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Inverse probability weighting leads to more accurate incidence estimates for healthcare-associated infections in intensive care units – results from two national surveillance systems

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SUMMARY

Background: Two main approaches are employed to monitor healthcare-associated infections (HAIs): longitudinal surveillance, which allows the measurement of incidence rates, and point prevalence surveys (PPSs). PPSs are less time-consuming; however, they are affected by length-biased sampling, which can be corrected through inverse probability weighting. We assessed the accuracy of this method by analysing data from two Italian national surveillance systems.

Methods: Ventilator-associated pneumonia (VAP) and central-line-associated bloodstream infection (CLABSI) incidence measured through a prospective surveillance system (GiViTI) was compared with incidence estimates obtained through conversion of crude and inverse probability weighted prevalence of the same HAIs in intensive care units (ICUs) measured through a PPS. Weighted prevalence rates were obtained after weighting all patients inversely proportional to their time-at-risk. Prevalence rates were converted into incidence per 100 admissions using an adapted version of the Rhame and Sudderth formula.

Findings: Overall, 30,988 patients monitored through GiViTI, and 1435 patients monitored through the PPS were included. A significant difference was found between incidence rates estimated based on crude VAP and CLABSI prevalence and measured through GiViTI (relative risk 2.5 and 3.36; 95% confidence interval 1.42–4.39 and 1.33–8.53, P=0.006 and 0.05, respectively). Conversely, no significant difference was found between incidence rates estimated based on weighted VAP and CLABSI prevalence and measured through GiViTI (P=0.927 and 0.503, respectively).

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Conclusions: When prospective surveillance is not feasible, our simple method could be useful to obtain more accurate incidence rates from PPS data.

Introduction

Healthcare-associated infections (HAIs) have a significant clinical and economic burden [1,2]. Intensive care unit (ICU) patients are particularly susceptible to HAIs and severe outcomes [3—5]. The majority of HAIs in ICUs are associated with the use of invasive devices such as endotracheal tubes and central lines [5]. Previous studies have estimated that a significant proportion of HAIs are avoidable with appropriate infection prevention and control (IPC) interventions, in particular related to invasive devices [3,6]. Monitoring HAI rates through surveillance is considered a key element of IPC programmes [7].

Two main approaches to assessing the impact of HAIs have been proposed: longitudinal surveillance, which allows the measurement of incidence rates, and cross-sectional (prevalence) studies. Incidence surveillance is resource intensive and logistically challenging, requiring prospective data collection for every patient, and is not always feasible in every clinical setting. Point prevalence studies (PPSs) require collecting data for all patients at one particular point in time, and are relatively easier to conduct, less expensive, and less time-consuming compared with longitudinal studies [8—10]. However, PPSs are affected by important limitations: data are collected at a specific moment in time, without follow-up, and variations in the period during which data are collected can affect estimates [9]. Further, length-biased sampling can lead to an over-representation of cases and to an overestimation of HAI prevalence [11]. These limitations notwithstanding, repeated PPSs can be used to monitor the effectiveness of IPC programmes and guide their implementation, providing a benchmark and highlighting areas where improvement interventions should be focused [8,9].

Methods for assessing HAI burden more often rely on incidence rather than prevalence rates [1,2]. Incidence rates can be calculated from prevalence data; however, the validity of predicted incidence has been debated [9]. The most commonly applied method for estimating incidence from prevalence was developed by Rhame and Sudderth in 1981 [12]. Among the limitations of this method, the estimator proposed by Rhame and Sudderth requires approximating the average length of infection (i.e., the number of days between diagnosis of infection, symptom onset, or beginning of treatment and end of symptoms or treatment, which is unavailable due to study design) with the difference between the average length of stay of patients who acquire one or more HAIs and the average interval between admission and onset of the first HAI for those patients who acquire one or more HAIs. It has been suggested that data from other sources, in particular regarding overall length of stay, or estimators based on more advanced statistical techniques could be necessary to provide accurate estimations of average length of infection and incidence rates [13].

