JOURNAL OF CLINICAL MICROBIOLOGY, Oct. 2002, p. 3551–3557 Vol. 40, No. 10
0095-1137/02/$04.00+0 DOI: 10.1128/JCM.40.10.3551–3557.2002

MINIREVIEW

Role of Sentinel Surveillance of Candidemia: Trends in Species Distribution and Antifungal Susceptibility

M. A. Pfaller[1,2]* and D. J. Diekema[1,3]

Departments of Pathology[1] and Medicine,[3] College of Medicine, and Department of Epidemiology, College of Public Health,[2] University of Iowa, Iowa City, Iowa 52242

The threat posed by antimicrobial resistance was clearly outlined in the 1995 report of the American Society for Microbiology (ASM) Antimicrobial Resistance Task Force (2). That report strongly recommended increased research on antimicrobial resistance, including the establishment of surveillance programs to detect emerging resistance, to monitor resistance rates, and to guide infection control and formulary intervention programs. Since that time, numerous federal and nonfederal surveillance programs have been established (12, 16–20, 27, 29, 32, 50, 54). Although the strengths and weaknesses of these programs may be debated (16–19, 29, 32, 50, 54), it is clear that there is now a better appreciation of the antimicrobial resistance problem and that the infrastructure now exists for longitudinal tracking of resistance issues for antibacterial agents and bacterial pathogens (16–20).

Although the ASM report did not highlight mycotic diseases, it is apparent that the same issues pertain to this field of infectious diseases (13, 37). Not only have invasive mycoses emerged as a significant public health issue (13, 14, 21, 30, 37, 49), but also there is a growing concern about a shortage of effective antifungal agents and an increase in the resistance of fungal pathogens to the existing agents (8, 9, 34, 38, 57).

Among the invasive mycoses, none is more important or common than candidiasis (14, 22, 30, 37, 38, 49). Candidiasis, specifically candidemia, has been shown in numerous studies to be the most frequent mycotic infection of hospitalized patients and is associated with a significant attributable mortality and excess length of hospital stay (4, 6, 12–14, 21, 30, 48, 49, 53, 56, 64). Along with a recognition of the importance of candidemia and an emphasis on surveillance of bacterial infections and antibacterial resistance has come an interest in developing surveillance efforts to monitor trends in this important infectious disease (13, 21, 37).

SURVEILLANCE PROGRAMS FOR CANDIDEMIA

Although still relatively few in number, surveillance programs for candidemia are growing steadily (1, 4, 5, 7, 10–12, 15, 21, 26, 31, 35, 51, 55, 58, 60, 61, 63, 66; G. M. Lyon, G. Ponce-De-Leon, A. N. Sofair, M. E. Brandt, M. A. Ciblak, B. A. Arthington-Skaggs, L. Thomson, S. M. Huie, S. F. Yeo, M. Pass, L. H. Harrison, D. W. Warnock, and R. A. Hajjeh, 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 217, 2000). Existing programs can be categorized into population-based surveillance and sentinel and nosocomial surveillance programs (Table 1).

Because active population-based surveillance is designed to detect all candidemias in a defined population, it may provide accurate incidence rates and better descriptive epidemiology than other surveillance designs (13, 21, 49, 62; Lyon et al., 40th ICAAC). The cases detected in population-based surveillance are by definition representative of the population surveyed, and such surveillance provides the opportunity to assess risk factors for candidemia (13, 49; R. A. Hajjeh, 6th ASM Conference on *Candida* and Candidiasis, abstr. S-6, p. 15, 2002). Furthermore, the isolates obtained in the course of such surveillance provide a truly representative picture of species and strain distribution and of antifungal resistance rates (21; Hajjeh, 6th ASM Conf. *Candida* and Candidiasis; Lyon et al., 40th ICAAC), provided that care is taken to ensure that all infections are captured. Conversely, population-based surveillance is expensive and difficult to conduct and thus by necessity must be limited to a specific geographic area and a limited period of time. So although population-based surveillance may provide a very accurate view of candidemia in a given area or region, the data may not be generalizable to an entire country or a prolonged period of time.

Sentinel surveillance programs, on the other hand, can be criticized for being nonrepresentative of all hospitals, potentially missing data and thus underrepresenting the burden of disease and failing to provide a true estimate of disease incidence (49). Conversely, sentinel programs are quite flexible and allow sampling of consecutive episodes of infection from a large number of institutions over a broad geographic area and for prolonged periods of time (18, 19, 27, 41–47). The study protocol can be brief but standardized, and the specific aims are more limited (e.g., defining species rank order and antifungal susceptibility profiles of *Candida* bloodstream infection [BSI] isolates) than those of population-based programs. The more modest goals of sentinel surveillance programs and the use of a central reference laboratory for organism identification and antifungal susceptibility testing allow such programs to provide more rapid reporting of results and important feedback to participating centers (17–19, 27, 29, 32, 50).

The population-based and sentinel surveillance programs

* Corresponding author. Mailing address: Medical Microbiology Division, C606 GH, Department of Pathology, University of Iowa College of Medicine, Iowa City, IA 52242. Phone: (319) 384-9566. Fax: (319) 356-4916. E-mail: michael-pfaller@uiowa.edu.

TABLE 1. Surveillance programs for candidemia[a]

Type	Surveillance program	Reference(s)
Population-based surveillance	Centers for Disease Control	
	San Francisco and Atlanta, 1992–1993	21
	Baltimore and Connecticut, 1998–2000	—[b]
Sentinel surveillance and nosocomial infection surveillance	National Epidemiology of Mycoses Study	4, 39, 49, 56
	Surveillance and Control of Pathogens of Epidemiologic Importance	12, 40
	SENTRY	10, 41–43, 45, 46
	Emerging Infections and the Epidemiology of Iowa Organisms	11
	National Nosocomial Infection Surveillance System	6, 14, 53, 62
	Sweden	7
	Quebec	60
	European Confederation of Medical Mycology	1, 15, 35, 61

[a] List is not all-inclusive.
[b] Hajjeh, 6th ASM Conf. *Candida* and Candidiasis; Lyon et al., 40th ICAAC.

listed in Table 1 and discussed herein exclude those efforts that focus on reporting the activity of an antifungal agent at a given point in time and those reports of the experience of a single institution over time. Although useful, such surveys are not necessarily well positioned to identify general trends in species distribution or antifungal resistance over time. The surveillance data discussed in this review represent the findings of programs that are multi-institutional and span at least 2 years. The data generated from such programs are more generalizable than those representing the experience of a single institution.

