Communicable Respiratory Threats in the ED: Tuberculosis, Influenza, SARS, and Other Aerosolized Infections

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Communicable diseases are infections that are caused by microorganisms that can be transmitted from one infected person to another [1]. In spite of improvements in methods to prevent, detect, and decrease transmission of these infections, communicable diseases still represent a significant public health threat. The relative burden of communicable diseases varies globally, accounting for 10% of the overall global disease burden, but nearly 50% of deaths in developing countries [2]. The recent occurrence of emerging and biological threats has heightened awareness of the potential devastation associated with an unexpected infectious disease outbreak [3].

Respiratory infections are the most common communicable infectious diseases [2]. Transmission can occur by a number of routes including contact transmission (direct or indirect exposure to infected patients), droplet transmission (contact with contagious large respiratory droplets that do not stay suspended in the air), and airborne transmission (contact with small, less than 5 micromolar particles that can remain suspended in the air for extended periods of time and be disseminated and inhaled by susceptible hosts) [4]. Airborne transmissible respiratory infections represent the most significant public health risk, as the route of transmission puts large numbers of persons at risk and introduces the greatest potential for hospital outbreaks and epidemics. The most common of these include influenza, tuberculosis, and measles, which together account for approximately 25% of infectious causes of death worldwide [2]. Also included in this discussion are emerging and biothreat agents, which follow the same route of

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transmission. Most prominent examples include severe acute respiratory syndrome (SARS) and pneumonic plague (smallpox is discussed in the chapter by Saks and Karras elsewhere in this issue).

Emergency departments (EDs) serve as the frontline for patients with communicable respiratory diseases because of the acute nature of these illnesses and because the ED serves as the principal site of health care for many of those at highest risk for these diseases (see Fig. 1). A discussion of each of these contagious respiratory agents follows with attention to epidemiology, pathogenesis, diagnosis, and treatment. Emphasis will be given to the pivotal role of the ED as a public health prevention arena for communicable aerosolized respiratory infectious diseases, with attention to the three critical arms of prevention: primary (education and disease prevention), secondary (early identification of disease in patients at risk), and tertiary (reduction of illnesses in patients with diseases) [5].

Five communicable respiratory threats

Tuberculosis

Epidemiology and pathophysiology

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis,* which is a slow-growing, acid-fast bacillus. It is the second most common cause of infectious disease–related deaths worldwide, after HIV/AIDS [6], with 8.8 million incident cases per year and 1.7 million deaths per year [7]. In the United States, the disease burden is lower but still significant, with approximately 15 million people infected overall [8]. Although public health preventive measures over the past decade have resulted in a favorable trend in the incidence of TB in the United States (with a peak of 10.5 cases per 100,000 in 1992, to 5.1 cases per 100,000 in 2003), rates of decline have recently slowed [8]. This slowing in the rate of decline, along with the recent emergence of multidrug-resistant tuberculosis (MDRTB) [9], makes this disease one of the leading public health threats to our nation.

TB is spread by tiny 1- to 5-μm airborne droplet nuclei, which can remain airborne for hours after expectoration caused by coughing, sneezing, or talking. The infectious nuclei are inhaled and lodge in the distal alveoli where host defenses are activated. A variety of potential subsequent events follow, based on pathogen load and host responsiveness. In most cases, cell-mediated immunity results in immediate destruction of the organism. In some cases, however, initial infection is established when the organism is transported to regional lymph nodes. Here, further cell-mediated immune response results in containment of infection, or in those with less-effective immune systems, development of immediate disease (ie, primary active TB). For the majority of infected individuals who successfully contain the infection, bacteria remain contained in granulomas or tubercles where replication of the organism is limited. This latent infectious state generally lasts
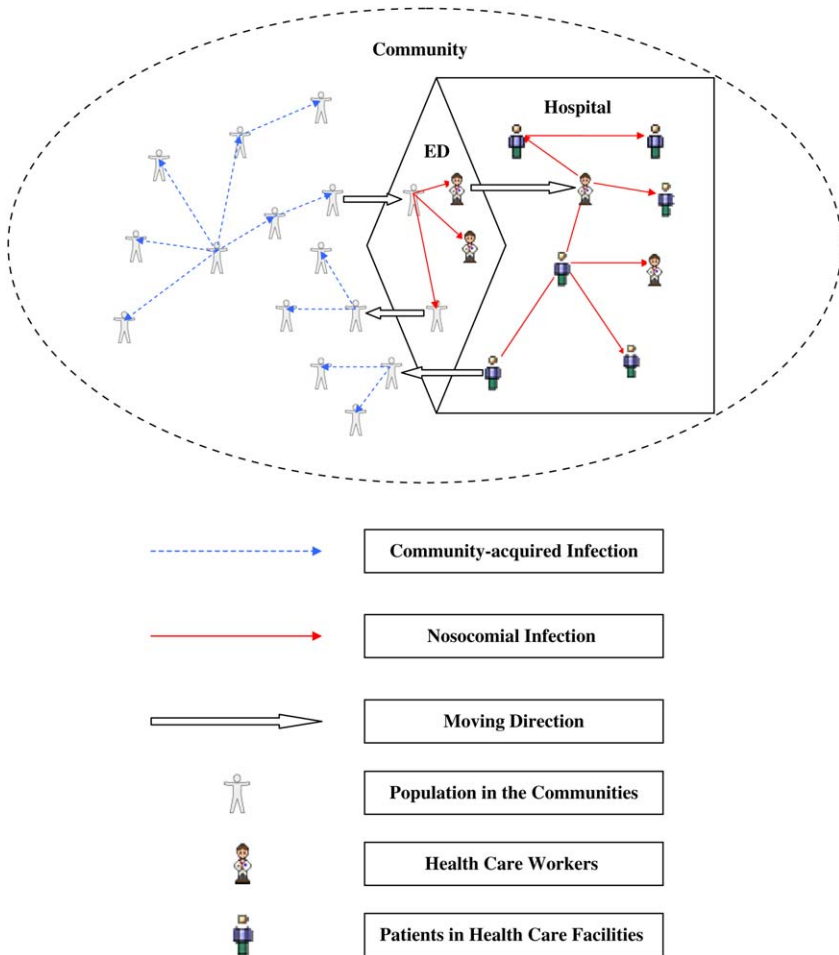
Fig. 1. Emergency department (ED) as potential bridge between community and nosocomial aerosolized respiratory infections.

for the life of the infected patient. In others, reactivation of infection occurs when the host's immune response is no longer capable of containment. Those at highest risk for reactivation include the very young, the elderly, and patients with chronic immunocompromising diseases, particularly HIV [10]. For immunocompetent individuals, the overall lifetime risk of re-activation of TB is 10%; for those with HIV the risk of reactivation is significantly higher, estimated to be about 7% per year.

