct. The ECDC set varying guidelines for the number of hospitals to be

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TABLE 1

Prevalence of all patients with nosocomial infections and patients with nosocomial infections acquired during current hospital stay*

Parameter	Total no. of participating hospitals	Representative sample	NIDEP 1 1994
No. of hospitals	132	46	72
Median bed count	359	216	<400
Patients	41 539	9626	14 966
Prevalence of all patients with nosocomial infections	5.08% 95% CI: 4.72 to 5.44	5.07% 95% CI: 4.51 to 5.67	–
Prevalence of patients with nosocomial infections acquired during current hospital stay	3.76% 95% CI: 3.50 to 4.02	3.37% 95% CI: 2.95 to 3.82	3.46% 95% CI: 3.1 to 3.9
Prevalence of antibiotic use	25.54% 95% CI: 24.49 to 26.60	23.33% 95% CI: 21.25 to 25.48	17,7 %

*Prevalence of antibiotic use both for all participating hospitals and for the representative sample versus the 1994 study
95% CI: 95% confidence interval

included in the study, according to countries' population numbers and hospital structures. The number of acute care hospitals to be included in Germany was 46.

An appropriate random sample was established by the National Reference Center on the basis of the German hospital register for 2008, and the selected hospitals were invited to participate in the study. The point prevalence study was also presented in an issue of the *Epidemiologisches Bulletin* (Epidemiological Bulletin), and all interested hospitals were invited to participate (11). All the hospitals in Germany's KISS system (Krankenhaus-Infektions-Surveillance-System, Hospital Infection Surveillance System) were also contacted in writing to inform them that they could participate. Where a hospital that had been selected at random was not interested in participating, the next hospital by bed count in the group of hospitals not selected as part of the representative sample but interested in study participation was included in the representative sample. The selection methods are described in detail in the supplement "Description of selection methods for the random sample of German hospitals for the European prevalence study on nosocomial infections and antibiotic use" (*eMethods*).

The point prevalence study had three main endpoints. Its primary endpoint was the prevalence of nosocomial infections, in line with the ECDC's instructions. This included all nosocomial infections, regardless of whether they had been acquired in the hospital in question or before admission. The aim was to record the total burden of nosocomial infections in a particular country. The prevalence of nosocomial infections acquired during the current hospital stay was also recorded, as this information is relevant to comparison between hospital groups. Finally, the prevalence of antibiotic use was recorded.

The study defined surgical wound infections, pneumonia, urinary tract infections, and sepsis accord-

ing to European definitions (12–15). There are only minor differences between these and those used in the KISS system (16). For all other cases the definitions of nosocomial infections established by the Centers for Disease Control and Prevention (CDCs) were used (17). Only infections that were active or under antibiotic treatment on the day of the study were included. Only results of investigations that were available on the day of the prevalence study were included. The Anatomical Therapeutic Chemical (ATC) classification established by the WHO (World Health Organization) (18) was used to record antibiotic use. Antiviral drugs and tuberculostatics were not recorded.

Employees of the participating hospitals (usually the hygiene team) were familiarized with the study protocol, how to diagnose NIs, and how to record antibiotic use according to the ECDC's instructions at six one-day introductory courses in different locations in Germany. Data were gathered from September to October 2011. Over time, the hygiene team or other trained hospital employees attended the hospital's wards (at least one full ward per day) in order to gather the necessary data by examining patients' medical records and consulting ward staff. Additional clinical examinations of patients were performed only in exceptional cases and were carried out together with the ward physician.

Data were gathered using three machine-readable questionnaires, in line with the ECDC's instructions: one hospital questionnaire, one ward questionnaire, and one patient questionnaire. The last was to be completed for each patient in whom antibiotics were used or who had symptoms of an NI on the day of the study.

For antibiotic use, the type of antibiotic, route of administration (parenteral, oral, etc.), indication, and whether the indication was listed in the patient's medical record were recorded. For nosocomial infections, questionnaires included information on the type of infection, onset of infection, any device relationship (e.g.

whether a urinary catheter had been fitted before onset of infection), and other details. Information on whether the nosocomial infection had already been present on admission or had been acquired during the current hospital stay, and the pathogen that had caused the infection, were also recorded. Multiple-choice lists provided most answers to these questions.

