

Active Bacterial Core Surveillance of the Emerging Infections Program Network

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Active Bacterial Core surveillance (ABCs) is a collaboration between the Centers for Disease Control and Prevention and several state health departments and universities participating in the Emerging Infections Program Network. ABCs conducts population-based active surveillance, collects isolates, and performs studies of invasive disease caused by *Streptococcus pneumoniae*, group A and group B *Streptococcus*, *Neisseria meningitidis*, and *Haemophilus influenzae* for a population of 17 to 30 million. These pathogens caused an estimated 97,000 invasive cases, resulting in 10,000 deaths in the United States in 1998. Incidence rates of these pathogens are described. During 1998, 25% of invasive pneumococcal infections in ABCs areas were not susceptible to penicillin, and 13.3% were not susceptible to three classes of antibiotics. In 1998, early-onset group B streptococcal disease had declined by 65% over the previous 6 years. More information on ABCs is available at www.cdc.gov/ncidod/dbmd/abcs. ABCs specimens will soon be available to researchers through an archive.

Bacterial infections are prototypical emerging diseases (1), and their recent history challenges the premature view that the battle against infectious diseases had been won. In the last 25 years, disease caused by multidrug-resistant *Streptococcus pneumoniae* became established on several continents, reaching the United States by the 1990s (2-4), and fatal infections caused by *S. pyogenes* (group A *Streptococcus*), a problem of the 19th century (5),

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have returned in toxic and necrotic forms (6). By the 1970s, group B *Streptococcus* replaced gram-negative bacteria and *Staphylococcus aureus* as the leading cause of sepsis in newborns (7,8). Researchers tackled the public health challenge of developing vaccines to protect children against the major causes of bacterial meningitis: *Haemophilus influenzae* type b, *S. pneumoniae*, and *Neisseria meningitidis* (9,10). A critical step for response to microbial adaptation is establishing a reliable tracking system. We describe active, population-based surveillance for serious bacterial infections that was established by the Centers for Disease Control and Prevention

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(CDC) as part of its response to emerging infectious diseases (11,12).

Active Bacterial Core surveillance (ABCs) was designed to estimate the burden of community-acquired invasive bacterial infections that typically manifest as sepsis and meningitis. The system determines incidence and trends of these diseases in a multistate population and uses molecular and microbiologic methods to characterize the organisms causing infection. As prevention strategies against some pathogens are used routinely (9,13,14), ABCs evaluates their impact and identifies missed opportunities for their application. Established in four states in 1995, ABCs now operates within the eight states of the Emerging Infections Program (EIP) network, representing a population of more than 30 million and ascertaining cases from more than 600 clinical microbiology laboratories. A ninth EIP state, Colorado, initiated ABCs during 2000. ABCs currently focuses on surveillance and special studies related to five pathogens: *S. pneumoniae*, *H. influenzae*, *N. meningitidis*, group A *Streptococcus* (*S. pyogenes*), and group B *Streptococcus* (*S. agalactiae*).

ABCs' predecessor was the active surveillance program for invasive bacterial diseases established in 1988 (also sponsored by CDC), which evaluated the efficacy of *H. influenzae* type b vaccines in infants (15), identified dietary risk factors for sporadic listeriosis (16,17), and compared the cost-effectiveness of strategies for preventing group B streptococcal disease in newborns (18). ABCs has expanded the scope of targeted conditions to address additional emerging infections such as necrotizing fasciitis (the so-called flesh-eating disease) and streptococcal toxic-shock syndrome, both severe manifestations of disease caused by group A *Streptococcus*. ABCs also now monitors the emergence of drug resistance in the community-acquired pathogen *S. pneumoniae*. ABCs is one of three core activities conducted by EIPs; the others are FoodNet (19) and the Unexplained Critical Illness and Death Project (20). This article, a progress report of the first 5 years of the EIP network's ABCs project, identifies easily accessible resources from this system for public health and infectious disease constituencies.

ABCs Methods

In 1999, ABCs was conducted in Connecticut as well as in part or all of the following states:

California, Georgia, Maryland, Minnesota, New York, Oregon, and Tennessee (Figure 1). (For certain pathogens, surveillance is conducted statewide in Georgia, Maryland, Minnesota, and Oregon). The total population under surveillance in 1998 ranged from approximately 17.4 million for *S. pneumoniae* to 30.4 million for *N. meningitidis*.