Inverse probability weighting has been proposed as a simple method for correcting length-biased sampling in PPSs [11]. In this study, we analysed data from two Italian national surveillance systems and compared incidence rates of HAIs in ICUs directly measured through prospective surveillance to incidence estimates obtained by converting crude and inverse probability weighted HAI prevalence measured through the third European Centre for Disease Prevention and Control (ECDC) PPS. Given the importance of accurate HAI burden estimates in guiding quality improvement interventions, we aimed to validate a simple method which could be applied to cost-effective PPSs.

Methods

Study design and data sources

In this study, ventilator-associated pneumonia (VAP) and central-line associated bloodstream infection (CLABSI) incidence measured through the prospective surveillance system GiViTI, Italian group for the evaluation of interventions in ICU, was compared with incidence estimates obtained through conversion of crude and inverse probability weighted prevalence of the same HAIs in ICUs measured through a national PPS. A diagram illustrating study design is provided in Figure 1.

Data collection — GiViTI

The surveillance system GiViTI monitors clinical characteristics and outcomes of patients from admission to ICUs until hospital discharge, aiming to improve patient safety and quality of care. The surveillance system is coordinated by the Istituto di Ricerche Farmacologiche Mario Negri and has been previously described in detail [14,15]. Briefly, regional health systems or single ICUs can participate in the surveillance system on a voluntary basis. Data are collected by ICU personnel at ward and patient levels. The latter are collected prospectively for all patients admitted to participating wards, continuously throughout the year and using dedicated software. Only data from ICUs with at least four months of valid data are analysed [14].

Collected data include demographic and clinical characteristics, procedures patients undergo during their stay in the ICU, and outcomes including the occurrence of infection. GiViTI employs both US (National Healthcare Safety Network, NHSN) and European (Hospitals in Europe Link for Infection Control through Surveillance, HELICS) HAI definitions [15]. Infections are considered ICU-acquired if they occur $\geq$48 h from ICU admission. In particular, CLABSsI are defined as primary bloodstream infection (BSI) in patients with a central line within 48 h preceding the onset of BSI and not related to an infection at any other foci. VAP is defined as pneumonia occurring from the second day of ventilation to two days after the end of ventilation [15].

As shown in Figure 2, during the year 2022, ICUs of 15 out of 21 regions of Italy participated in the surveillance system. For the current analysis, we considered data collected from adult