After the relevant hospital staff had completed the questionnaires, the data were entered into a database at the study site using optical character recognition (OCR) (Teleform) and validated. Finally, the employees of the participating hospitals were given the opportunity to verify and approve their data using a web-based interface. Analysis was performed following further approval processes at the study site. Confidence intervals (95% CIs) were calculated including a factor for overdispersion to adjust for the effect caused by hospitals as clusters.

Results

A total of 132 hospitals participated in the study, with 41 539 patients included. This represents approximately 8% of acute care hospitals in Germany (19). The representative sample included 46 hospitals with 9626 patients. 53.8% of the 132 hospitals were routine care hospitals, and 16.7% were tertiary hospitals.

2248 nosocomial infections (NIs) in 2109 patients were recorded, reflecting 1.07 NIs per patient with nosocomial infection. 1666 NIs in 1560 patients had been acquired during the current hospital stay. The number of patients receiving antibiotics on the day of the study was 10 607. *Table 1* shows the results of this study and compares them to those of the study conducted in 1994.

Other data concern all 132 participating hospitals and all nosocomial infections, not only those acquired during the current hospital stay. By type of ward, the highest prevalence rates of nosocomial infections (18.6%) and antibiotic use (50.5%) were observed in intensive care units. *Table 2* shows the prevalence of NIs and antibiotic use by specialty.

Surgical wound infections (24.3% of the total), urinary tract infections (23.2%), and lower respiratory tract infections (21.7%) were the most common nosocomial infections, followed by *Clostridium difficile* infections (6.4%) and primary sepsis (5.7%) (*Table 3*).

Microbiological evidence of a pathogen is not always necessary for the diagnosis of an NI. If, on the day of the study, material had already been procured for microbiological examination but the results were not yet available, the results were not included later; this was stated in the ECDC protocol, with the aim of minimizing the time required for the study. It is therefore not possible to show microbiological findings in full here. The most common pathogens causing nosocomial infections were *E. coli* (18.0%), enterococci (*E. faecalis* and *E. faecium*) (13.2%), *S. aureus* (13.1%), and *C. difficile* (8.1%).

Table 4 shows the indications for antibiotic use and compares them to the 1994 study. For patients with no

TABLE 2

Prevalence of nosocomial infections (NIs) and antibiotic use by specialty (no. of hospitals = 132)

Specialty	Patients	Prevalence of NIs (%)	Prevalence of antibiotic use (%)
ICUs	1652	18.64	50.5
Surgery	14 405	5.62	29.8
Internal medicine	15 070	4.92	27.3
Pediatrics	1017	0.79	23.9
Gynecology/obstetrics	2423	2.81	21.4
Geriatrics	1206	8.13	16.4
Psychiatry	3119	0.87	2.3
Other	1423	3.44	22.7
Specialty not assigned	1224	N/A	N/A
All specialties	41 539	5.08	25.5

N/A: not analyzed

TABLE 3

Most common nosocomial infections (no. of hospitals = 132)

Type of infection	No.	Prevalence (%)	Percentage of total
Surgical wound infection	547	1.31	24.3
Urinary tract infection	522	1.26	23.2
Lower respiratory tract infection	487	1.17	21.7
<i>Clostridium difficile</i> infection	144	0.34	6.4
Primary sepsis, including catheter-associated infections	129	0.31	5.7
Other gastrointestinal infection	103	0.24	4.6
Skin and soft tissue infection	53	0.13	2.4
Systemic infection	48	0.12	2.1
Bone and joint infection	40	0.10	1.8
Eye, ear, nose, or mouth infection	28	0.07	1.2
Cardiovascular system infection	15	0.04	0.7
Central nervous system infection	12	0.03	0.5
Reproductive tract infection	12	0.03	0.5
Other infection	108	N/A	N/A

N/A: not analyzed

TABLE 4

Comparison of indications for antibiotic use in the NIDEP 1 study and the current study (no. of hospitals = 132)

Reason for antibiotic use	Antibiotic administrations	Percentage in current prevalence study, 2011	Percentage in NIDEP 1 study, 1994
Outpatient infection	6811	48.3	47.9
Nosocomial infection	2670	19.0	16.9
Prophylaxis	4011	28.5	35.2
Other*	584	4.2	No category
Total	14 076	100.0	100.0

* Other: e.g. erythromycin as prokinetic agent or unknown indication

TABLE 5

Percentages of indications for prophylactic administration of antibiotics

Type of prophylaxis	Number	Percentage
Nonsurgical indication	1022	30.7
Perioperative prophylaxis: single dose	575	17.3
Perioperative prophylaxis <1 day	146	4.4
Perioperative prophylaxis >1 day	1587	47.6
Total	3330	100.0

infection on the day of the prevalence study and for whom the indication recorded was prophylaxis, the study also enquired into the reasons for prophylaxis. For surgical indications (perioperative prophylaxis), the very high proportion of perioperative prophylaxis continuing after the day of surgery is striking (*Table 5*).