A recent critique of antimicrobial surveillance programs by Richet (54) identified only one program reporting data on *Candida* spp. among reports published between 1 January and 31 October 2000. In contrast, we have identified several surveillance programs reporting species and antifungal susceptibility data on *Candida* BSI (Table 1) (1, 4, 5, 7, 10–12, 15, 21, 26, 31, 35, 51, 55, 58, 60, 61, 63, 66; Lyon et al., 40th ICAAC). The programs listed in Table 1 do not represent all *Candida* surveillance programs but do provide a demonstration of programs with published data on candidemia and which used central laboratories for species identification and antifungal susceptibility testing and either a population-based or sentinel surveillance program design. As with the antibacterial surveillance programs (2, 17–19, 29, 32, 50, 54), there has been little sharing of structure and/or coordination between the various *Candida* surveillance programs; however, as will be discussed in this review, the data derived from these various programs are remarkably consistent and thus provide a broader view of candidemia than is generally appreciated.

SPECIES DISTRIBUTION IN CANDIDEMIA

Virtually all of the surveillance efforts focusing on candidemia have provided a rank order of species distribution (Table 2) (4, 10, 11, 12, 21, 39–43, 45, 46, 48, 56, 62; Lyon et al., 40th ICAAC). In one of the earliest efforts, the Centers for Disease Control and Prevention (CDC) population-based surveillance study conducted in 1992 to 1993 in the San Francisco Bay and Atlanta metropolitan areas (21) found *Candida albicans* to be the most common species, followed in order by *C. parapsilosis*, *C. tropicalis*, and *C. glabrata* (Table 2).

Subsequent surveillance programs, including the most recent CDC population-based effort (Lyon et al., 40th ICAAC), have noted an increase in the proportion of *Candida* BSI caused by species other than *C. albicans* and especially an increase in the frequency of BSI due to *C. glabrata* (Table 2) (Lyon et al., 40th ICAAC). The United States-based surveillance programs have clearly demonstrated this trend (4, 10−12, 39–41, 43, 45, 46, 48), and longitudinal data from the National Nosocomial Infections Surveillance Program, a surveillance program conducted by the CDC (6, 53, 62), has shown that *C. glabrata* was the only species of *Candida* that increased in frequency as a cause of BSI over the past decade (62; Hajjeh, 6th ASM Conf. *Candida* and Candidiasis). Likewise, the SENTRY Surveillance Program has shown *C. glabrata* to rank second overall, accounting for approximately 20% of *Candida* BSI in the United States over the past 5 years, 1997 to 2001 (Table 3) (10, 41–43, 45, 46). In contrast, surveillance data from other countries continue to reflect the importance of *C. parapsilosis* over *C. glabrata* (1, 5, 7, 9, 10, 15, 26, 31, 38, 41–43, 45, 51, 55, 61, 63).

The importance of patient age in determining the rank order of *Candida* species causing BSI has also been noted in virtually every program that has examined this relationship (Table 3) (4, 21, 25, 46, 48, 56; Hajjeh, 6th ASM Conf. *Candida* and Candidiasis; Lyon et al., 40th ICAAC). Both population-based and sentinel surveillance programs have demonstrated the predominance of *C. albicans* and *C. parapsilosis* and the lack of *C. glabrata* and other species of *Candida* as etiologic agents of candidemia in the neonatal and pediatric age groups (Table 3). In contrast, the increased importance of *C. glabrata* with increasing patient age has been noted in both population-based and sentinel surveillance data (Table 3).

Both the SENTRY and Emerging Infections and the Epidemiology of Iowa Organisms sentinel surveillance programs demonstrated a significant trend towards a decreased proportion of BSI due to *C. albicans* and an increased proportion due to *C. glabrata* with increasing patient age (Fig. 1) (11, 46). Such observations have important implications for infection control (e.g., nosocomial transmission of *C. parapsilosis* in neonatal intensive care units) (21, 25, 39, 46, 56; Hajjeh, 6th ASM Conf. *Candida* and Candidiasis) and for empirical therapy and dosing of systemic antifungal agents (46, 52). The increased importance of *C. glabrata* and also *C. krusei* (22, 46, 52) in the elderly gives rise to the need to consider higher doses of both fluconazole and amphotericin B when treating *Candida* BSI in older patients (52). Furthermore, using an alternative agent such as an echinocandin in the elderly patient may also be

TABLE 2. *Candida* species distribution as reported by sentinel and population-based candidemia surveillance programs

Surveillance program[a]	Years	Reference(s)	No. of isolates reported	% of total					
				C. albicans	*C. glabrata*	*C. parapsilopsis*	*C. tropicalis*	*C. krusei*	*Candida* spp.
CDC	1992–1993	21	837	52	12	21	10	4	1
NEMIS	1993–1995	48	79	56	15	15	10	0	4
SCOPE	1995–1998	12, 40	934	53	20	10	12	3	2
CDC	1998–2000	—[b]	944	45	24	13	12	2	4
EIEIO	1998–2001	11	254	58	20	7	11	2	2
SENTRY	1997–2000	46	2,047	54	16	15	10	2	3

[a] CDC, Centers for Disease Control; NEMIS, National Epidemiology of Mycoses Study; SCOPE, Surveillance and Control of Pathogens of Epidemiologic Importance; EIEIO, Emerging Infections and the Epidemiology of Iowa Organisms; NNIS, National Nosocomial Infection Surveillance System.
[b] Hajjeh, 6th ASM Conf. *Candida* and Candidiasis; Lyon et al., 40th ICAAC.

considered, as the efficacy of this class of antifungal agents against *C. glabrata* has been demonstrated (3, 22).