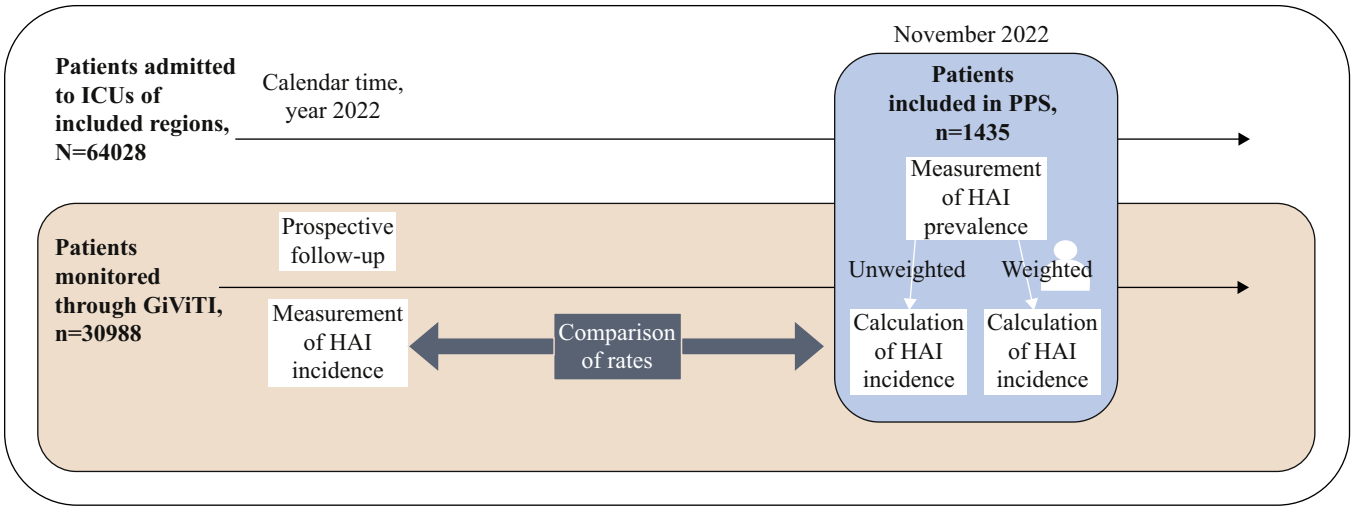

Figure 1. Study design. The study compared healthcare-associated infection (HAI) incidence directly measured through the prospective surveillance system GiViTI to incidence estimates obtained through conversion of HAI prevalence measured through a point prevalence survey (PPS), conducted during one month of the same calendar year within intensive care units (ICUs) of the same regions of Italy. Incidence estimates obtained from both crude and inverse probability weighted prevalence were calculated. GiViTI, Italian group for the evaluation of interventions in ICU.

patients (≥17 years old) admitted to general ICUs participating in GiViTI from 1st January 2022 to 31st December 2022. To increase generalizability, patients admitted to specialized ICUs such as cardio-surgical, surgical, neuro-surgical, or high dependency units were excluded.

Data collection — PPS

In November 2022, Italy carried out the third edition of the ECDC PPS of HAIs and antimicrobial use in acute-care hospitals, which is repeated throughout Europe every 5 years. An adapted version of the ECDC PPS protocol version 6.0 was applied, including HAI definitions (NHSN and HELICS) and methods for data collection [16,17]. For the current analysis, VAP and CLABSI were defined, respectively, as healthcare-related pneumonia and BSI in which a related device was *in situ* (even intermittently) within 48 h before onset.

The Department of Public Health and Paediatrics of the University of Turin was the Italian national coordination centre. Concerning the national sample, in order to guarantee regional representativeness, each Italian region was requested to provide a minimum number of acute-care hospitals in proportion to its population, acute-care hospitals bed-days and discharges for ordinary admissions to acute facilities [17]. Overall, 325 hospitals from 19 regions of Italy participated in the PPS, however the same 15 regions participating in GiViTI were considered for the purposes of the current analysis (Figure 2). We chose not to extend the analysis to the remaining four regions as HAIs in ICUs are exclusively monitored through another surveillance system, which does not apply the same protocol as GiViTI [18].

Full details of the methodology for data collection are available elsewhere [4,19]. Data collection was performed by trained local hospital staff, including doctors and infection control nurses at hospital, ward and patient levels. Within each participating hospital, all wards (excluding Accident and Emergency departments) were eligible for inclusion, and data were collected within one day per ward, and over a period of three weeks within each hospital. All patients admitted to wards before 8 a.m. on the day of the survey and still present at the time of the PPS were included.

For each included patient, demographic and clinical data were collected, including severity of underlying conditions according to the McCabe score (non-fatal disease: expected survival ≥5 years, fatal disease: expected survival <5 years) and other risk factors for HAIs such as presence of invasive devices. Supplementary information was collected in case of patients receiving one or more antimicrobial treatment or in case of active HAIs. According to the ECDC PPS protocol, a HAI is considered active when signs and symptoms of infection are present on the day of the PPS or when signs and symptoms were previously present, and the patient is still receiving antimicrobial treatment for the same HAI on the day of the PPS [16]. An online software for data collection was employed, in compliance with the EU's General Data Protection Regulation (GDPR).

For the current analysis, adult patients (≥17 years old) requiring intensive care in hospitals of the same regions participating in GiViTI were considered. Intensive care patients were identified based on consultant/patient specialty, i.e., the specialty of the physician in charge of the patient or the main specialty for which the patient was admitted to the hospital. In line with inclusion criteria applied to GiViTI data, the following specialties were included: medical, polyvalent-general and COVID-19 intensive care. Surgical, specialized, and other ICUs were excluded.

Ethics

The GiViTI protocol was approved by relevant local ethics committees at the participating centres. Written informed consent for use of clinical data was obtained according to national regulations. All patient data were pseudonymized before transmission to the national co-ordinating centre.