Clinical presentation, diagnosis, and treatment

ED diagnosis and public health control measures are challenging because clinical presentation of TB can be highly variable and culturing the

organism takes days to weeks. Primary TB is most frequently asymptomatic and identifiable only by a positive skin test (PPD, purified protein derivative). In rare cases, active disease may develop, which is clinically similar to reactivation TB. Signs and symptoms of reactivation TB can be either pulmonary only (80% of cases) or systemic.

Early recognition of TB in the clinical area requires maintaining a high level of clinical vigilance. Populations recognized to be at increased risk of infection include foreign-born persons from areas where TB is common (eg, Asia, Africa, Latin America, and countries that were part of the former Soviet Union), medically underserved patients, low-income populations, racial and ethnic minority groups (eg, African Americans, Hispanics, Asians and Pacific Islanders, and Native Americans), the residents of long-term care facilities (eg, correctional facilities and nursing homes), injection drug users (IDUs), migrant farm workers, homeless persons, and persons who may have had a personal or occupational exposure to TB [11].

The most common symptoms of TB are fever, productive cough, and dyspnea. Other symptoms include night sweats, malaise, fatigue and weight loss, hemopytysis, and pleuritic chest pain. In one ED-based study of a series of patients who later were identified as having contagious TB, cough was present in only 64% of cases and was the chief complaint in less than 20% of cases. Furthermore, only 36% of patients reported any pulmonary complaints at triage [12]. TB can involve nearly every organ system but the most common extrapulmonary sites infected are the lymph nodes, central nervous system (CNS), bones, and joints. CNS presentations are usually subacute with findings including indolent headache, fever, and occasionally altered mental status. Although TB can affect nearly every joint, the spine is the most commonly affected site (Pott's disease). Disseminated TB can involve multiple organ systems, including the lungs. Diagnosis should be suspected in those with a miliary pattern on chest radiographs.

Patients with suspected TB should be isolated in negative pressure isolation rooms as early as possible until TB has been ruled out with certainty. Definitive diagnosis is not possible in the ED, since culture is the gold standard and requires several weeks for growth. A presumptive diagnosis of TB can be made by Ziehl-Neelson staining, which identifies acid-fast bacilli; sensitivity of this method is only 50% to 80%, however, and requires obtaining multiple positive sputum samples for confirmation. New laboratory-based molecular diagnostics such as polymerase chain reaction hold promise for rapid definitive diagnosis, but are not yet accepted as routine for clinical decision making [13]. Chest radiographs should be obtained on patients with suspected TB. Classic radiographic findings are upper-lobe infiltrates, cavitary infiltrates, and hilar or paratracheal adenopathy. It is critical to keep in mind, however, that radiographic findings with TB are highly variable, with atypical findings more common in those with immunosuppressive states, such as advanced HIV [14].

Disposition and treatment decisions for ED patients with suspected or confirmed TB should be made in consultation with infectious disease specialists. Hospital epidemiologist and public health services should be notified for all new cases (suspected or confirmed) and respiratory isolation patients should be maintained. Outpatient treatment is considered acceptable in those instances in which compliance and home isolation can be assured. Admission with inpatient respiratory isolation should be arranged for any patient with uncertain diagnosis, question regarding outpatient medication compliance, concern for MDRTB, or other obvious clinical parameters requiring hospitalization (ie, hypoxemia). Beginning treatment (which is beyond the scope of this review) consists of three- or four-drug therapy until drug susceptibility can be confirmed.

Disease burden in the ED

Emergency departments are particularly vulnerable to the threat of TB, and represent high-risk sites for potential propagation of disease. Contributing factors include characteristics of the patient populations served, ED infrastructure, and the inherent nonspecific clinical features and highly contagious nature of the disease [15–17]. As described above, those groups at highest risk for TB (eg, the homeless, the uninsured, immigrants, IDUs, and HIV/AIDS patients) often use the ED as their principal or sole site of care [18–20]. Busy inner-city waiting rooms and overcrowded conditions with long wait times and lack of adequate isolation rooms and personal protective equipment further contribute to the potential spread of TB [21]. One recent retrospective study from an urban teaching hospital found that 44 active TB patients made 66 contagious ED visits over a 30-month period that went unrecognized before diagnosis [12]; a similar retrospective study found that nearly 50% of newly diagnosed TB cases had an antecedent visit within 6 months of diagnosis [22]. Several studies from high-risk urban EDs have demonstrated delayed disease recognition with reports of lengthy ED stays (median 13 hours) [23], and significant delays in time to isolation (median time of 8 hours from triage to isolation) [24].

Increased risk of TB infection among health care workers (HCWs) versus the general population is evident. The results are principally derived from the evaluation of PPD conversion studies, with one recent review reporting an overall incidence of PPD positivity 100 times higher in HCWs versus that found in the general population [25]. Risk of TB infection significantly increases when clinical procedures that produce large amounts of aerosol are performed, such as induced sputum or intubation [26]. ED staff reportedly have PPD conversion rates up to six times higher than other hospital workers, with rates of conversion ranging from 1% to 12% [27]. Principal explanations for the high rates of ED HCW PPD conversion include the high frequency of atypical presentations for patients with TB at initial presentation, the lack of consistent implementation of triage screening for TB, and the lack of availability of adequate infection control facilities in EDs [21].

Public health interventions

Interventional approaches to TB control can be primary, secondary, or tertiary. Consistent application of simple public health measures can convert the ED from a site that represents a high-risk venue for further disease transmission, to one that can improve disease prevention, recognition, and control. The principles of TB control described in the 1994 Centers for Disease Control and Prevention (CDC) guidelines for hospitals and other health care facilities encompass three areas of intervention: administrative, engineering, and use of personal protective equipment (PPE) [28]. Although there are no specific guidelines for TB control provided by the American College of Emergency Physicians (ACEP), most texts use the CDC guidelines as a standard [28].

Administrative interventions include development of methods to ensure early isolation of persons with suspected disease, development of hospital-wide TB control plans, and maintenance of an active PPD skin-testing program among HCWs. Engineering controls focus on handing of air: negative-pressure respiratory isolation rooms, UV light fixtures, and HEPA (high-efficiency particulate air) filters [29]. PPE involves routine use of the N-95 particulate respirator for HCWs who are in close contact with suspected cases. Several studies conducted since 1994 have demonstrated that adherence to these guidelines significantly increases identification of cases and reduces disease transmission in HCWs [16,23]. For example, the introduction of TB control measures including engineering upgrades and improved access to PPE in one inner-city ED resulted in a nearly sixfold diminution in PPD conversion among HCWs [16]. Similar administrative and facilities improvement in another high-risk ED resulted in decreased wait times and increased rates of appropriate isolation for ED patients with suspected TB [23].