ANTIFUNGAL RESISTANCE TRENDS AND NEW DRUG EVALUATION

Just as the rank order of species distribution changes with patient age, there is also decreased susceptibility to both azoles and amphotericin B among isolates of *Candida* spp. causing BSI in older patients (46). This has been observed in the data from the SENTRY program and is entirely driven by the decreased frequency of *C. albicans* and the increased frequency of *C. glabrata* and *C. krusei* as causes of *Candida* BSI in patients over the age of 65 years compared to the younger age groups (46).

Trends in the susceptibility of *Candida* spp. BSI isolates to fluconazole over time have been assessed using both population-based and sentinel surveillance programs. The two CDC population-based surveillance efforts show little, if any, resistance to fluconazole emerging among BSI isolates of *Candida* spp. between 1992 and 2000 (21; Lyon et al., 40th ICAAC). Likewise, data from SENTRY and other sentinel surveillance programs indicate that fluconazole resistance, as assessed by National Committee for Clinical Laboratory Standards (NCCLS) reference testing methods (33), is very uncommon among BSI isolates of *C. albicans*, *C. parapsilosis*, and *C. tropicalis* (Table 4) (7, 11, 21, 46, 60; Lyon et al., 40th ICAAC).

Resistance to fluconazole among *C. glabrata* organisms has been noted in approximately 10% of BSI isolates, with the exception of data from Sweden (Table 4). Examining the profile of fluconazole susceptibility observed over 3 years (1997 to 1999) in the SENTRY program finds no increase in resistance among the most common species causing *Candida* BSI (45). Notably, one study showed a trend towards increased susceptibility to fluconazole among *C. glabrata* isolates (45). Although the reasons underlying this apparent trend are unclear, the possibility of improved utilization and dosing of fluconazole in recent years with the resultant suppression of fluconazole resistance in this species is worth investigating (45).

Sentinel surveillance programs have also been very important in assessing the potential usefulness of investigational and newly introduced antifungal agents (10, 31, 42, 44, 45, 47). The ability to access large collections of recent clinically important isolates of *Candida* spp. from geographically diverse sources provides a much more informative assessment of the spectrum and potency of a new antifungal agent than does a more limited evaluation using isolates from a single institution (Fig. 2). In addition, the collection of BSI isolates from more than 100 institutions over several years in sentinel surveillance programs such as the SENTRY program provides the requisite number of relatively rare phenotypes (such as fluconazole-resistant *C. albicans* BSI isolates) required to meaningfully assess cross-resistance among new agents of the same class (Fig. 2) (47). Such an assessment would be difficult to conduct without the large clinical isolate collection provided by a longitudinal multicenter surveillance program.

TABLE 3. *Candida* species distribution in adults and neonates as reported by different candidemia surveillance programs

Study population	Surveillance program[a]	Yrs	References	% of total					
				C. albicans	*C. glabrata*	*C. parapsilopsis*	*C. tropicalis*	*C. krusei*	*Candida* spp.
Adults	NEMIS	1993–1995	4, 48	48	24	5	19	0	0
	NNIS	1989–1999	—[d]	59	12	10	11	NA[c]	NA
	CDC	1998–2000	—[b]	48	25	12	14	NA	NA
	SENTRY	1997–2000	46	50	23	12	10	2	NA
Neonates	CDC	1992–1993	21	53	0	45	0	0	2
	NEMIS	1993–1995	48, 56	63	6	29	0	0	3
	NNIS	1989–1999	—[d]	54	2	38	4	0	2
	SENTRY	1997–2000	46	60	3	24	7	0	6

[a] See Table 2, footnote *a*, for surveillance program abbreviations.
[b] See Table 2, footnote *b*.
[c] NA, data not available.
[d] Hajjeh, 6th ASM Conf. *Candida* and Candidiasis.

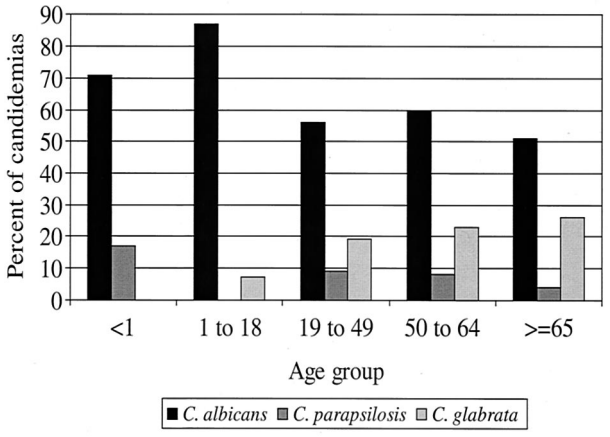

FIG. 1. Percentage of all candidemias due to selected *Candida* species in each age group. Data are from the Emerging Infections and the Epidemiology of Iowa Organisms survey, 1998 to 2001. $P = 0.02$ for trend of increased frequency of *C. glabrata* with increasing age. Adapted from reference 11 with permission.