For a relatively high proportion of antibiotic use (27%), patients' medical records did not state why antibiotics were used. However, within the study indication could not be established in any other way. The most common route of antibiotic administration was parenteral (63.9%), followed by oral (35.5%).

The five most commonly used classes of antibiotics were second-generation cephalosporins (15.1%), followed by fluoroquinolones (13.8%), penicillins with beta-lactamase inhibitors (12.5%), third-generation cephalosporins (10.4%), and carbapenems (5.9%) (*Table 6*).

Discussion

132 acute care hospitals were prepared to participate in the point prevalence study (PPS) on a voluntary basis. Their data were entered into the database. Most of the participating hospitals were selected at random and contacted, but many other hospitals were also interested in participating in the PPS and were able to do so, including 10 university hospitals. In 1994 very few hospitals were prepared to take part in this type of

study, so the only feasible way to conduct a national prevalence study was to use external staff to record data. The increase in the number of hospitals prepared to participate is very important, because it highlights not only how much interest in such investigations has developed since 1994, but also that studies of this type can be conducted with a relatively favorable cost/benefit ratio in Germany. The possibility of regularly (e.g. every three or five years) conducting such national prevalence studies, as is done in France, Norway, and Spain, for example, and establishing them as an additional tool for internal quality management for hospitals might therefore be considered (20–22).

The available data from Germany cannot yet be compared to data from other European countries, as the ECDC has not yet completed summary analysis. A European pilot study that has already been conducted and involved 66 hospitals from 23 countries yielded a prevalence rate for all NIs of 7.1%, with 34.6% of patients receiving at least one antibiotic on the day of the prevalence study (8).

In this PPS, the overall NI prevalence rate was 5.1%. Approximately 74% of these NIs had been acquired during the current hospital stay (prevalence rate 3.8%). There were no differences between the participating hospitals and those that had been representatively selected, and no differences between this study and the 1994 study (7).

When comparing these results with those of 1994, however, it should be remembered that it was not possible to use identical study protocols, as this study had to be conducted in line with the ECDC's instructions. In addition, in this PPS infections were recorded by hospital staff, whereas in the 1994 study they were recorded on-site by specially trained physicians. NIDEP 1 recorded only NIs acquired in the hospital in question. This means that this is the only prevalence figure that can be compared.

The risk factors for NIs in patients can be assumed to have risen between 1994 and 2011, because the mean age of German hospital patients—an important risk factor for many nosocomial infections—increased over the period (23–25). At the same time, patients' mean length of hospital stay has decreased significantly, by

TABLE 6

Most commonly used classes of antibiotics for therapeutic or prophylactic use

Class of antibiotics	No. of uses (percentage) of class of antibiotic for therapeutic or prophylactic use						
	All	Therapeutic			Prophylactic		
		Total	Infection acquired before admission	Nosocomial infection	Total	Perioperative	Nonsurgical
Second-generation cephalosporins	1932 (15.1)	864 (9.8)	686 (11.2)	178 (6.7)	1068 (26.6)	953 (35.9)	115 (8.5)
Fluoroquinolones	1764 (13.8)	1300 (14.8)	899 (14.6)	401 (15.0)	464 (11.6)	231 (8.7)	233 (17.2)
Penicillins combined with beta-lactamase inhibitors	1607 (12.5)	1205 (13.7)	866 (14.1)	339 (12.7)	402 (10.0)	274 (10.3)	128 (9.5)
Third-generation cephalosporins	1330 (10.4)	1054 (12.0)	838 (13.6)	216 (8.1)	276 (6.9)	177 (6.7)	99 (7.3)
Carbapenems	751 (5.9)	673 (7.6)	377 (6.1)	296 (11.1)	78	32	46
Imidazole derivatives	676 (5.3)	420	335	85	256 (6.4)	210 (7.9)	46
Broader-spectrum penicillins	675 (5.3)	471 (5.3)	368 (6.0)	103	204	115	89 (6.6)
Macrolides	454 (3.5)	410	356	54	44	15	29
Lincosamides	450 (3.5)	331	239	92	119	96	23
First-generation cephalosporins	429 (3.4)	104	84	20	325 (8.1)	309 (11.6)	16
Sulfonamides combined with trimethoprim, including derivatives	419 (3.3)	189	97	92	230	40	190 (14.0)
Glycopeptides	377 (2.9)	335	132	203 (7.6)	42	18	24
Other classes of antibiotics (e.g. aminoglycosides, tetracycline)	1960 (15.3)	1457 (16.5)	866 (14.1)	591 (22.1)	503 (12.5)	186 (7.0)	317 (23.4)
Total	12 824	8813	6143	2670	4011	2656	1355