The PPS received the Institutional Review Board approval of the Bioethics Committee of the University of Turin (protocol

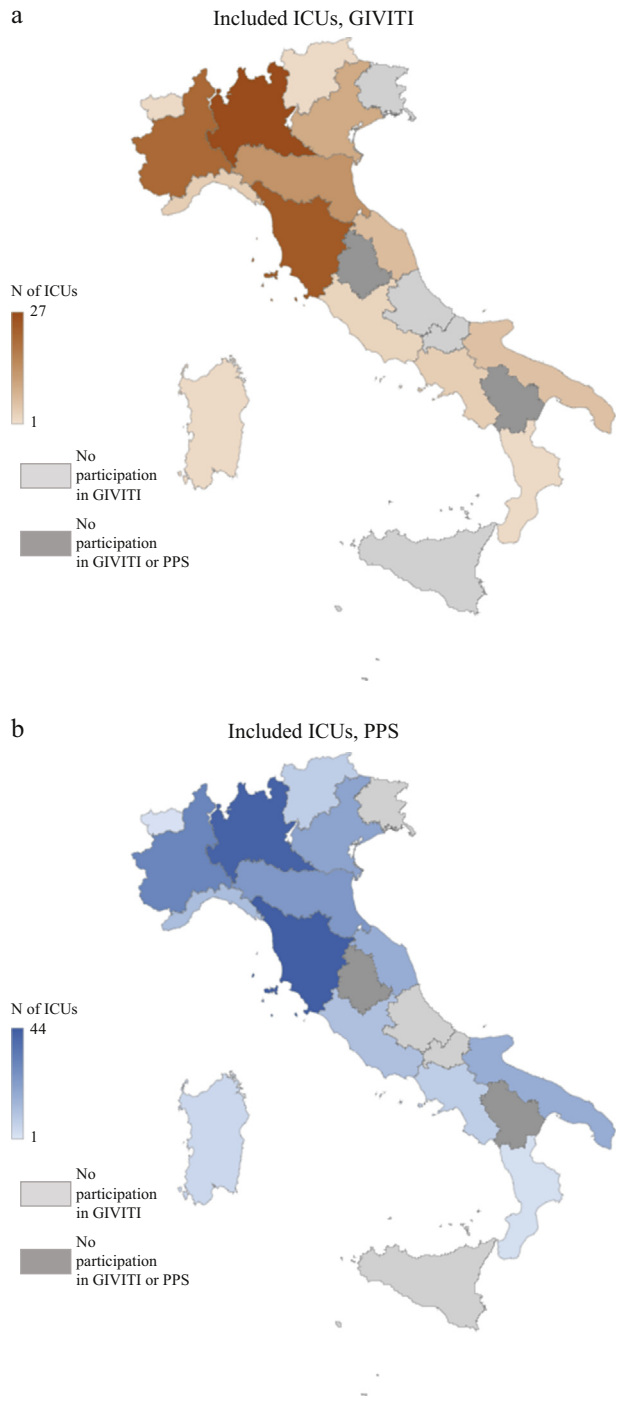

Figure 2. Participation in GiViTI (a) and point prevalence survey (PPS) (b), Italy, 2022. GiViTI, Italian group for the evaluation of interventions in ICU; ICU, intensive care unit.

number 0421518, 29/07/2022). As the PPS was an infectious disease surveillance and quality improvement programme promoted by national entities, namely Italian National Health Institute (ISS), Italian Centre for Disease Control (CCM), and Ministry of Health, written consent was waived. An information sheet notifying patients of their participation in the PPS and explaining the study and its objectives was made available in included wards.

Statistical analysis

Descriptive analyses were employed to summarize hospital, ward, and patient characteristics for the two surveillance systems, using Chi-squared test and Wilcoxon rank sum test with continuity correction when appropriate. Concerning patient characteristics, patients monitored through GiViTI were assigned an expected survival based on the presence of selected comorbidities (Supplementary material). According to the GiViTI protocol, patients were classified as COVID-19 patients based on clinical diagnosis of respiratory failure (with symptoms compatible with SARS-CoV-2 infection) and/or based on the results of laboratory testing; whereas patients included in the PPS that were identified as positive for healthcare-acquired COVID-19 based on ECDC definitions, or admitted for COVID-19 (patient specialty), were classified as COVID-19 patients [16,20].