Figure 1. States included in Active Bacterial Core surveillance in 1999. Surveillance for all pathogens was conducted statewide in Connecticut but in selected counties only for some or all pathogens in the other states.

A case is defined as isolation of one of the five pathogens from a usually sterile site (e.g., blood, cerebrospinal fluid, pleural fluid) in a resident of one of the surveillance areas. Detailed methods of case-finding, data collection, and laboratory audits conducted within ABCs have been described (10,21). The key features are active ascertainment of cases by state-based surveillance officers, who make regular contact with microbiology or infection control practitioners in all clinical microbiology laboratories processing sterile site cultures for the surveillance area; collection of isolates of the specified pathogens for laboratory testing by ABCs personnel (Table 1); and semiannual audits of all participating laboratories to identify missed cases. Because the surveillance is population-based and cases identified by audits are included in the final database, ABCs data are used to monitor incidence of these diseases in a large, defined population. With the use of race- and age-adjustment, ABCs data also permit annual projections of the estimated incidence as well as the estimated number of cases and deaths occurring in the entire United States. For national projections, cases with unknown race

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Table 1. Laboratory characterization of isolates collected as part of the Active Bacterial Core surveillance program

Pathogen	Test(s)
Group A <i>Streptococcus</i>	<i>emm</i> - and T-typing for all invasive isolates; antimicrobial susceptibility testing of periodic samples
Group B <i>Streptococcus</i>	Serotyping and antimicrobial susceptibility testing of isolates for selected surveillance areas
<i>Haemophilus influenzae</i>	Serotyping of all isolates (a-f); molecular subtyping of isolates as part of special projects
<i>Neisseria meningitidis</i>	Molecular subtyping of isolates in conjunction with vaccine development; antimicrobial resistance on isolates periodically
<i>Streptococcus pneumoniae</i>	Antimicrobial susceptibility testing for all invasive isolates; serotyping on all invasive isolates since January 1, 1998; subtyping of a sample of isolates using genotyping methods

are distributed by area, on the basis of reported race distribution for known cases within eight age categories. U.S. census data for counties under surveillance and natality data on live births are the sources of denominators for incidence calculations; the most recent year's population data available with age and race information at the county level are used for rate calculations.

Core surveillance activities include collecting epidemiologic and clinical data and characterizing isolates in terms of antimicrobial susceptibility, serotype or serogroup, and subtyping. ABCs also conducts special studies that use the surveillance infrastructure but require collection of additional data by chart review, patient interviews, or analysis of ABCs data together with complementary data sources. ABCs uses the following indicators to monitor performance: sensitivity of >90% for active surveillance (based on total cases detected by surveillance and the laboratory audit); collection of >85% of isolates from cases; and enrollment of 90% of eligible participants into special studies.

ABCs is overseen by a steering committee consisting of CDC and state EIP representatives as well as external advisors from the public health, infectious disease, and microbiology fields. These parties convey views from key constituents and annually evaluate the need to add or subtract pathogens for surveillance. In 1999, CDC's National Center for Infectious Diseases awarded \$10.7 million through cooperative agreements to eight EIP states; approximately \$2.5 million (23%) of these funds supported ABCs-related activities.

Results

Surveillance Highlights

In 1998, 6,992 cases of invasive disease caused by the five pathogens were reported from the eight sites. The rates of invasive disease (per 100,000) ranged from 1.0 for *N. meningitidis* to 24.1 for *S. pneumoniae* (Table 2). An estimated 97,000 invasive infections and 10,000 deaths per year in the United States are due to *S. pneumoniae*, group A and B streptococci,

Table 2. Incidence, case-fatality ratio, projected U.S. cases and deaths, and proportion nonsusceptible to penicillin of invasive disease identified in the Active Bacterial Core surveillance (ABCs), 1998

	Group A <i>Streptococcus</i>	Group B <i>Streptococcus</i>	<i>Haemophilus</i> <i>influenzae</i>	<i>Neisseria</i> <i>meningitidis</i>	<i>Streptococcus</i> <i>pneumoniae</i>
Aggregate incidence ^a	3.8	6.5	1.4	1.0	24.1
Range by area ^a	2.6 - 4.1	4.8 - 8.5	1.1 - 2.3	0.6 - 2.0	20.0-28.9
Case-fatality ratio in ABCs areas	12.2%	9.5 %	13.9%	13.7%	9.3%
Projected U.S. cases	10,200	17,400	3,900	2,500	63,000
Projected U.S. deaths	1,300	1,700	500	400	6,100
Penicillin nonsusceptibility ^b	0	0	-	1.1%	25.0%

^aIncidence = cases per 100,000.