Development of methods for rapid identification of cases of TB at ED triage has met with mixed results. One study that evaluated the use of a simple triage guideline found that the sensitivity and specificity of their screening tool was only 63% and 78%, respectively [30]. Explanations for the relatively low sensitivity of the tool included lack of consistent compliance with guideline implementation and failure of a subset of patients to report key risk factors and symptoms at ED triage (which were elicited later during the ED evaluation). An alternate TB screening tool that was retrospectively derived from a population of culture-positive cases had a much higher sensitivity (96%) [31]. The final decision instrument involved assigning a 1-point score to each of several variables (abnormal chest x-ray, temperature greater than 101°F, homeless/shelter dwelling, and TB history), with a positive screen assigned to any patient with more than 2 points. The principal limitation of this method, which restricts applicability for triage decision making, is the need for chest radiographic findings to assign a score. However, the tool may be appropriate for determining need for isolation.

A tertiary public health intervention for TB control involves routine PPD testing in ED patients. The one study conducted to date to evaluate the

feasibility of this approach reports promising findings. Sixty percent of eligible patients consented to testing, and more than half returned for follow-up, which is comparable to that seen in other public health venues [32]. Optimal strategies for targeted screening found that it is possible to identify a ''high-risk'' group, which would identify nearly 90% of cases while testing only about 50% of the ED population. Although promising, further research is required to evaluate the cost-effectiveness of this strategy.

General principles for management of patients with suspected TB for emergency physicians include maintaining a high index of suspicion and immediately providing a mask (to decrease rates of transmission) to any patients with TB risk factors or suspected symptoms. Early chest radiography should then be performed and implementation of full airborne precautions should be established for any patients with suggestive findings on radiographs or high clinical suspicion of disease. High-risk clinical procedures that will aerosolize *M tuberculosis* should be minimized as much as possible in the ED unless isolation facilities with proper ventilation are available [33].

Influenza

Epidemiology and pathophysiology

Influenza is a seasonal disease that occurs in the winter months, with the vast majority of cases reported from November through March. Annual outbreaks and sporadic pandemics result in significant morbidity and mortality. Globally, epidemics of influenza result in 3 to 5 million cases of severe illness and approximately 250,000 to 500,000 deaths each year. In the United States, influenza accounts for more than 100,000 hospitalizations and nearly 40,000 deaths each year, the majority occurring in susceptible populations, the elderly, or the very young [34].

During the past century, three pandemics (global epidemics) of influenza have occurred. The ''Spanish flu'' in 1918 to 1919 was responsible for 40 million deaths worldwide, and 650,000 in the United States. More recent pandemics, which have had less impact in the United States, include the ''Asian flu'' 1957 to 1958 (34,000 deaths in the United States), and the ''Hong Kong flu'' 1968 to 1969 (70,000 US deaths) [35]. In contrast to the annual epidemics of influenza, deaths during influenza pandemics frequently occur in young, otherwise healthy, individuals [36].

Influenza is a single-stranded RNA virus, which belongs to the family Orthomyxoviridae. There are three major types of influenza viruses (A, B, and C), which are structurally similar but vary antigenically. Only Types A and B cause infections in humans. Influenza A is more common and virulent than B and is divided into subtypes based on viral surface antigens hemagglutinin and neuraminidase. ''Antigenic drift'' is produced by point mutations in the viral antigen that occur during viral replication and result in slightly different, new strains of influenza for which there is diminished immunologic recognition. ''Antigenic shift'' is a sudden major change in the

surface peptides that occurs when two different strains of influenza infect the same individual simultaneously. This results in mixing of the surface antigens and a new subtype of influenza for which humans have little or no protective immunity. All of the recent influenza pandemics were caused by antigenic shift [37].

In 1997, the avian strain A (H5N1), the first avian virus known to have been transmitted directly from birds to humans [38], began to appear in several Asian nations [39,40]. This strain has proven to be highly virulent with nearly 200 deaths reported to date worldwide. Although several family clusters of avian influenza suggest that human-to-human transmission may have occurred, there is no evidence that efficient transmission can occur via this route [41–43]. Significant public health concern exists regarding reassortment of avian influenza with the human virus, which could then produce a strain of flu that would be both extremely virulent and contagious, potentially triggering the next pandemic [44].

Influenza A and B can be transmitted from person to person via a number of routes including (1) direct or indirect contact with contaminated articles; (2) droplet (>10 μm) transmission produced by release of contagious droplets produced by coughing or sneezing by an infected host, resulting in contact with the nasal mucosa, conjunctiva, or mouth of another person; or (3) airborne transmission leading to inhalation of small (<5 μm) nuclei that remain suspended in the air and can be disseminated by air currents [4]. Evidence exists that transmission may begin 1 to 6 days before the onset of symptoms, and that viral shedding and human infectivity may persist for several weeks, particularly among those who are immunocompromised.

Clinical presentation, diagnosis, and treatment

In adults the classic presentation of influenza is abrupt onset of high fever, myalgia, headache, and malaise, with accompanying respiratory symptoms (cough, sore throat, and rhinitis). In children, otitis media, nausea, and vomiting are also common [45]. Unfortunately, these signs and symptoms are highly nonspecific, making ED diagnosis challenging. One recent systematic review reported that no individual or combination of clinical signs and symptoms can reliably confirm or exclude the diagnosis of influenza [46]. Data from a recent ED-based study supporting this conclusion noted that more than 50% of laboratory-confirmed cases of influenza had atypical or nonclassic symptoms on presentation (particularly among those with comorbid conditions) [47]. Therefore, it is recommended that physicians be aware of both local and national epidemiologic data to determine if influenza is in a particular community, and then have a low index of suspicion for consideration of this disease [46]. With increasing concern about other acute communicable respiratory illnesses, emergency physicians should also be aware of new and evolving algorithms that may help clinicians differentiate common influenza from avian influenza, SARS, anthrax, or other emergent biothreats [48].

Suspected cases of influenza can either be managed empirically or have rapid testing performed to assist with treatment decision making. The value of diagnostic testing has been well described and includes limiting use of unnecessary antibiotics, more specific use of antivirals, identification of atypical cases of disease, decreased length of ED stay, and improved surveillance by local and state health departments regarding presence, subtype, and strain of influenza [47,49]. Clinical data supporting routine testing is more compelling in children than adults [50,51], although testing is advised by the CDC during suspected influenza outbreaks as part of the broader surveillance and public health strategy aimed at controlling the spread of disease in a health care facility. Laboratory tests currently available include rapid antigen testing, polymerase chain reaction (PCR), immunofluorescence, serology, and viral culture from various types of respiratory specimens (nasopharyngeal swab, throat swab, nasal wash, nasal aspirate, sputum, and bronchial wash) or serum. Commercially available rapid tests can provide results in the ED within 30 minutes. Performance characteristics of the tests are variable, but generally sensitivity is greater than 70% and specificity is greater than 90%. The CDC recognizes the limited sensitivity of the rapid test and recommends that samples should always be sent for viral culture, which is considered gold standard confirmation with viral culture [45].