USE OF SURVEILLANCE PROGRAMS IN ASSESSING MECHANISMS OF RESISTANCE

Currently, the various *Candida* surveillance programs present antifungal susceptibility test information without investigating the mechanism of resistance among strains expressing a resistant phenotype. By accumulating large numbers of *Candida* BSI isolates from around the world, longitudinal sentinel surveillance programs may allow investigators to address these issues as they pertain to both licensed and investigational agents such as the new "extended-spectrum" triazoles. It is now known that although rare, isolates of *C. albicans* exhibiting high-level resistance to fluconazole (MIC, ≥64 μg/ml) may express several mechanisms of resistance (36, 65). Those isolates of *C. albicans* with a phenotype of high-level resistance to both fluconazole (MIC, ≥64 μg/ml) and itraconazole (MIC, ≥1 μg/ml) (the RR phenotype) may overexpress both *MDR* and *CDR* efflux pumps with or without ERG16 mutations or overexpression, whereas a strain with high-level resistance to fluconazole and susceptibility to itraconazole (MIC, ≤0.12 μg/ml) (the RS phenotype) may overexpress the *MDR* pump but not the *CDR* pump (36, 65).

Thus, one can use these phenotypes to track these resistance mechanisms among clinically important isolates as well as to assemble collections of strains for evaluation of the newer triazoles and other antifungal agents (47). To date, it is apparent that both the RR and RS phenotypes are quite rare among *C. albicans* strains isolated from BSI (47). However, when they occur, these phenotypes may also predict the efficacy of the newer triazoles (Table 5) (44, 47). The RS phenotype appears to be susceptible to the newer agents, such as voriconazole, ravuconazole, and posaconazole (44, 47), whereas strains with the RR phenotype are significantly less susceptible to these agents than are those with the RS phenotype (Table 5) (44, 47). Thus, surveillance programs may identify resistance phenotypes that may be characterized further with respect to resistance mechanism and, by tracking these phenotypes, may also provide a better understanding of the frequency of the resistance mechanisms, thereby serving to guide empirical therapy and dosing recommendations.

DIFFERENT PROGRAMS PROVIDE COMPLEMENTARY DATA

Although discontinuous, the various sentinel, nosocomial, and population-based *Candida* surveillance programs, when taken as a whole, do provide a useful view of trends in candidemia over the past decade. As noted above, the observation from the two CDC population-based surveillance programs that *C. glabrata* has emerged to become the second most common cause of candidemia is supported by the consecutive sentinel surveillance programs National Epidemiology of Mycoses Study (1993 to 1995), Surveillance and Control of Pathogens of Epidemiologic Importance (1995 to 1998), and SENTRY (1997 to 2002), as well as the longitudinal observations of the National Nosocomial Infections Surveillance program (Table 2) (11, 12, 40, 46, 48, 62; Hajjeh, 6th ASM Conf. *Candida* and Candidiasis). Likewise, the SENTRY program has demonstrated differences in *Candida* species distribution among various countries that has been further substantiated by sentinel studies in Europe (1, 15, 35, 61).

The influence of patient age on the frequency of various species causing candidemia has also been demonstrated by both population-based and sentinel surveillance programs (Table 3 and Fig. 1) (4, 21, 46, 48, 56; Hajjeh, 6th ASM Conf. *Candida* and Candidiasis; Lyon et al., 40th ICAAC). The consistent observation of an increasing prominence of *C. glabrata* as a cause of BSI with increasing patient age is very important and should prompt more detailed investigations concerning changes in mucosal immunity with age and their influence on mucosal colonization with various species of *Candida* (22, 23,

TABLE 4. Fluconazole resistance among *Candida* BSI isolates as determined by different surveillance programs[a]

Surveillance program	Yrs	References	No. of BSI tested	% Resistant to fluconazole[b]			
				C. albicans	*C. glabrata*	*C. parapsilopsis*	*C. tropicalis*
CDC	1992–1993	21	394	1	14	0	2
CDC	1998–2000	—[c]	944	1	10	0	6
Sweden	1994–1998	7	233	0	40	15	0
Quebec	1996–1998	60	442	1	9	0	0
SENTRY	1997–2000	46	2,047	1	7	0	1
EIEIO	1998–2001	11	254	0	10	0	0

[a] See Table 2, footnote *a*.
[b] Determined by using NCCLS broth microdilution and interpretive criteria (MIC ≥64 μg/ml) (36).
[c] Lyon et al., 40th ICAAC.

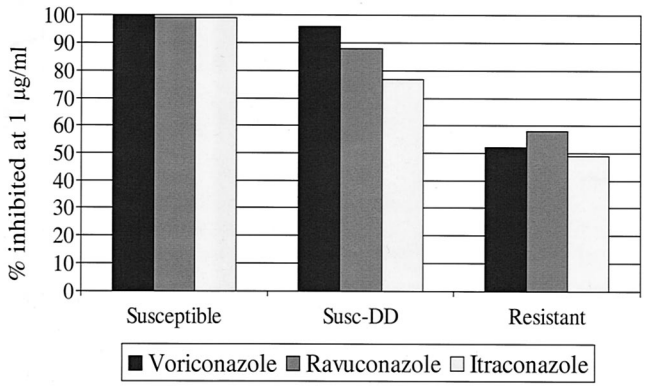

FIG. 2. In vitro activity of newer azoles stratified by fluconazole susceptibility. There were 6,268 susceptible (fluconazole MIC, ≤8 μg/ml), 463 susceptible dose-dependent (susc-DD; fluconazole MIC, 16 to 32 μg/ml), and 239 resistant (fluconazole MIC, ≥64 μg/ml) strains. Data are from reference 47.

28). Finally, the consistent use of the standardized NCCLS method for assessing antifungal susceptibilities of *Candida* BSI isolates in the various surveillance programs has provided a uniform observation of a sustained high level of susceptibility to fluconazole among the most common species of *Candida* (Table 4 and Fig. 2).

The greater the care in selecting a particular organism (*Candida*) from a well-defined type of infection (bloodstream), the more likely that results from different surveys will be comparable and validate one another. Thus, the sentinel surveillance programs discussed in this review all focus on *Candida* spp. and BSI identified consecutively at the participating institutions. The fact that the isolates from the National Epidemiology of Mycoses Study, Surveillance and Control of Pathogens of Epidemiologic Importance, SENTRY, and Emerging Infections and the Epidemiology of Iowa Organisms surveillance programs were all processed by the same central laboratory using validated reference identification and susceptibility testing methods also provides a level of standardization and continuity that facilitates comparison of results from study to study.