^bNonsusceptible includes isolates classified as either intermediate or resistant to penicillin. Results reflect testing of group A streptococcal isolates from 1997 (n=183) and group B streptococcal isolates from 1997 and 1998 combined (n=188).

H. influenzae, and *N. meningitidis*. Despite continued availability of effective antimicrobial agents for each pathogen, approximately 1 in 10 cases results in death (Table 2). Substantial geographic variation exists in the incidence of invasive infections caused by each pathogen (Table 2). Among invasive *S. pneumoniae* infections, the proportion caused by drug-resistant organisms was three times higher in some areas than others (4); 8.4% of invasive pneumococci from New York were fully resistant to penicillin (MIC ≥ 2.0), while 25.4% of isolates from Tennessee were penicillin resistant. No penicillin-nonsusceptible (intermediate or resistant) strains of group A or group B *Streptococcus* have been detected to date.

Recent temporal changes are most dramatic for invasive group B streptococcal disease among infants less than 1 week old (i.e., early-onset disease), which declined 65% from 1993 to 1998 (Figure 2), during a period when the incidence of disease in older infants and adults remained stable (22). Data from ABCs provide a reliable standard for evaluating alternative methods for surveillance of drug resistance in *S. pneumoniae*, including sentinel surveillance methods (4) and use of aggregate data from antibiograms from multiple hospitals (23). The recent emergence of serogroup Y meningococci, demonstrated by ABCs, suggests that vaccine companies should consider incorporating serogroup Y in new meningococcal vaccines. In addition, the diversity in the outer membrane proteins of serogroup B meningococcal strains suggests that vaccines against these

proteins may not be efficient means of preventing endemic serogroup B meningococcal disease.

Applied Research

The population-based collections of isolates from ABCs are used to evaluate subtyping methods (24), identify genetic mechanisms of antimicrobial resistance, determine vaccine formulations (25,26), and assess capsular switching among organisms (for vaccines based on capsular types) (27,28). ABCs has identified population-based risk factors for disease in various age groups (Table 3). A case-control study of invasive pneumococcal disease in young children showed that attendance at day care was associated with a substantial attributable risk for disease (29). A similar study of invasive pneumococcal disease in 18- to 64-year-old adults who were not immunocompromised identified active and passive smoking, in addition to household contact with a child in day care, as independent risk factors for disease (30). Models of age- and serogroup- or serotype-specific rates of invasive meningococcal and pneumococcal disease in the ABCs population have compared the potential impact of diverse immunization strategies for meningococcal and combined meningococcal-pneumococcal vaccines on disease prevention (32). The increased risk for pneumonia death occurring several days after illness onset associated with antimicrobial-resistant strains of *S. pneumoniae* was demonstrated by using multistate clinical and epidemiologic data from ABCs (33).

Figure 2. Invasive group B streptococcal disease in infants less than 1 week of age per 1,000 live births and in adults ≥ 65 years of age per 100,000 population, Active Bacterial Core surveillance, 1993-1998 (adapted from ref. 22).