Definitive laboratory diagnosis of influenza is not absolutely required for management [46], and many ED texts recommended using laboratory testing only in those instances where testing would influence treatment decisions [52]. Thus, in the midst of a known influenza outbreak, a patient with typical signs and symptoms who can be managed with empiric therapy need not be subjected to testing. Instances in which laboratory testing may be indicated include cases in which the diagnosis is in doubt (because of early or late seasonal presentation or atypical clinical presentation) or in those cases where treatment decisions may be aided by a definitive test (eg, those patients in whom complications of untreated influenza are more likely) [53]. The most common complications associated with influenza are primary influenza viral pneumonia and secondary bacterial pneumonia. Other less frequent complications include encephalopathy, transverse myelitis, Reye's syndrome, myositis, myocarditis, and pericarditis.

General guidelines regarding treatment issued by the CDC in 2004 to 2005 are as follows: CDC encourages the use oseltamivir or zanamivir for treatment as supplies allow, in part to minimize the development of adamantane resistance (used for prophylaxis) among circulating influenza viruses. Treatment with antiviral medication is advised for (1) any person experiencing a potentially life-threatening influenza-related illness, and (2) any person at high risk for serious complications of influenza and who is within the first 2 days of illness. Prompt diagnosis and treatment also has the beneficial effect of reducing the duration of host infectivity. (Pregnant women should consult with their primary providers regarding use of

influenza antiviral medications. Further details and the most up-to-date treatment and prophylaxis recommendations can be found on the CDC Web site).

Disease burden in the ED

During flu season, influenza is one of the leading causes of ED visits, especially among children and among adults aged 65 and older [54]. Several US- and Canadian-based studies that evaluated emergency medical system (EMS) diversion as a proxy for ED overcrowding have reported high correlations between influenza season and EMS diversion [55,56]. Another study, conducted in Europe during peak flu season, found that approximately one third of all ED visits for children younger than 1 year of age were attributable to influenza [57]. Although several nosocomial outbreaks of influenza in health care workers have been documented, there has been relatively little research describing transmission in the ED. One study conducted in an acute-care hospital during the 1986 to 1987 flu season found that one third of Influenza A cases identified could be traced to the ED, and that the estimated nosocomial influenza attack rate was 0.3 per 100 hospital admissions [58]. The ED thus represents a high-risk location for nosocomial transmission.

Public health interventions

Several interventions help to decrease the likelihood of individuals contracting influenza and lessen the likelihood and burden of a public health crisis associated with an influenza outbreak. The principal known preventive measure is routine and widespread use of vaccination [59]. Current CDC recommendations for populations to vaccinate include adults aged 65 years and older; persons aged 2 to 64 years with underlying chronic medical conditions; all women who will be pregnant during the influenza season; residents of nursing homes and long-term care facilities; children aged 2 to 18 years on chronic aspirin therapy; health care workers involved in direct patient care; and out-of-home caregivers and household contacts of children aged younger than 6 months [60].

Several studies lend support for using the ED settings for routine influenza immunization [61]. Data demonstrate high rates of ED visits for unimmunized individuals who are at high risk for influenza (eg, nursing home patients and the elderly) as well as moderate to high rates of physician and patient acceptability for ED-based immunization [62–66]. One recent randomized clinical trial comparing on-site ED-based vaccination to education and referral demonstrated that ED-based vaccination was significantly more efficacious both for pediatric patients as well as their accompanying family members [67]. Other potential vaccination strategies that remain relatively unexplored include use of EMS [68] either as a routine preventive measure or in the event of an epidemic outbreak. In the wake of the flu vaccine shortage, and in preparation for future inevitable influenza outbreaks,

the ACEP issued a policy statement in 2004 highlighting ED priorities during suspected or known influenza outbreaks (Box 1) [69].

Severe Acute Respiratory Syndrome (SARS)

Epidemiology and pathophysiology

The first documented cases of SARS occurred in November of 2002, in the Guangdong Province of China, initially presenting as an atypical pneumonia [70,71]. Over the next several months, a surge in cases of pneumonia were reported in the surrounding regions, with a disproportionate number of hospital workers affected and several unexpected deaths [72]. Months

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Box 1. Use of the emergency department during outbreaks of influenza (approved by the ACEP board of directors November 2004)

1. Ensure that emergency care and critical providers, including emergency medical services (EMS) personnel, nurses, and ancillary staff involved in direct patient care, are immunized against influenza.
2. Implement rapid screening, identification, and appropriate respiratory infection control interventions for all individuals arriving in the ED.
3. End the practice of boarding admitted patients in the ED when no inpatient beds are available. Hospitals operating at full capacity may be required to distribute boarded patients to inpatient hallways, solariums, admission units, and other spaces outside the ED, but this practice is preferable to packing seriously ill influenza patients together in the hallways of an ED.
4. Implement regional protocols to monitor hospital inpatient and ED capacity, as well as ambulance diversion status.
5. Adopt regional protocols to govern when, how, why, and for how long crowded hospital Eds can divert inbound ambulances.
6. Require hospitals and communities that are severely affected by influenza to postpone elective admissions until the crisis abates.
7. Provide federal and state emergency funding to compensate hospitals and EDs for the unreimbursed costs of meeting this grave public health challenge.

From American College of Emergency Physicians. Emergency Department Utilization During Outbreaks of Influenza. Policy #400558, approved November 2004; with permission.

after the initial case of this atypical pneumonia, a physician from Guangdong traveled to Hong Kong, infecting up to 16 others during a brief hotel stay. This triggered a global pandemic with outbreaks in Hong Kong, Singapore, Vietnam, and Canada [73,74]. In spite of early evidence that these illnesses represented an emerging infectious disease (based on number of cases, lack of responsiveness to standard therapy, and high transmissibility), hospitals were generally slow to implement respiratory isolation procedures. It was not until several hundred more cases were reported that the World Health Organization (WHO) issued a global health alert, resulting in establishment of an international laboratory reporting network and standardized protocols for infection containment [75]. These measures contributed to the definitive identification of SARS (a novel previously uncharacterized Coronavirus) as the causative pathogen [73,76].