Based on GiViTI surveillance data, VAP and CLABSI incidence rates were calculated as the number of cases occurring per 100 admitted patients and the number of cases per year. The latter was obtained by applying the proportion of yearly ICU admissions monitored through GiViTI over all ICU admissions in regions participating in the surveillance system in 2020, which was the most recent year for which data were available at the time of writing [21].

Concerning PPS data, crude VAP and CLABSI prevalence rates (P) were measured as the percentage of patients with at least one active HAI on the day of the survey over all included patients. VAP and CLABSI weighted prevalence rates (Pw) were obtained after weighting all patients inversely proportional to their time-at-risk (that is length of stay to PPS) [11]. 95% confidence intervals (CIs) for prevalence rates were obtained using Fisher's Exact method (Clopper–Pearson).

P and Pw were converted into incidence per 100 admissions (I) using an adapted version of the Rhame and Sudderth formula [12]:

$$I = P \times \frac{LA}{LN - INT}$$

$$Iw = Pw \times \frac{LA}{LN - INT}$$

where LA is the mean length of stay from admission to the day of the PPS of all patients included in the PPS, LN is the mean length of stay from admission to the day of the PPS of patients who acquire one or more HAI and INT is the average interval between admission and onset of the first HAI for those patients who acquire one or more HAI. Yearly incidence rates were obtained by applying incidence per 100 admissions to the number of admissions in ICU in regions participating in GiViTI in 2020 [21].

Incidence rates per 100 admissions converted from P and Pw were compared with incidence rates measured through GiViTI, using Mid-P exact tests; 95% CI for incidence rates and relative risks were obtained with Taylor series. Yearly incidence rates calculated from prevalence rates were compared with incidence rates measured through GiViTI, using Byar method for rate ratio. Analyses were conducted using IBM SPPS v. 28.0.1, with significance set at two-tailed 0.05.

Results

Overall, 117 hospitals, 117 ICUs, and 30,988 patients monitored through GiViTI, and 173 hospitals, 237 ICUs, and 1435

patients monitored through the PPS were included in our analysis. Descriptive characteristics at hospital, ward and patient levels are summarized in Table I. Comparing participants of both surveillance systems, smaller hospitals and hospitals providing primary care were more frequently represented in the PPS. Conversely, wards of similar size participated in both surveillances. Patients participating in GiViTI were more frequently female, had a higher proportion of fatal comorbidities, were more frequently exposed to urinary catheters and intubation, and a higher proportion received surgery since admission. Patients enrolled in the PPS were more frequently exposed to central vascular catheters and antibiotics. A significantly higher proportion of COVID-19 patients were recorded through GiViTI. As could be expected, the median length of stay to PPS was shorter than the overall length of stay of patients participating in GiViTI. In both surveillances, median lengths of stay of patients developing HAIs were double those of patients not developing HAIs. Interestingly, the median number of days from admission to HAI onset was significantly longer among PPS patients than GiViTI patients (12 vs eight days).

Table I
Descriptive characteristics of hospitals, wards and patients included in the respective surveillance systems

Hospital/ICU characteristics, *N* (%)	GiViTI	PPS	*P*
	N = 117	*N* = 173	
Hospital size, *N* (%)			
<300 beds	47 (40.17)	92 (53.17)	<0.05
300–800 beds	55 (47)	60 (34.68)	<0.05
>800 beds	9 (7.69)	18 (10.41)	NS
Unknown	6 (5.13)	3 (1.73)	NS
Level of care provided, *N* (%)			
Primary	0 (0)	18 (10.40)	<0.001
Secondary	31 (27.43)	91 (52.60)	<0.001
Tertiary	82 (72.57)	57 (32.95)	<0.001
Specialized	0 (0)	3 (1.73)	NS
Unknown	4 (3.42)	4 (2.31)	
No. of beds per ICU, median (IQR)	8 (6–12)	8 (6–14)[a]	NS
Patient characteristics	*N* = 30,988	*N* = 1435	
Age group, *N* (%)			
17–45 years	3619 (11.68)	169 (11.78)	NS
46–65 years	9178 (29.62)	425 (29.62)	NS
66–75	8545 (27.58)	424 (29.55)	NS
>75 years	9646 (31.13)	415 (28.92)	NS
Unknown	0	2 (0.14)	
Sex, *N* (%)			
Female	12169 (39.27)	512 (35.68)	<0.05
Male	18818 (60.73)	923 (64.32)	<0.05
Unknown	1	0	
Length of stay, median (IQR)			
All patients	14 (7–26)	9 (3–20)[b]	<0.001
HAI patients	30 (18–48)	18 (9.5–34)[b]	<0.001
Days to HAI (HAI patients), median (IQR)	8 (4–16)	12 (6–26)	<0.001
Comorbidities, *N* (%)			
Non-fatal	15873 (51.22)	704 (28.36)	NS
Fatal	15115 (48.78)	606 (42.23)	<0.001
Unknown	0	125 (8.71)	
Invasive device use, *N* (%)			
Central vascular catheter	22450 (72.45)	1125 (78.40)	<0.001
Urinary catheter	29799 (96.16)	1131 (78.82)	<0.001
Intubation	23362 (75.39)	828 (57.70)	<0.001
Antibiotic use, n (%)	19382 (62.55)	947 (65.99)	<0.05
Surgery since admission, *N* (%)	14799 (47.76)	565 (39.37)	<0.001
COVID-19 patients, *N* (%)	2601 (8.39)	67 (4.67)	<0.001