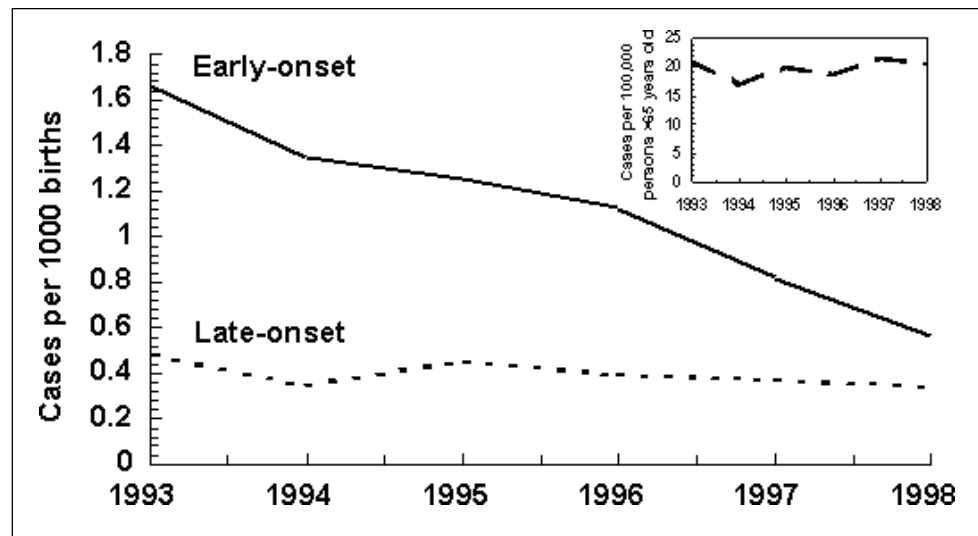


Table 3. Population-based risk factors for invasive disease, identified by Active Bacterial Core surveillance

Pathogen	Age group, other criteria	Factors associated with increased risk by multivariate analysis	References
<i>Streptococcus pneumoniae</i>	<5 years old	Child-care attendance, underlying conditions, lack of breast-feeding, household crowding	29
	18-64 years old, not immunocompromised	Active or passive smoke exposure, black race, chronic diseases, household contact with child in day care	30
<i>Neisseria meningitidis</i>	All ages	Active or passive smoke exposure, underlying conditions, steroid use, attendance at new school	31
Group B <i>Streptococcus</i>	<7 days old	Black race, low birth weight, maternal age <20 years	CDC, unpub. data

Infrastructure

ABCs provides participating state health departments active contact with all acute-care hospitals and reference microbiology laboratories in the surveillance area. This network provides an infrastructure for public health communication and education, as well as a network of key contacts available for response to new or emerging concerns. Periodic surveys of laboratories within ABCs determined the adequacy of methods used to detect group B *Streptococcus* from prenatal screening specimens (34), the computerization of clinical microbiology laboratories and readiness for electronic laboratory-based reporting, and the routine procedures used by ABCs laboratories to detect antimicrobial resistance among *S. pneumoniae*, *S. aureus*, and several other organisms (35). ABCs and other EIP personnel have provided assistance with multistate response efforts to determine the burden of Creutzfeldt-Jakob disease (36) and contributed to efforts to determine the rate of rotavirus vaccine-related intussusception (37). Further, the presence of ABCs personnel in state health departments and academic institutions has strengthened communication links required for accurate reporting and feedback.

Prevention

Since publication of consensus guidelines for the prevention of group B streptococcal disease in newborns, ABCs assessed the implementation of prevention practices and identified opportunities for preventing more cases. ABCs showed that hospital obstetric programs' adoption of policies to prevent group B streptococcal infection increased significantly (38) and that hospitals

that had adopted or revised a policy in 1996 had significantly fewer cases in 1997 (39). ABCs is also tracking the characteristics of newborn group B streptococcal cases that continue to occur despite prevention guidelines to determine whether these represent failures of intrapartum antibiotic prophylaxis or failure to offer such prophylaxis to mothers at risk. In several EIPs, pilot prevention programs are in place to identify efficient ways to reduce the incidence of disease caused by ABCs pathogens. These include a multifaceted program to reduce inappropriate antibiotic use in the Baltimore metropolitan area and efforts to promote pneumococcal polysaccharide vaccine in populations at high risk in Rochester, New York; Minneapolis-St. Paul, Minnesota; metropolitan Atlanta, Georgia; and Portland, Oregon. The Connecticut and Minnesota health departments conducted demonstration projects that integrated prevention of group B streptococcal disease into routine perinatal care, building on successes with hepatitis B perinatal prevention programs and contributing to reduction of perinatal HIV transmission (40,41).