The peak period of the SARS pandemic occurred in late 2002 and early 2003, during which time cases were reported in more than 25 countries spanning five continents. Although the exact number of cases is unknown, it is estimated that there have been more than 8000 probable cases, and 774 deaths as of July 2003, at which time human-to-human transmission was essentially contained [77,78]. The largest number of SARS cases have occurred in mainland China, Hong Kong, Taiwan, and Canada (where a significant outbreak occurred in the city of Toronto). In the United States, there have been 29 cases of probable SARS, all of which have been linked with preceding international travel to an endemic area [79,80]. There have been no US SARS-attributable deaths to date. Sporadic cases of SARS continue to be reported. Four cases were reported in Guangdong in late 2003; three separate laboratory-related incidents were reported in Singapore, Taiwan, and China, one of which resulted in a small contained community outbreak [81].

Clinical presentation, diagnosis, and treatment

Clinical symptoms associated with SARS typically emerge 2 to 10 days after an exposure, with a mean incubation period of 5 days in most infected individuals. Initial clinical presentation and the clinical course of patients with SARS is variable and generally nonspecific, making diagnosis challenging [82]. Since definitive diagnosis relies on advanced laboratory testing, ED consideration of SARS must rely on having a high clinical suspicion, which should be guided by history (focusing on potential exposure), characteristic clinical features, and laboratory and radiographic findings as described in the following paragraphs.

During the first stage of infection, patients infected with SARS typically present with flu-like symptoms. The most common finding on initial presentation is fever (greater than 38°C), although exceptions occur in the elderly and in those with chronic underlying illness. Other clinical features occurring in more than 50% of cases include chills, rigors, cough, and myalgias. Less frequent but also commonly appearing are rhinorrhea, dyspnea, watery nonbloody diarrhea, and headache [74,83–85].

Common laboratory findings associated with SARS including lymphopenia, thrombocytopenia, derangements in clotting profiles, and various electrolyte abnormalities. The majority of patients with SARS have abnormal radiographs. The most common chest x-ray finding in a patient with SARS is a unilateral infiltrate early on, followed by bilateral interstitial or confluent infiltrates. These findings are usually indistinguishable from viral or atypical pneumonias. One study suggests that the presence of an air-space opacity on chest radiographs may be a helpful early diagnostic clue to SARS [86].

For public health surveillance purposes, WHO defines a clinical case of SARS as an individual with (1) a history of fever, or documented fever ≥38°C (100.4°F); (2) one or more symptoms of lower respiratory tract illness (cough, difficulty breathing, shortness of breath); (3) radiographic evidence of lung infiltrates consistent with pneumonia or acute respiratory distress syndrome (ARDS), or autopsy findings consistent with the pathology of pneumonia or ARDS without an identifiable cause; and (4) no alternative diagnosis that can fully explain the illness [87].

Laboratory testing for SARS should include both respiratory and blood samples. Laboratory diagnosis can be made by any one of three assays according to WHO standards: (1) any of one nucleic acid test for the SARS-CoV in two specimens or two nucleic acid tests in one specimen; (2) seroconversion by ELISA or IFA (immunofluoresence assay); or (3) isolation of the SARS-CoV using validated testing methods and appropriate quality assurance mechanisms [87].

Approximate 20% to 30% of SARS cases require treatment in the intensive care unit. The case fatality rate of SARS is estimated at approximately 10% to 15% globally, with increased rates seen in older patients with co-morbid disease [83]. The clinical course of disease can be mild to fulminant. Respiratory decompensation typically occurs in a week to 10 days, although some patients may have a more rapid progression requiring intubation at the time of initial presentation. In one of the largest SARS cohorts from Hong Kong, a triphasic progression of disease was described: phase 1 is a brief period of malaise, fever, and flu-like symptoms, which resolves with antibiotics; phase 2 occurs several days later and is characterized by recurrent fevers, diarrhea, oxygen desaturation, and progression of x-ray findings; only a small subset of patients (approximately 20%) progress to phase 3, which is marked by severe sepsis and multiorgan system failure, most notably ARDS [85].

Disease burden in the ED

Transmission of SARS from infected patients to health care workers, visitors, and other patients was well documented during the SARS pandemic [88]. Early on it was recognized that overcrowded, understaffed emergency departments with limited resources represent extremely high-risk sites for disease transmission [89–94]. One study that tracked 322 SARS patients in Beijing, China, found that of all heath care workers, ED staff had the

highest attack rate (11.9%) [95]. Another detailed epidemiologic investigation from Toronto found that transmission of SARS to ED staff who had contact with SARS patients ranged from 0% to 22%, with a calculated attack rate of 13.6 per 1000 nursing hours, exceeding that found in the ICU [94]. Factors believed to contribute to the high rates of contagion in the ED included difficulty with early identification and isolation of patients (particularly those with atypical symptoms), use of aerosol treatments for patients with respiratory symptoms in the ED, and poor compliance with basic (ie, hand washing) and other recognized public health control measures for reducing transmission of respiratory infections [96]. Implementation and adherence with systematic preventive measures resulted in significant reduction of disease transmission throughout the world, and are discussed further below [92,97].

Public health interventions

The 2003 SARS pandemic forced a widespread shift in thinking regarding the role of the ED, from that of emergent treatment and stabilization of patients with acute illnesses, to central coordination of a public health response plan in the face of an emerging pandemic [92,98]. Recognition that EDs serve as the primary portal of entry for patients with a highly contagious and potentially lethal disease was paramount to the development of rationale and well-organized infection control programs [99].

One recent comprehensive literature review describes the cumulative experiences of hospitals and health care organizations [100]. SARS was found to be spread principally by the respiratory droplet route, making PPE use the mainstay of infection control. While use of N95 masks offers theoretical advantages over surgical masks, no studies have documented significant additional benefits in patient care settings. Importantly, consistent compliance with PPE has been proven to decrease risk of disease transmission. Indirect evidence from ''super-spreading'' events in hospitals has suggested that SARS may be aerosolized [101,102]. Infectious disease experts advise that special care should be taken to decrease aerosol-generating procedures as much as possible and to observe additional precautions when these procedures are necessary. Recommended environmental interventions include placing surgical masks on patients with suspected SARS at triage and during transport, limiting the movement of patients with suspected SARS, and making use of physical isolation measures, including warding and use of negative-pressure isolation rooms when available [103]. Successful policies for containment of SARS in EDs demand strict attention and enforcement of ED operational protocols (including procedures for recycling of supplies and equipment, and guidelines for optimization of patient and staff traffic) [97]. The SARS outbreak exemplified the need for modified ED staffing owing to the increased demands of patient care that occurred during the period of the greatest disease threat and burden [98].