This table shows the 12 most commonly used classes of antibiotics in decreasing order in the "All" column.

The subgroups show the classes of antibiotics that account for the six highest percentages of the total; the three most common are shown in bold

more than four days (19). Both these factors, which are likely to have opposing effects, must be borne in mind when interpreting the study results.

There are few changes in the distribution of NIs by frequency. One noticeable change is the high proportion of *Clostridium difficile* infections, which accounted for only a very small number of infections in the 1994 study. More focus will undoubtedly need to be placed on this infection and its prevention in the future. There were also few changes since the 1994 prevalence study in terms of the pathogens causing NIs.

The points mentioned above must also be taken into account when interpreting the increase in the prevalence of antibiotic use. The indications for antibiotic use have barely changed since 1994 in percentage terms. The most striking finding relating to antibiotic use is the high percentage associated with perioperative prophylaxis that continued after the day of surgery. If this non-evidence-based indication for antibiotics were consistently not applied, a substantial proportion, 10% to 20%, of antibiotic use in Germany could be abolished in one fell swoop (26). The first national prevalence study did not gather data on the classes of antibiotics administered; this is therefore the first time it has been possible to present such findings. Second-generation cephalosporins are the most commonly used

class of antibiotics, accounting for 15.1% of the total. The most significant reason for this is that they are the most commonly used class for perioperative prophylaxis. Fluoroquinolones and third-generation cephalosporins—broad-spectrum classes of antibiotics—alone account for more than 24% of all antibiotic use.

Naturally, first and foremost, this point prevalence study (PPS) has the limitations inherent in the design of prevalence studies. In particular, it must be mentioned that patients with NI risk factors usually have longer hospital stays, and there is therefore also a higher probability of an NI that occurs in these patients being recorded than there would be in prospective surveillance of nosocomial infections (e.g. in Germany's KISS surveillance system). In addition, there is a higher probability of recording such infections that are actually associated with longer duration of hospital stay, such as surgical wound infections. It is therefore impossible to convert prevalence data on nosocomial infections and antibiotic use to incidence rates, so corresponding national projections cannot be given without further information.

A further limitation is that information was reported by many different individuals. All these individuals had received training at an introductory course and were

able to consult the research staff on difficult cases. Nevertheless, different reporters are likely to have had differing sensitivity and specificity. In parallel to the 2011 prevalence study, the ECDC also conducted a validation study. This included two German hospitals and evaluated 200 cases. According to this validation study, the sensitivity of on-site reporters versus a gold-standard reporter trained by the validation study team was 100% (95% CI: 81 to 100), and their specificity was 91% (95% CI: 84 to 94).

Most patients included in the prevalence study were not clinically examined for symptoms of infection. This means that some infected patients may have been overlooked as a result of insufficient documentation. Another limitation results from the use of microbiological testing results: In many hospitals such results on patients' clinical picture were not yet available on the day of the study. As evidence of a pathogen is an important criterion for the diagnosis of many nosocomial infections, it is therefore likely that some infections that were actually present could not be recorded. The prevalence rate established here is therefore likely to be an underestimate.