The similar study design used in all of these surveillance efforts has allowed us to compare and contrast species distribution and antifungal susceptibility profiles among different countries and institutions, different age groups, hospital locations (intensive care unit versus ward), and inpatient versus outpatient settings (4, 10–12, 39, 40, 42, 43, 45, 46, 48, 56).

TABLE 5. Cross-resistance of *C. albicans* isolates to licensed and investigational triazoles[a]

Antifungal agent	Susceptibility category[b]	No. of isolates	Cumulative % inhibited at MIC (μg/ml):						
			0.12	0.25	0.5	1	2	4	8
Voriconazole	RR	37	0	2.7	10.8	18.9	37.8	40.5	40.5
	RS	38	2.6	26.3	55.3	94.7	100		
Ravuconazole	RR	32	12.5	18.8	25.0	40.6	43.8	46.9	46.9
	RS	38	50.0	89.5	97.4	100			

[a] Adapted from reference 47 with permission.
[b] RR, fluconazole MIC ≥64 μg/ml and itraconazole MIC ≥1 μg/ml; RS, fluconazole MIC ≥64 μg/ml and itraconazole MIC ≤0.12 μg/ml.

The comparability of these data with those generated by the less frequently performed population-based surveillance studies (21; Hajjeh, 6th ASM Conf. *Candida* and Candidiasis; Lyon et al., 40th ICAAC) demonstrates the usefulness of sentinel surveillance programs as a complement to the more labor- and resource-intensive population-based efforts.

SUMMARY AND CONCLUSIONS

If the goal of surveillance programs is to identify emerging infectious threats, to monitor trends in antimicrobial resistance, and to contribute data that may be used by individual practitioners and institutions and in drug development efforts (2, 16–19, 29, 32, 50), then the combination of population-based and sentinel surveillance programs for candidemia has served its purpose to date. It is important to realize that there is not one single best way to conduct surveillance and provide useful information (17–19, 29, 32). Whereas the population-based surveillance efforts are unsurpassed in providing incidence data and risk factor profiles, they are limited in time and space due to expense and labor intensiveness. Sentinel surveillance programs designed to capture organisms and patient demographic data from representative sites spanning a larger geographical area and over a longer period of time serve to fill in the gaps in time and space that are necessarily left by the more intensive yet intermittent population-based programs. The establishment of an infrastructure necessary for conducting sentinel surveillance may facilitate more intensive surveillance in certain areas, such as a single state, and provide information that may approximate that obtained from a population-based program (e.g., Emerging Infections and the Epidemiology of Iowa Organisms) (11).

Improvements in data handling and reporting may provide more rapid communication of surveillance results to participating centers (17–19, 29, 32). In the case of candidemia, sentinel surveillance programs may provide identification confirmation and access to antifungal susceptibility testing services that may not otherwise be available to participating institutions. Thus, such programs should be supported and continued as yet another means of aiding in the fight against opportunistic mycoses. Expansion of existing programs to include less frequent mycotic infections, such as those due to *Aspergillus* spp. and other filamentous fungi, will further expand our knowledge of these increasingly important infectious pathogens.

ACKNOWLEDGMENTS

Linda Elliott provided excellent support in the preparation of the manuscript.

This work was funded in part by the Prevention Epicenters Program of the Centers for Disease Control and Prevention (UR8/CCU715091-03-3) for the EIEIO study and by unrestricted educational and research grants from Pfizer, Bristol Myers Squibb, and Schering Plough Research Institute.

REFERENCES

1. **Ainscough, S., R. Barnes, V. Gant, W. R. Gransden, R. Holliman, B. McCrae, J. Perry, J. Wilson, S. Schelenz, and C. C. Kibbler.** 2000. Blood stream infections due to *Candida* species in England and Wales. Data from ECMM epidemiological survey of candidemia in Europe. Rev. Iberoam. Micol. **17:** S143.
2. **American Society for Microbiology.** 1995. Report of the ASM Task Force on antibiotic resistance. Antimicrob. Agents Chemother. Suppl., p. 1–23. ASM Press, Washington, D.C.