Secondary prevention measures for SARS have involved methods for early disease detection. Early detection requires a reliable definition of cases. The WHO definition of SARS cases, although useful for epidemiologic purposes, was found to be insufficiently sensitive for assessing patients in ED triage areas. Consequently, physicians had to develop clinical prediction rules that could more accurately identify patients with SARS during an acute outbreak [104–107]. One group from Taiwan derived a simple SARS decision rule that relied on combinations of symptoms and laboratory findings. The scores were reported to have greater than 90% sensitivity and were found to be highly reliable when validated in a separate cohort [105,107]. A more recent study from Hong Kong, which included nearly one third of the SARS cases from 2003, reported similar results with key variables including exposure history, symptoms, and laboratory values [104]. Although determination of which prediction rule will be most effective is not known, these studies provide compelling support for integration of ED-based decision guidelines in future respiratory outbreaks. Potential gains include early identification and isolation of high-risk patients, reduction of disease transmission in the ED, and optimization of use of limited resources. Principal limitations of these decision tools include lack of proven reliability in nonendemic areas and the need for validation with each new outbreak, based on potential strain and geographic variation that may alter clinical presentation.

Future challenges

Dr Anthony Fauci, director of the National Institutes of Allergy and Infectious Diseases, suggests that SARS teaches a valuable lesson: it demonstrates the ever-present threat of emerging and reemerging infectious diseases [108]. Dr Fauci and Dr Julie Gerberding, director of the CDC, emphasize the importance of a strong public health preparedness and response system, which in addition to use of personal and environmental infection control parameters includes a system capable of early detection [109].

As the frontline of the health care system, the nation's EDs are receiving renewed recognition as pivotal sites for early detection surveillance systems. A number of national surveillance systems were put in place largely in response to the 2003 SARS outbreak. Effective disease control will require a reliable national surveillance program, as well as consistency in local hospital-based education, and practice of proven risk-reduction measures.

Biothreat (BT) agents

General principles

A civilian target in a bioterrorism act has the potential to create a large number of casualties, civil panic, and disruption. Early detection and preattack preparedness is central to any response. Timely, coordinated intervention triggered by early recognition will result in improved patient outcome,

disease containment, preservation of the medical infrastructure, and effective law enforcement responses. This is evidenced by the lowest fatality rate ever recorded for inhalational anthrax following the 2001 bioterrorist attacks in the United States.

Serving in the frontline, emergency physicians play a critical role in responding to such an attack. Early recognition requires prior knowledge of typical clinical syndromes of the various bioterrorism agents. However, diagnosis of index cases may be difficult as clinical presentations of the BT agents are generally nonspecific, and laboratory confirmations are often delayed for these otherwise rare disease entities. ED-based syndromic surveillance systems with autonomous sensing and reporting capabilities can provide early warning and earlier recognition of suspicious patterns. Epidemiologic patterns peculiar to a biological attack, which can help differentiate it from a natural outbreak of disease, include (1) an extraordinary number of patients arriving from a similar geographical area with similar symptoms and acuity; (2) rapid rise and fall of epidemic curves over a short period of time (hours to days); (3) steady rise in cases instead of peaks and troughs seen in natural outbreaks; (4) rapidly fatal cases; (5) a lower attack rate in people who were indoors than in those who were outdoors; and (6) increased infected and dying animals [110].

Once a bioterrorist attack is suspected, the first order of business is to initiate early protective infection control measures (eg, contact, droplet, or airborne precautions) and identify the causal agent. Local- and state-level health care authorities should be notified immediately. As soon as the attack has been confirmed, prompt therapy, postexposure prophylaxis, and vaccination should be initiated. Advance preparation for EDs will be essential in mitigating the effects of a bioterrorist attack. Key components of a bioterrorism response plan should include (1) specific guidelines for plan activation and notification of proper authorities; (2) facility protection from contamination and secondary transmission; (3) methods of decontamination; (4) expansion of service capacity; (5) ensuring an adequate cache of medical supplies; (6) staff education and training; (7) incident command system for controlled management; and (8) coordination and communication with the surrounding community [111].

The CDC has divided biological agents that are critical biothreat agents into categories based on their risks for causing mass casualties [112]. Category A agents, the highest priority, represent organisms that pose a risk to national security because they can be easily disseminated or transmitted person-to-person, have a high risk of mortality, and have the potential to cause public panic and social disruption. These agents include *Bacillus anthracis* (anthrax), *Variola major* (smallpox), *Yersinia pestis* (plague), *Francisella tularensis* (tularemia), viral hemorrhagic agents, and *Clostridium botulinum* toxin. Other potential agents of concern but posing a less imminent threat were assigned to categories B or C. A comprehensive review of the individual BT is beyond the scope of this discussion.

The principal route of delivery of most BT agents is by the inhalation of aerosols, which in some cases may result in pulmonary manifestations, such as cough and sputum production, and can be easily mistaken for common respiratory illnesses. The spectrum of potential pulmonary consequences that result from these biothreat agents is broad and reflects the variety of agents that could be involved. Category A agents, which can be easily aerosolized for weaponization, include inhalational anthrax, pneumonic plague, inhalational tularemia, and viral hemorrhagic fever. Only a subset of these agents, specifically *Y pestis* and the viral hemorrhagic fever viruses, have the potential for secondary human-to-human spread through respiratory droplets or airborne transmission. Of note, despite its general lack of prominent respiratory symptoms, smallpox can also be highly contagious via droplet or airborne transmission of the virus. Other significant aerosolizable category B agents with pulmonary manifestations include *Coxiella burnetti* (Q fever), *Brucella* species (brucellosis), and *Burkholderia mallei* (glanders); however, only *B mallei* has the potential for human-to-human transmission. From the ED perspective, it is critical that patients who are suspected to be infected with such communicable agents be cared for in respiratory isolation for disease containment. Need for isolation should be determined by suspicion before definitive diagnosis. With these exigencies in mind, we will focus our discussion on pneumonic plague as an example of a communicable respiratory biothreat agent.

Yersinia pestis (plague)

Epidemiology and pathogenesis

Plague is a zoonosis with a rodent host and a flea vector, which is caused by the gram-negative bacillus, *Yersinia pestis*. Transmission to humans is from the bite of an infected rodent flea. The bacilli multiply intracellularly resulting in painful swollen regional lymph nodes called buboes. Septicemic plague and pneumonic plague can occur secondarily as a complication of hematogenous dissemination of bubonic plague. The vector is not essential for infection; however, inhalation of aerosolized bacillus from cough or deliberate dissemination can result in primary pneumonic plague.