GiViTI, Italian group for the evaluation of interventions in ICU; HAI, healthcare-associated infection; ICU, intensive care unit; IQR, interquartile range; NS, not significant; PPS, point prevalence survey.
[a] Calculated over 128 ICUs due to missing data.
[b] Length of stay to PPS.

VAP prevalence and incidence rates are provided in Table II. As shown in Table II, a significant difference was found between incidence rates estimated based on crude VAP prevalence and measured through GiViTI. Conversely, no significant difference was found between incidence rates estimated based on weighted VAP prevalence and measured through GiViTI (both per 100 admissions and annual incidence).

CLABSI prevalence and incidence rates are provided in Table III. As shown in Table III, a significant difference was found between incidence rates estimated based on crude CLABSI prevalence and measured through GiViTI. No significant difference was found between CLABSI incidence rates per 100 admissions estimated based on weighted prevalence and measured through GiViTI, however a significant difference was found comparing annual incidence rates.

Discussion

This study allowed us to estimate the accuracy of a simple method for prevalence to incidence conversion, based on data from two Italian national surveillance systems. In line with other authors, our results suggest length bias significantly affects the accuracy of prevalence estimates [11]. Length bias is a type of selection bias, in which patients have different probabilities of being sampled due to different length of stay [11]. For both VAP and CLABSI, incidence rates estimated based on crude prevalence significantly differed from those measured through prospective surveillance. The difference in study designs did not allow a comparison of overall lengths of stay among patients participating in GiViTI and PPS, however, it was possible to compare the number of days from admission to HAI onset among patients developing an HAI (INT in the Rhame and Sudderth formula), which was significantly longer according to PPS results. Conversely, weighting prevalence inversely proportional to time-at-risk gave incidence estimates that did not significantly differ from those measured through prospective surveillance. This bias could explain the high estimated HAI burden we found when applying the ECDC Burden of Communicable Disease in Europe (BCoDE) methodology to 2017 Italian PPS data, which involved crude prevalence to incidence conversion [1,2].

An updated version, the Burden of HAIs (BHAI) methodology, was more recently proposed [22]. Both approaches apply to PPS designs and similarly involve prevalence to incidence

Table II
Ventilator associated pneumonia (VAP) prevalence and incidence rates estimated from the two surveillance systems

	PPS		GiViTI		Relative risk/rate ratio		
	Value	95% CI	Value	95% CI	Value	95% CI	*P*
VAP prevalence per 100 patients							
Crude	10.94	9.37–12.67					
Weighted	4.26	2.45–6.71					
VAP incidence per 100 admissions							
Crude	10.83	5.97–18.59	4.34	4.12–4.57	2.5	1.42–4.39	0.006
Weighted	4.22	1.38–10.45			0.97	0.38–2.48	0.927
Annual VAP incidence (2022)							
Crude	6931.73	3820.55–11,902.81	2777	922–2926.08	2.5	2.39–2.61	<0.001
Weighted	2699.59	881.67–6690.93			0.97	0.92–1.03	0.296

CI, confidence interval; GiViTI, Italian group for the evaluation of interventions in ICU; PPS, point prevalence survey.