3. **Arathoon, E. G., E. Gotuzzo, L. M. Noriega, R. S. Berman, M. J. DiNubile, and C. A. Sable.** 2002. Randomized, double-blind, multicenter study of caspofungin versus amphotericin B for treatment of oropharyngeal and esophageal candidiasis. Antimicrob. Agents Chemother. **46:**451–457.
4. **Blumberg, H. M., W. R. Jarvis, J. M. Soucie, J. E. Edwards, J. E. Patterson, M. A. Pfaller, M. S. Rangel-Frausto, M. G. Rinaldi, L. Saiman, R. T. Wiblin, R. P. Wenzel, and the NEMIS Study Group.** 2001. Risk factors for candidal blood stream infections in surgical intensive care unit patients: the NEMIS Prospective Multicenter Study. Clin. Infect. Dis. **33:**177–186.
5. **Bulmer, G. S., M. L. Marquez, L. Co-Barcelona, and R. A. Fromtling.** 1999. Yeasts and fluconazole susceptibility in the Philippines. Mycopathologia **146:**117–120.
6. **Centers for Disease Control and Prevention.** 1999. National Nosocomial Infections Surveillance (NNIS) system report, data summary from January 1990–May 1999. Am. J. Infect. Control **27:**520–532.
7. **Chryssanthous, E.** 2001. Trends in antifungal susceptibility among Swedish *Candida* species bloodstream isolates from 1994 to 1998: comparison of the Etest and the Sensititre Yeast One Colorimetric Antifungal Panel with the NCCLS M27-A reference method. J. Clin. Microbiol. **39:**4181–4183.
8. **Collin, B., C. J. Clancy, and M. H. Nguyen.** 1999. Antifungal resistance in non-albicans *Candida* species. Drug Resist. Update **3:**9–14.
9. **Colombo, A. L., M. Nucci, and R. Salomao.** 1999. High rate of non-*albicans* candidemia in Brazilian tertiary care hospitals. Diagn. Microbiol. Infect. Dis. **34:**281–286.
10. **Diekema, D. J., M. A. Pfaller, S. A. Messer, A. Houston, R. J. Hollis, G. V. Doern, R. N. Jones, and the SENTRY Participants Group.** 1999. In vitro activities of BMS-207–147 against over 600 contemporary clinical blood stream isolates of *Candida* species from the SENTRY Antimicrobial Surveillance Program in North America and Latin America. Antimicrob. Agents Chemother. **43:**2236–2239.
11. **Diekema, D. J., S. A. Messer, A. B. Brueggemann, S. L. Coffman, G. V. Doern, L. A. Herwaldt, and M. A. Pfaller.** 2002. Epidemiology of candidemia: three-year results from the Emerging Infections and the Epidemiology of Iowa Organisms study. J. Clin. Microbiol. **40:**1298–1302.
12. **Edmond, M. B., S. E. Wallace, D. K. McClish, M. A. Pfaller, R. N. Jones, and R. P. Wenzel.** 1999. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin. Infect. Dis. **29:**239–244.
13. **Ellis, D., D. Marriott, R. A. Hajjeh, D. Warnock, W. Meyer, and R. Barton.** 2000. Epidemiology: surveillance of fungal infections. Med. Mycol. **38**(Suppl. 1)**:**173–182.
14. **Fridkin, S. K., and W. R. Jarvis.** 1996. Epidemiology of nosocomial fungal infections. Clin. Microbiol. Rev. **9:**499–511.
15. **Grillot, R., O. Faure, J. Fruit, B. Sendid, P. Rispail, A. Datry, M. F. Biava, L. Kures, O. Morin, D. Toubas, S. Bretagne, B. Bouteille, B. Lebeau, S. Cassaing, B. Cuisenier, I. Grawey, J. L. Poirot, O. Eloy, C. Kauffmann-Lacroix, C. deChamps, G. Kac, V. Lavarde, M. Baixench, M. E. Bougnoux, L. Lachaud, C. Lamy, E. Pellet, C. Biodni, and the Groupe d'Etude des Mycoses Opportunistes.** 2000. Working group: ECMM candidemia. ECMM prospective epidemiological survey of candidemia in Europe: report from France (682 cases). Rev. Iberoam. Micol. **17:**S144.
16. **Hunter, P. A., and D. S. Reeves.** 2002. The current status of surveillance of resistance to antimicrobial agents: report on a meeting. J. Antimicrob. Chemother. **49:**17–23.
17. **Jones, R. N.** 1996. The emergent needs for basic research, education, and surveillance of antimicrobial resistance. Problems facing the report from the American Society for Microbiology Task Force on Antibiotic Resistance. Diagn. Microbiol. Infect. Dis. **25:**53–61.
18. **Jones, R. N.** 2000. Detection of emerging resistance patterns within longitudinal surveillance systems: data sensitivity and microbial susceptibility. J. Antimicrob. Chemother. **46**(Topic T2)**:**1–8.
19. **Jones, R. N., and R. Masterton.** 2001. Determining the value of antimicrobial surveillance programs. Diagn. Microbiol. Infect. Dis. **41:**171–175.
20. **Jones, R. N., and M. A. Pfaller.** 1998. Bacterial resistance: a world-wide problem. Diagn. Microbiol. Infect. Dis. **31:**379–388.
21. **Kao, A. S., M. E. Brandt, W. R. Pruitt, L. A. Conn, B. A. Perkins, D. S. Stephens, W. S. Baughman, A. L. Reingold, G. A. Rothrock, M. A. Pfaller, R. W. Pinner, and R. A. Hajjeh.** 1999. The epidemiology of candidemia in two United States cities: results of a population-based active surveillance. Clin. Infect. Dis. **29:**1164–1170.
22. **Kauffman, C. A.** 2001. Fungal infections in older adults. Clin. Infect. Dis. **33:**550–555.
23. **Kleinegger, C. L., S. R. Lockhart, K. Vargas, and D. R. Soll.** 1996. Frequency, intensity, species, and strains of oral *Candida* vary as a function of age. J. Clin. Microbiol. **34:**2246–2254.
24. **Klepser, M. E.** 2001. Antifungal resistance among *Candida* species. Pharmacotherapy **21:**124S–132S.
25. **Kossoff, E. H., E. S. Buescher, and G. M. Karlowicz.** 1998. Candidemia in a neonatal intensive care unit: trends during fifteen years and clinical features of 111 cases. Pediatr. Infect. Dis. J. **17:**504–508.
26. **Lamagni, T. L., B. G. Evans, M. Shigematsu, and E. M. Johnson.** 2001. Emerging trends in the epidemiology of invasive mycoses in England and Wales. Epidemiol. Infect. **126:**397–414.