Historically, plague was responsible for three pandemics, killing millions of people throughout the centuries. The most recent pandemic originated in China and spread worldwide at the turn of the twentieth century [113]. From 1987 to 2001, 36,876 plague cases were reported in 24 countries [114]. In the Western Hemisphere, the incidence of plague is highest in the Andes and the southwestern United States [115]. From 1916 to 1947, 390 cases of plague were reported in the United States, 84% of which were bubonic, 13% septicemic, and 2% pneumonic. Concomitant case fatality rates were 14%, 22%, 57%, respectively. Although pneumonic plague has rarely been the dominant manifestation of the disease, large outbreaks of pneumonic plague have occurred [116].

Advances in living conditions, public health, and antibiotic therapy make future pandemics improbable. However, outbreaks following use of plague as a biological weapon represent plausible threats. In World War II, plague-infected fleas bred by the billions were released over Chinese cities and resulted in multiple epidemics [117]. Of greater concern is that the biological weapons program by the former Soviet Union has reportedly developed techniques to aerosolize plague directly, eliminating the dependence on fleas as vectors [118]. In 1997, the WHO reported that in the worse case scenario, if 50 kg of *Y pestis* were released as an aerosol over a city of 5 million people, 150,000 cases of pneumonic plague would result, with 36,000 expected deaths [119].

Clinical presentation, diagnosis, and treatment

Inhalation of aerosolized *Y pestis* following a biothreat attack would result in primary pneumonic plague, which can be distinguished from secondary pneumonic plague by the absence of buboes. Infected patients may experience chest pain, progressive tachypnea and dyspnea, productive cough (sputum may be watery, frothy, blood-tinged, hemorrhagic, or purulent), and hypoxia. Prominent gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, may be present. Pneumonic plague is a fulminant process with rapid progression to exudative pulmonary consolidation and respiratory failure [120]. Many patients with pneumonia develop profound septic shock with multiorgan system failure. Inhalation of infectious aerosol may also produce plague pharyngitis, with focal suppuration and prominent cervical buboes. Plague pneumonia is almost always fatal if treatment is not initiated within 24 hours of the onset of symptoms.

Early diagnosis of individual cases requires a high index of suspicion, especially in areas without endemic, zoonotic plague. Clinical suspicion of pneumonic plague in the context of a bioterrorist attack may be based on presentation of many patients with rapidly progressive pneumonia with hemoptysis. There are no pathognomonic radiographic characteristics of primary pneumonic plague. In primary infections radiographic signs usually begin as localized unilateral alveolar infiltrates that quickly advance to patchy, diffuse, and bilateral pneumonitis; in secondary pneumonic cases infiltrates are mostly bilateral, involving lower lung fields [121]. Early presumptive diagnosis can be made by Gram, Wright-Giemsa, or direct fluorescent antibody (DFA) staining of peripheral blood, sputum, or lymph node aspirates that will reveal a bipolar "safety pin" morphology that distinguishes plague bacilli from other gram-negative organisms. The first clinical or laboratory suspicion of plague should lead to immediate notification of the hospital epidemiologist or infection control specialist, hospital and reference laboratories, local and state health departments, and the CDC. Confirmation of *Y pestis* is made by culture, serology, or PCR.

Parenteral aminoglycosides (eg, streptomycin or gentamicin) are considered first-line plague therapy [120]. Doxycycline or ciprofloxacin are recommended for postexposure prophylaxis or in mass casualty settings. All persons developing a fever (>38.5°C) or new cough should be promptly treated with parenteral antibiotics. Close contacts with untreated pneumonic plague should receive postexposure antibiotics for 7 days. A vaccine is available, but it is not protective against pneumonic plague [122].

Public health interventions

The available evidence indicates that person-to-person transmission of pneumonic plague is through respiratory droplet, not droplet nuclei. Accordingly, routine protection from respiratory droplets, including mask, eye protection, gowns, and gloves should be used by medical personnel attending infected patients who have not been on antibiotics for at least 48 hours. Exposed persons who refuse to take antibiotic prophylaxis but who are not symptomatic do not require isolation but need to be watched and treated when the first sign of cough or fever occurs. Microbiology laboratory personnel should practice biosafety level 3 precautions when handling potentially infectious samples during high-risk laboratory procedures.

Measles

Despite recent attention toward emerging and biothreat pathogens, viruses that have coexisted with the human population for hundreds of years continue to have a profound, worldwide impact. Measles virus is one such virus. It is highly contagious via the respiratory route. Although effective vaccines have been available for more than 40 years, measles remains one of the most frequent causes of vaccine-preventable childhood death, with the greatest mortality seen in poor regions of the world where adequate vaccine coverage has not been achieved [123]. Even in developed nations, endemic outbreaks of measles can be reestablished following an importation from foreign countries if high immunization coverage is not sustained. In addition to disease surveillance for outbreak control, emergency physicians can play a pivotal role in outbreak prevention by identifying underimmunized individuals who often use the ED as their principal source of primary care.

Epidemiology and pathophysiology

In 2001, the WHO estimated a global incidence of 39.9 million measles cases, 777,000 deaths, and 28 million disability-adjusted life years [124]. About half of these deaths occurred in Africa, in which fewer than 50% of children aged 1 year have received at least one dose of measles vaccine. Factors that contribute to the high case-fatality rates in developing countries include crowding, poor nutritional state, occurrence of infection at young age, underlying immune deficiency disorders, and limited access to health care. In 2001, the WHO and United Nations Children's Fund (UNICEF)

established the goal of reducing measles deaths by 50% by 2005 (compared with 1999 estimates) through mass vaccination campaigns worldwide [124]. As a result, global measles mortality decreased by 39% between 1999 and 2003, with the largest gains (46%) occurring in the African regions [125]. In the United States, routine measles vaccination has been part of a childhood immunization program since 1963, resulting in a downward trend in the incidence of disease. However, resurgence occurred between 1989 and 1991 because of low vaccination coverage. Since 1997, the incidence of measles in the United States has been sustained at record low levels of approximately 100 cases per year [126]. Unfortunately, efforts toward measles eradication in the US have been challenged by the continued high prevalence of measles outside our borders, as evidenced by identification of imported viral genotypes among the majority of incident US cases [127]. Efforts to ensure high immunization rates among people in both developed and developing countries must be sustained to control measles worldwide.

Clinical presentation, diagnosis, and treatment

Infection is acquired via the respiratory tract. Primary viremia occurs 2 to 3 days after exposure. Subsequent infection of the reticuloendothelial system results in secondary viremia with skin and respiratory tract manifestations after an incubation period of 10 to 12 days. The clinical prodrome is characterized by fever and is followed by the onset of cough, coryza, and conjunctivitis. Koplik's spots, lesions on the buccal mucosa, occur 1 to 2 days before the onset of rash. The measles rash occurs 2 to 4 days after the prodrome, and is usually first noted on the face and neck, before gradually spreading downward and outward to the trunk and extremities. Maculopapular lesions are generally discrete, but may become confluent. Fine desquamation may occur, and the rash fades in the same order that it appears, from head to extremities.