Discussion

Nearly 100,000 invasive infections and 10,000 deaths caused by ABCs pathogens occur annually in the United States. Because few states routinely collect data and isolates for all of these infections, ABCs helps monitor disease and evaluate prevention programs at the national level. ABCs has now developed robust estimates of the magnitude of disease and deaths attributable to the five invasive pathogens (Table 2). A number of future priorities have been identified

that take advantage of the careful characterization of isolates associated with invasive infection. Licensure and introduction of a seven-valent conjugate vaccine against *S. pneumoniae* necessitate evaluation of the impact of this new prevention tool on target populations (Table 4). Of particular interest will be evaluating whether indirect effects similar to those seen with the Hib vaccine (42) occur. The large birth cohort under surveillance through ABCs and the longitudinal data on both early-onset cases and hospital policies for disease prevention offer the opportunity to compare the two alternative strategies for group B streptococcal prevention (screening-based vs. risk-based) through two studies during the next few years. ABCs will continue to contribute to tracking progress in Hib elimination, monitor for emergence of other serotypes of *H. influenzae*, and provide data on strain-specific disease (e.g., serotype, serogroup, outer membrane type). Such information is valuable for evaluating new vaccines for group B *Streptococcus* and serogroup B meningococcus. ABCs data will also be used to define clusters of invasive group A streptococcal disease and to model the impact of possible strategies and new formulations of pneumococcal vaccines targeted against pneumococcal pneumonia in adults (Figure 3) as well as vaccines targeted against invasive group A *Streptococcus* syndromes.

The molecular biology revolution and improved understanding of host-pathogen interactions offer great potential to advance knowledge about ABCs bacteria. Emerging antimicrobial resistance and other forms of pathogen adaptation (e.g., capsular switching) lend an urgency to such research. Specimens from invasive disease surveillance represent well-characterized, population-based collections with relevant clinical and demographic information. These provide a

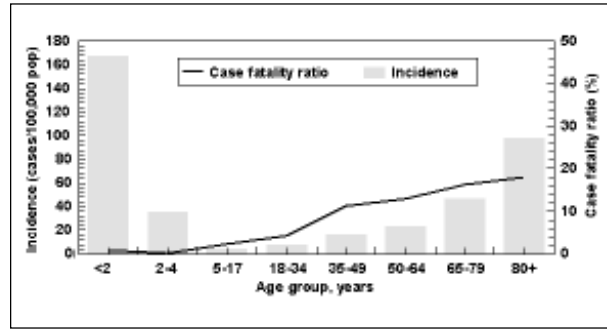


Figure 3. Age-specific incidence (per 100,000) and case-fatality ratio (percent) of invasive pneumococcal disease, Active Bacterial Core surveillance, 1998.

valuable resource for basic and applied research focused on issues as varied as new drug and vaccine development, evaluation of mechanisms of virulence and antimicrobial resistance, and genetic research. ABCs is planning to make these strains available to outside researchers and industry through a preserved collection. Such a specimen bank could provide a lasting legacy of the work of hundreds of infection control practitioners, clinical microbiology laboratories, and ABCs surveillance collaborators.

To ensure that ABCs' lessons learned within the EIP network reach other public health constituents, a number of efforts are under way. Additional details of the surveillance system and outreach materials are available at <http://www.cdc.gov/ncidod/dbmd/abcs>. Other educational materials are available at <http://www.cdc.gov/ncidod/dbmd/gbs> and at <http://www.cdc.gov/ncidod/dbmd/antibioticresistance>. For laboratories evaluating new strains of group A *Streptococcus*, genetic sequencing data of all strains described thus far are also available on the web. A similar site for meningococcal isolates is under development.

Conclusions

ABCs is a model of collaboration between public health and academia. The system provides reliable data that can be used to address critical public health concerns, improve understanding of emerging infections, and help prevent the consequences of these infections. While the past 5 years have helped quantify the magnitude of disease caused by these pathogens and document increasing antibiotic resistance in some of them, the future provides several challenges. To remain a vital component

Table 4. Future priorities for Active Bacterial Core surveillance (ABCs) project

1. Define invasive group A *Streptococcus* clusters.
2. Determine effectiveness of screening vs. risk-based prevention strategies for perinatal group B streptococcal disease.
3. Determine feasibility of eliminating invasive disease caused by *Haemophilus influenzae* type b.
4. Quantify culture-negative, polymerase chain reaction-positive meningitis.
5. Measure direct and indirect effects of introducing a seven-valent pneumococcal conjugate vaccine.

in the nation's efforts to prevent and control emerging infectious diseases, ABCs will need to incorporate surveillance and research tools of the 21st century, including electronic laboratory-based reporting, genotyping of pathogens, and improved communication to promote behavioral change and adoption of practice guidelines.

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