27. **Lewis, D.** 2002. Antimicrobial resistance surveillance: methods will depend on objectives. J. Antimicrob. Chemother. **49:**3–5.
28. **Lockhart, S. R., S. Joly, K. Vargas, J. Swails-Wenger, L. Enger, and D. R. Soll.** 1999. Defenses against oral *Candida* carriage break down in the elderly. J. Dent. Res. **78:**857–868.
29. **Masterton, R. G.** 2000. Surveillance studies: how can they help the management of infection? J. Antimicrob. Chemother. **46**(Topic T2)**:**53–58.
30. **McNeil, M. M., S. L. Nash, R. A. Hajjeh, M. A. Phelan, L. A. Conn, B. D. Plikaytis, and D. W. Warnock.** 2001. Trends in mortality due to invasive mycotic diseases in the United States, 1980–1997. Clin. Infect. Dis. **33:**641–647.
31. **Meis, J., M. Petrou, J. Bille, D. Ellis, D. Gibbs, et al.** 2000. A global evaluation of the susceptibility of *Candida* species to fluconazole by disk diffusion. Diagn. Microbiol. Infect. Dis. **36:**215–223.
32. **Morris, A. K., and R. G. Masterton.** 2002. Antibiotic resistance surveillance: action for international studies. J. Antimicrob. Chemother. **49:**7–10.
33. **National Committee for Clinical Laboratory Standards.** 1997. Reference method for broth dilution antifungal susceptibility testing of yeasts. Approved standard M27-A National Committee for Clinical Laboratory Standards, Wayne, Pa.
34. **Nguyen, M. H., J. E. Peacock, Jr., A. J. Morris, D. C. Tanner, M. L. Nguyen, D. R. Snydman, M. M. Wagener, M. G. Rinaldi, and V. L. Yu.** 1996. The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance. Am. J. Med. **100:**617–623.
35. **Peman, J., A. Cercos, M. C. Penalver, A. Viudes, E. Canton, A. Planes, E. Canes, A. del Palacio, J. Sevillano, J. Vinuelas, M. Elia, M. Gimernez, M. Pazo, J. J. Garcia, J. J. Palomar, J. M. Hernandez, E. Minguez, J. A. Martinez, Y. Fernandez, J. Martinez, C. Tapiol, M. S. Cuetara, and S. Giner.** 2000. Epidemiological survey of candidemia in Spain. Rev. Iberoam. Micol. **17:**S143.
36. **Perea, S., J. L. Lopez-Ribot, W. R. Kirkpatrick, R. K. McAtee, R. A. Santillan, M. Martinez, D. Calabrese, D. Sanglard, and T. F. Patterson.** 2001. Prevalence of molecular mechanisms of resistance to azole antifungal agents in *Candida albicans* strains displaying high-level fluconazole resistance isolated from human immunodeficiency virus-infected patients. Antimicrob. Agents Chemother. **45:**2676–2684.
37. **Pfaller, M. A.** 1998. The epidemiology of invasive mycoses—narrowing the gap. Clin. Infect. Dis. **27:**1148–1150.
38. **Pfaller, M. A.** 2001. The fungal pathogen shift in the United States. J. Crit. Illness **16**(Suppl.)**:**S35–S42.
39. **Pfaller, M. A., S. A. Messer, A. Houston, M. S. Rangel-Frausto, T. Wiblin, H. M. Blumberg, J. E. Edwards, W. Jarvis, M. A. Martin, H. C. Neu, L. Saiman, J. E. Patterson, J. C. Dibb, C. M. Roldan, M. G. Rinaldi, and R. P. Wenzel.** 1998. National Epidemiology of Mycoses Survey: a multicenter study of strain variation and antifungal susceptibility among isolates of *Candida* species. Diagn. Microbiol. Infect. Dis. **31:**289–296.
40. **Pfaller, M. A., R. N. Jones, S. A. Messer, M. B. Edmond, and R. P. Wenzel.** 1998. National surveillance of nosocomial bloodstream infection due to species of *Candida* other than *Candida albicans*: frequency of occurrence and antifungal susceptibility in the SCOPE Program. Diagn. Microbiol. Infect. Dis. **30:**121–129.
41. **Pfaller, M. A., R. N. Jones, G. V. Doern, H. S. Sader, R. J. Hollis, and S. A. Messer for the SENTRY Participant Group.** 1998. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and antifungal susceptibilities of isolates collected in 1997 in the United States, Canada, and South America for the SENTRY Program. J. Clin. Microbiol. **36:**1886–1889.
42. **Pfaller, M. A., R. N. Jones, G. V. Doern, A. C. Fluit, J. Verhoef, H. S. Sader, S. A. Messer, A. Houston, S. Coffman, and R. J. Hollis for the SENTRY Participant Group (Europe).** 1999. International surveillance of bloodstream infections due to *Candida* species in the European SENTRY Program: species distribution and antifungal susceptibility including the investigational triazole and echinocandin agents. Diagn. Microbiol. Infect. Dis. **35:**19–25.
43. **Pfaller, M. A., R. N. Jones, G. V. Doern, H. S. Sader, S. A. Messer, A. Houston, S. Coffman, R. J. Hollis, and the SENTRY Participant Group.** 2000. Bloodstream infections due to *Candida* species: SENTRY Antimicrobial Surveillance Program in North America and Latin America, 1997–1998. Antimicrob. Agents Chemother. **44:**747–751.
44. **Pfaller, M. A., S. A. Messer, R. J. Hollis, and R. N. Jones.** 2001. In vitro activities of posaconazole (Sch 56592) compared with those of itraconazole and fluconazole against 3,685 clinical isolates of *Candida* spp. and *Cryptococcus neoformans*. Antimicrob. Agents Chemother. **45:**2862–2864.
45. **Pfaller, M. A., D. J. Diekema, R. N. Jones, H. S. Sader, A. C. Fluit, R. J. Hollis, S. A. Messer, and the SENTRY Participant Group.** 2001. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and in vitro susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY Antimicrobial Surveillance Program. J. Clin. Microbiol. **39:**3254–3259.
46. **Pfaller, M. A., D. J. Diekema, R. N. Jones, S. A. Messer, R. J. Hollis, and the SENTRY Participant Group.** 2002. Trends in antifungal susceptibility of *Candida* spp. from pediatric and adult patients with bloodstream infections:

SENTRY Antimicrobial Surveillance Program, 1997 to 2000. J. Clin. Microbiol. **40:**852–856.
47. **Pfaller, M. A., S. A. Messer, R. J. Hollis, R. N. Jones, and D. J. Diekema.** 2002. In vitro activities of ravuconazole and voriconazole compared with those of four licensed systemic antifungal agents against 6,970 clinical isolates of *Candida* spp. Antimicrob. Agents Chemother. **46:**1723–1727.
48. **Rangel-Frausto, M. S., T. Wiblin, H. M. Blumberg, L. Saiman, J. Patterson, M. Rinaldi, M. Pfaller, J. E. Edwards, Jr., W. Jarvis, J. Dawson, and R. P. Wenzel.** 1999. National Epidemiology of Mycoses Survey (NEMIS): variations in rates of bloodstream infections due to *Candida* species in seven surgical intensive care units. Clin. Infect. Dis. **29:**253–258.
49. **Rees, J. R., R. W. Pinner, R. A. Hajjeh, M. E. Brandt, and A. L. Reingold.** 1998. The epidemiologic features of invasive mycotic infections in the San Francisco Bay Area, 1992–1993: results of a population-based laboratory active surveillance. Clin. Infect. Dis. **27:**1138–1147.
50. **Reeves, D. S.** 2002. Antimicrobial resistance surveillance: current initiatives are not enough. J. Antimicrob. Chemother. **49:**1.
51. **Rennert, G., H. S. Rennert, S. Pitlik, R. Finkelstein, and R. Kitzes-Cohen.** 2000. Epidemiology of candidemia—a nationwide survey in Israel. Infection **28:**26–29.
52. **Rex, J. H., T. J. Walsh, S. D. Sobel, S. G. Filler, P. G. Pappas, W. E. Dismukes, and J. E. Edwards.** 2000. Practice guidelines for the treatment of candidiasis. Clin. Infect. Dis. **30:**662–678.
53. **Richards, M. J., J. R. Edwards, D. H. Culver, and R. P. Gaynes.** 2000. Nosocomial infections in combined medical-surgical intensive care units in the United States. Infect. Control Hosp. Epidemiol. **21:**510–515.
54. **Richet, H. M.** 2001. Better antimicrobial resistance surveillance efforts are needed. ASM News **67:**304–309.
55. **Ronveaux, O., B. Jans, and H. Carsauw.** 1998. Epidemiology of nosocomial bloodstream infections in Belgium, 1992–1996. Eur. J. Clin. Microbiol. Infect. Dis. **10:**695–700.
56. **Saiman, L., E. Ludington, M. Pfaller, S. Rangel-Frausto, R. T. Wiblin, J. Dawson, H. M. Blumberg, J. E. Patterson, M. Rinaldi, J. E. Edwards, R. P. Wenzel, W. Jarvis, and the National Epidemiology of Mycosis Survey Study Group.** 2000. Risk factors for candidemia in neonatal intensive care unit patients. Pediatr. Infect. Dis. J. **19:**319–325.
57. **Sandven, P.** 2000. Epidemiology of candidemia. Rev. Iberoam. Micol. **17:** 73–81.
58. **Sandven, P., L. Bevanger, A. Digranes, P. Gaustad, H. H. Haukland, and M. Steinbakk.** 1998. Constant low rate of fungemia in Norway, 1991 to 1996. The Norwegian Yeast Study Group. J. Clin. Microbiol. **36:**3455–3459.
59. **Sheehan, D. J., C. A. Hitchcock, and C. M. Sibley.** 1999. Current and emerging azole antifungal agents. Clin. Microbiol. Rev. **12:**40–79.
60. **St-Germain, G., M. Laverdiere, R. Pelletier, A.-M. Bourgault, M. Libman, C. Lemieux, and G. Noel.** 2001. Prevalence and antifungal susceptibility of 442 *Candida* isolates from blood and other normally sterile sites: results of a 2-year (1996 to 1998) multicenter surveillance study in Quebec, Canada. J. Clin. Microbiol. **39:**949–953.
61. **Tortorano, A. M., M. A. Viviani, A. L. Rigoni, E. Biraghi, M. Cogliati, A. Astolfi, C. Ossi, S. Perin, C. Bonaccorso, L. Garlaschi, G. Viola, M. Saudelli, S. Frugoni, A. Mauri, R. Passerini, C. Farina, M. Tejada, C. Cavanna, A. Raballo, A. Grossi, C. Bezzi, M. Spinelli, S. Bramati, G. Pinsi, L. Colombo, L. Ferrari, P. Troupioti, G. L. Lombardi, M. Arghittu, C. Agrapii, L. Sturla, G. Gialluca, M. G. Musmanno, A. Ceraminiello, P. Casella, R. Sala, S. Pierdomenico, S. Gualterotti, P. Porri, and A. Lizioli.** 2000. ECMM survey of candidemia in Europe. Report from Italy. Rev. Iberoam. Micol. **17:**S143.
62. **Trick, W. E., S. K. Fridhin, J. R. Edwards, R. A. Hajjeh, R. P. Gaynes, and the National Nosocomial Infections Surveillance System Hospitals.** 2002. Secular trend of hospital acquired candidemia among intensive care unit patients in the United States during 1998-1999. Clin. Infect. Dis. **35:**627–630.
63. **Viscoli, C., C. Girmenia, and A. Marinus.** 1999. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). Clin. Infect. Dis. **28:**1071–1079.
64. **Wey, S. B., M. Mori, M. A. Pfaller, R. F. Woolson, and R. P. Wenzel.** 1988. Hospital acquired candidemia: attributable mortality and excess length of stay. Arch. Intern. Med. **148:**2642–2645.
65. **White, T. C., K. A. Marr, and R. A. Bowden.** 1998. Clinical, cellular, and molecular factors that contribute to antifungal drug resistance. Clin. Microbiol. Rev. **11:**382–402.
66. **Yamamura, D. L., C. Rotstein, L. E. Nicolle, and S. Ioannou.** 1999. Candidemia at selected Canadian sites: results from the Fungal Disease Registry, 1992–1994. Fungal Disease Registry of the Canadian Infectious Disease Society. Can. Med. Assoc. J. **160:**493–499.