The diagnosis of measles can usually be made on clinical grounds. Isolation of the measles virus is not recommended as a routine. However, as with influenza, virus isolates are important for molecular epidemiologic surveillance to help determine the geographic origin of the virus. A serologic test, most commonly by enzyme-linked immunoassay, can be used to establish the diagnosis. A fourfold rise in titer of IgG antibody to measles virus, or a positive result of serological testing for measles IgM antibody is considered diagnostic.

Complications from measles can involve every organ system, and the rates of complication vary by age and underlying conditions. Complications are more common among children under age 5 and adults over 20 years of age. Pneumonia is the most common fatal complication associated with measles, occurring in 56% to 86% of measles-related deaths [128]. Pneumonia may be caused by the measles virus alone or secondary viral or bacterial infection [129]. The prevalence of measles virus pneumonia is higher in pregnant women and patients who are immunocompromised as a result of

hematologic malignancy, AIDS, or immunosuppressive therapy [130]. Chest radiographic findings may include infiltrates, consolidations, hilar lymph node enlargement, and pleural effusions.

Treatment of the primary disease is mainly supportive. Bacterial superinfection should be promptly treated with appropriate antimicrobials, but prophylactic antibiotics to prevent superinfection are of no known value and are therefore not recommended. Vitamin A administration has been shown to reduce mortality, severity, and duration of complications in children with measles [131]. Immunocompromised children and infants younger than 1 year of age who are susceptible and have been exposed to measles may be given passive immunization within 6 days of exposure.

Public health interventions

Transmission of measles is primarily person-to-person via large respiratory droplets; however, airborne transmission via aerosolized droplet nuclei has been documented. Maximum communicability occurs from onset of prodrome through the initial 3 to 4 days of rash [132]. Although suspected patients should be placed in respiratory isolation to preclude airborne transmission, isolation and quarantine procedures may be of limited value given that exposure usually occurs before diagnosis is made, and the availability of passive immunization or vaccination of susceptible contacts has obviated quarantine.

The measles virus is an RNA virus belonging to the genus *Morbillivirus* in the family Paramyxoviridae. It has only one serotype and can, therefore, be prevented with a single monovalent vaccine. Measles vaccine is one of the safest and most effective of all vaccines [133]. It is a live attenuated vaccine, which is frequently given in a combined product with rubella vaccine (as MR vaccine) or with rubella and mumps vaccine (as MMR vaccine). Immunization produces a nontransmissible, asymptomatic infection. Approximately 5% of children who receive only one dose of MMR vaccine will remain susceptible owing to primary vaccine failure, but after a second immunization, more than 99% of vaccinees develop serologic evidence of measles immunity, which can be lifelong [134]. Recent experience has demonstrated that prevention of endemic outbreaks with single-dose vaccination is not possible even with high vaccination coverage, a two-dose vaccine schedule is thus recommended [135]. The first dose of MMR should be given on or after a child's first birthday, and the second dose may be given as soon as 1 month after the first, but should routinely be given at age 4 to 6 years. Postexposure prophylaxis with vaccination within 72 hours or passive immunization within 6 days of exposure should be given to susceptible contacts (ie, persons exposed and not fully vaccinated). All health care workers are at high risk for exposure and should be adequately vaccinated.

Prevention and control of vaccine-preventable disease outbreaks require that disease transmission be interrupted by sustained high levels of immunization (greater than 95% for measles). As part of the effort to ensure high

immunization rates, EDs may be well suited to capture nonimmunized children because they are often the primary sources of medical care for many of the urban poor who are considered the highest risk for underimmunization. Several studies have evaluated EDs as potential sites for routine vaccination and for accelerated vaccine delivery during outbreaks, with limited success [136,137]. Major barriers with measles vaccination have included high costs, lack of continuity, and difficulty in determining the true immunization status of patients [138,139]. Until these barriers are effectively addressed, ED providers can contribute to measles control by screening and referring underimmunized children to private or public health clinics in the community for vaccination. As with all emerging or reemerging infectious diseases, ED-based surveillance (which relies on early recognition and reporting of suspected cases) plays a key role in outbreak control.

Evolving approaches to prevention in the ED

Primary and secondary prevention are recognized as the most effective measures for containing infectious disease outbreaks. The role of EDs in instituting these preventive measures is rapidly evolving in response to increasing awareness of the critical role EDs serve as the initial encounter site for most patients with acute communicable infectious illnesses. Evidence and support for ED-based primary prevention strategies such as influenza vaccination or prophylaxis exists [67], although practical challenges regarding such issues as education, counseling, and sustainable funding present ongoing challenges. Secondary preventive measures using clinical decision rules to rapidly identify and sequester patients with diseases have also been demonstrated to be effective in ED settings [31,104], but are by no means failsafe; recognized limitations of decision guidelines include difficulties with ensuring routine and consistent application, and need to establish generalizability.

Disease surveillance is another method of secondary prevention that is recognized as a critical tool in prevention and control of communicable disease outbreaks (both natural and bioterrorist) [140]. The methodology involves continuous systematic collection, analysis, and interpretation of health-related data for timely dissemination to essential parties, who can then use this information for evaluating, planning, and implementing the most effective public health preventive measures [141]. Syndromic surveillance has been recognized to be especially applicable to airborne respiratory infections that can be insidious and highly contagious.

The ED serves as a rich, yet relatively untapped surveillance site that could contribute to control of respiratory infectious disease outbreaks. There are a large number of ED variables to track and evaluate, including ED ambulance diversion rates, numbers of ED patient visits by chief complaint, and ED discharge diagnosis and hospital/ICU admission rates [56,142]. The best-known ED-based surveillance network for infectious

diseases, *EMERGEncy ID Net*, was established in the mid-1990s as a cooperative research and operational program involving the CDC, the National Center for Infectious Diseases, and about 12 university-based EDs throughout the United States [143]. The surveillance network monitoring activities are varied, but have shown the capacity to effectively monitor various infectious disease outbreaks, including methicillin-resistant skin infections and respiratory *M tuberculosis*. Public health surveillance based on ED data is further discussed in the chapter by Varney and Hirshon elsewhere in this issue.

Development and testing of novel molecular techniques for rapid real-time detection of infectious diseases is another evolving public heath approach for ED evaluation of aerosolized infectious diseases [144]. Rapid laboratory-based disease surveillance systems have the potential to detect infected individuals even before the onset of symptoms. This could represent one step ahead of traditional clinical syndromic surveillance. Although promising, further technical advancement in automation, optimization of detection, sensitivity and specificity is required before their true impact can be determined.

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