Table III
Central-line associated bloodstream infection (CLABSI) prevalence and incidence rates estimated from the two surveillance systems

	PPS		GiViTI		Relative risk/rate ratio		
	Value	95% CI	Value	95% CI	Value	95% CI	*P*
CLABSI prevalence per 100 patients							
Crude	6.9	5.64–8.34					
Weighted	2.44	1.2–4.51					
CLABSI incidence per 100 admissions							
Crude	4.3	1.426–10.55	1.28	1.16–1.41	3.36	1.33–8.53	0.05
Weighted	1.52	0.0–6.756			1.19	0.25–5.78	0.503
Annual CLABSI incidence (2022)							
Crude	2756.21	913.04–6754.95	818.22	742.73–902.8	3.37	3.12–3.64	<0.001
Weighted	972.74	0.0–4325.73			1.19	1.08–1.31	<0.001

CI, confidence interval; GiViTI, Italian group for the evaluation of interventions in ICU; ICU, intensive care unit; PPS, point prevalence survey.

conversion via the estimated duration of infection (LN-INT in the Rhame and Sudderth formula). However, the BCoDE methodology uses a median estimator of length of infection, that is the median number of days from HAI onset to the day of the survey, whereas BHAI uses the Grenander estimator for length of infection [13,22]. The Grenander estimator ensures the monotonicity of the distribution of length of stay and length of infection, without making assumptions on the distributions of these variables [13]. We used a mean estimator, which performed better than the median estimator in simulation studies [13]. An advantage of our approach is that all estimates used in the Rhame and Sudderth formula (LA, LN, and INT) were derived from PPS data.

This study had several limitations. First, concerning the representativity of our results, as participation in both surveillance systems occurs on a voluntary basis, we cannot exclude a degree of selection bias. Due to GDPR requirements, we could not verify that the same units participated in both surveillance systems. As we compared two different surveillance systems with different study designs, definitions of some variables (such as severity of underlying comorbidities and COVID-19 status) had to be adapted for the purposes of this study, and results of Table I suggest some residual inaccuracies. However, concerning the main outcomes of this study, VAP and CLABSI episodes, both surveillance networks apply the same standardized international definitions. We did not account for seasonality in the PPS, which was conducted in the month of November. We also did not consider the impact of the COVID-19 pandemic on HAI rates, nor on the intensity of IPC activities [20,23]. Additionally, in our analysis we considered results from all ICUs combined, which could reduce variability [24]. Further research should investigate whether our method remains valid at hospital or ICU-level. Also due to study design, we considered cumulative incidence (per 100 admissions) rather than incidence per 1000 days of exposure to the respective invasive devices, which is highly correlated with infection risk [5]. Finally, the main limitations of the Rhame and Sudderth continue to apply to our method, namely the assumptions that (i) HAIs occur independently, i.e., the probability of one patient becoming infected does not depend on whether or not other patients are infected in the same ward/hospital, and (ii) for patients developing an HAI, the probability of subsequent HAIs does not depend on the number of prior infections [12].

In conclusion, PPSs are designed to be conducted hospital-wide and usually include all HAI types, as such they can be used to identify targets for quality improvement interventions, namely clinical specialties, patient groups, or procedures [8,24]. Conducting repeated PPSs allows one to monitor trends and evaluate the impact of quality improvement interventions when continuous surveillance is not feasible [10]. Prospective surveillance is generally targeted towards specific HAIs or clinical settings and involves a standardized follow-up period. Prospective studies generate detailed information on patient outcomes and allow more in-depth analysis. Given their different objectives, both PPSs and longitudinal surveillance have value and should be considered complementary to each other [24,25].

When prospective surveillance is not feasible, our simple method could be useful to obtain more accurate incidence rates from PPS data, without requiring external data. Obtaining accurate HAI incidence estimates from PPS data could help identify high-burden HAIs and clinical settings that should be prioritized for IPC interventions, including longitudinal surveillance.

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Conflict of interest statement

The authors have no conflicts of interest relevant to this manuscript to declare, including relevant financial interests, activities, relationships and affiliations.

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Appendix A. Supplementary data

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