Acknowledgement

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KEY MESSAGES

- Nosocomial infections remain a major problem for health care, and measures to reduce them should continue to be given high priority.
- Because there has been a marked increase in *Clostridium difficile* infections (now accounting for 6.4% of all nosocomial infections in Germany), they should attract more attention, with more intensive research and prevention measures.
- The high percentage of broad-spectrum antibiotics, particularly fluoroquinolones and third-generation cephalosporins (more than 24% of all antibiotic use) should be grounds for improving rational antibiotic use.
- The high percentage of antibiotics used for prolonged perioperative prophylaxis, which is not evidence-based, indicates that merely avoiding this use of antibiotics could reduce inpatient use of antibiotics by approximately 10% to 20%. Relevant initiatives should be started.
- The substantial interest in study participation opens up the possibility of conducting such studies regularly nationwide, at intervals of several years. Such studies increase local interest and attention focused on this issue, can contribute to identifying local problems, and make it possible to monitor the situation all over Germany with a favorable cost/benefit ratio.

Conflict of interest statement

Dr. Behnke, Dr. Hansen, Dr. Leistner, Dipl. Inform. Peña Diaz, Stud. Inform. Gropmann, Dr. Sohr, and Dr. Piening declare that no conflict of interest exists. Professor Gastmeier has received fees for preparing scientific continuing education events from Pfizer, Siemens, and Roche.

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Erratum

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In the article “Acute Liver Failure—A Life-Threatening Disease” by Canbay et al. in *Deutsches Ärzteblatt International*, issue 42 (2011), an error occurred on page 715 regarding the daily therapeutic dose of acetaminophen: The second sentence in the paragraph “Acetaminophen toxicity” should read: “Acetaminophen toxicity does not inevitably lead to ALF, but various risk factors increase the probability of acute liver damage even at “therapeutic doses” (e.g., **4 to 5 g** daily).”

E-METHODS

Nosocomial Infection and Antibiotic Use

A Second National Prevalence Study in Germany

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Description of selection methods for the random sample of German hospitals for the European prevalence study on nosocomial infections and antibiotic use

An appropriate random sample was established by the National Reference Center for Surveillance of Nosocomial Infections on the basis of the German hospital register for 2008, which contains 2025 hospitals. The selected hospitals were asked to participate in the study. The size of the sample, 46 hospitals, was set by the European Centre for Disease Prevention and Control (ECDC), as was the request that selection take account of hospital size.

The random sample was established as follows:

The hospitals included in the hospital register were sorted by increasing bed count, and a starting point in the list was chosen at random (by throwing dice). Beginning at this starting point, hospitals were selected at regular intervals (the size of the interval was calculated by dividing the total number of hospitals in the register by the size of the sample). The two hospitals that came after each selected hospital in the list were selected as a reserve.

The selected hospitals were contacted and asked to participate in the study. For each hospital refusing participation a reserve hospital was invited. In all, 33 of the hospitals either initially selected at random or invited as reserve hospitals participated in the prevalence study.

In addition, the prevalence study organized by the ECDC was presented in issue 19/2011 of the *Epidemiologisches Bulletin* (Epidemiological Bulletin). Interested hospitals were invited to participate. All the hospitals in Germany's KISS system (Krankenhaus-Infektions-Surveillance-System, Hospital Infection Surveillance System) were also contacted in writing to inform them that they could participate. This resulted in the participation of an additional 112 interested hospitals.

Where neither the representatively selected hospital nor the reserve hospitals were prepared to participate, the next hospital in the same size category in the group of hospitals that had expressed an interest in participating was included in the representative sample ($n = 13$).

After attending an introductory course and before the beginning of the study, 11 hospitals withdrew from it as a result of acute work overload. The data from two hospitals were not used as they were implausible. The final number of participating hospitals was therefore 132, including 76 KISS participants. Of the 46 hospitals in the representative sample, 24 were KISS participants.

Inclusion and exclusion criteria for acute care hospitals, wards, and patients:

Acute care hospitals

Inclusion criteria:

All, regardless of size

Exclusion criteria:

Nursing facilities, rehabilitation centers

Wards

Inclusion criteria:

All wards in acute care hospitals (e.g. acute psychiatry, neonatology)

Exclusion criteria:

Nursing wards in acute care hospitals, first aid wards

Patients

Inclusion criteria:

All patients on the ward at 8 a.m. and not discharged before the prevalence study was conducted; neonates if born before 8 a.m. on the day of the prevalence study; patients who were only temporarily away from the ward, e.g. for diagnostic interventions, on the day of the prevalence study.

Exclusion criteria:

Outpatients (e.g. outpatient surgery, outpatient dialysis)