Medical surveillance for the emerging occupational and environmental respiratory diseases

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Purpose of review
To highlight the important issues to consider in deciding whether to pursue and how to conduct medical surveillance for the emerging occupational and environmental respiratory diseases. It provides several recent examples illustrating implementation and usefulness of medical surveillance and the lessons learned from these experiences.

Recent findings
Medical surveillance conducted after sentinel outbreaks of constrictive bronchiolitis in microwave popcorn and flavoring production plants have shown the usefulness of this approach in documenting the burden of disease, identifying particular problem areas as targets for preventive interventions, and in tracking the progress. They have also identified the usefulness of longitudinal spirometry, which allows comparison of the individuals' results to their own previous tests. The importance of recognizing a sentinel outbreak needing greater investigation is demonstrated by the cluster of cases of constrictive bronchiolitis recognized in military veterans returning from Iraq and Afghanistan. The World Trade Center disaster has demonstrated the importance of having baseline lung function data for future comparison and the importance of rapidly identifying exposed populations at greatest risk for health effects, and thus potentially having the greatest benefit from medical surveillance.

Summary
When used appropriately, medical surveillance is a useful tool in addressing the emerging occupational and environmental respiratory diseases by facilitating improvements in primary prevention and enabling interventions to help individuals through secondary prevention.

Keywords
constrictive bronchiolitis, medical surveillance, respiratory disease, spirometry, World Trade Center

INTRODUCTION

The World Health Organization defines an emerging disease as 'one that has appeared in a population for the first time, or that may have existed previously but is rapidly increasing in incidence or geographic range' [1]. Emerging occupational and environmental respiratory diseases meeting this definition continue to occur. Sometimes they are unanticipated. Earliest recognition of unanticipated emerging diseases depends on identifying sentinel cases or outbreaks, often through reporting by clinicians to public health agencies. Examples include alveolar proteinosis associated with indium tin oxide exposure [2▪▪] and constrictive bronchiolitis caused by exposure to diacetyl [3▪]. Sometimes, emerging respiratory diseases are anticipated after potentially hazardous emerging occupational and environmental exposure scenarios are recognized. Examples include workers exposed to new nanomaterials [4▪▪] and exposures of residents and response workers in the wake of the World Trade Center (WTC) disaster [5]. After a sentinel event is recognized or it is recognized that an emerging exposure may lead to an emerging disease, there is often a desire to implement medical surveillance to assess disease burden, identify problem areas, target interventions, and track progress in disease prevention. However, in the setting of an emerging disease, there is often much uncertainty about

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KEY POINTS

- Medical surveillance can help to guide primary and secondary prevention efforts, and thus be a useful tool in addressing the emerging occupational and environmental respiratory diseases.
- Uncertainties can be a challenge, but before embarking on a program of medical surveillance for an emerging occupational and environmental respiratory disease, carefully consider whether the cost is balanced by potential for benefit and determine program specifics such as target population, tests to be performed, frequency of surveillance, duration of surveillance, and how data will be acted on at the individual and population level.
- Longitudinal spirometry with the comparison of individuals' results to their own previous tests has emerged as a useful tool in respiratory medical surveillance and has been useful in the early detection of declines of pulmonary function in flavoring-induced lung disease, which can progress rapidly.
- Medical surveillance for emerging occupational and environmental respiratory disease after large-scale disasters is facilitated if baseline surveillance data already exist for the monitored population, and if the need for medical surveillance is determined relatively early on so that steps can be taken to assure collection of appropriate exposure information and to identify the exposed population that might benefit most from medical surveillance.

whether medical surveillance would be sufficiently beneficial to merit its recommendation and, if so, how to implement it. This review will highlight the important issues to consider in making these decisions and provide several recent examples of medical surveillance for the emerging occupational and environmental respiratory diseases.

OVERVIEW OF MEDICAL SURVEILLANCE FOR THE EMERGING OCCUPATIONAL AND ENVIRONMENTAL RESPIRATORY DISEASES

Occupational health surveillance has been defined as 'the ongoing systematic collection, analysis, and dissemination of exposure and health data on groups of workers for the purpose of preventing illness and injury' [6]. Medical and hazard surveillance data are gathered for the practical purpose of assessing whether the preventive measures in place to protect workers are functioning effectively or whether gaps in these measures are allowing hazardous exposures and adverse health outcomes to occur. Occupational health surveillance is an essential part of a comprehensive occupational safety and health program.

Medical surveillance is the part of occupational health surveillance involving initial and periodic health evaluation of people who have had potentially hazardous work-related exposures. This ongoing effort can document individual sentinel cases of illness or, through evaluation of aggregated data, changes in population health. Findings can identify the problem areas that are opportunities for improvements in primary prevention. For example, if excess disease is associated with performing certain tasks or working in particular areas, this information can help in targeting the efforts to correct the situation. Another benefit of medical surveillance can be at the individual level. If surveillance identifies individuals at early stages of disease, it can trigger individual clinical interventions to prevent progression or even to reverse the disease process before it advances to greater severity. This is termed secondary prevention. If a major reason for conducting medical surveillance is to identify the individuals who might benefit from secondary prevention, the surveillance is often referred to as 'medical screening' or 'medical monitoring'.

It is challenging to design and implement a program of medical surveillance for an emerging occupational or environmental respiratory disease or in the face of an emerging potentially hazardous exposure. Uncertainty is a major challenge. Specific organ toxicities associated with emerging exposures may be poorly documented or unknown; this knowledge is needed to choose appropriate medical tests for use in surveillance. Exposure–response relationships may be unknown, making it difficult to target appropriate populations for surveillance. Favorable cost–benefit ratio is an important motivator of investment in medical surveillance. But cost–benefit of medical surveillance can often only be guessed at in emerging situations in which the population burden of emerging disease and the diagnostic performance of the medical tests chosen to screen a population for it are unknown.

Figure 1 shows a general approach that can be applied to medical surveillance in the setting of an emerging occupational and environmental respiratory disease. In making the decision whether to pursue medical surveillance, anticipation of potential disease emergence is very important. Once disease is anticipated and the decision is made to conduct medical surveillance, the next task is to design the specific surveillance program. A number of factors are important to consider (see list below). What is the target population for surveillance? Are there exposure groups anticipated to be at highest risk and thus the highest priority for surveillance?

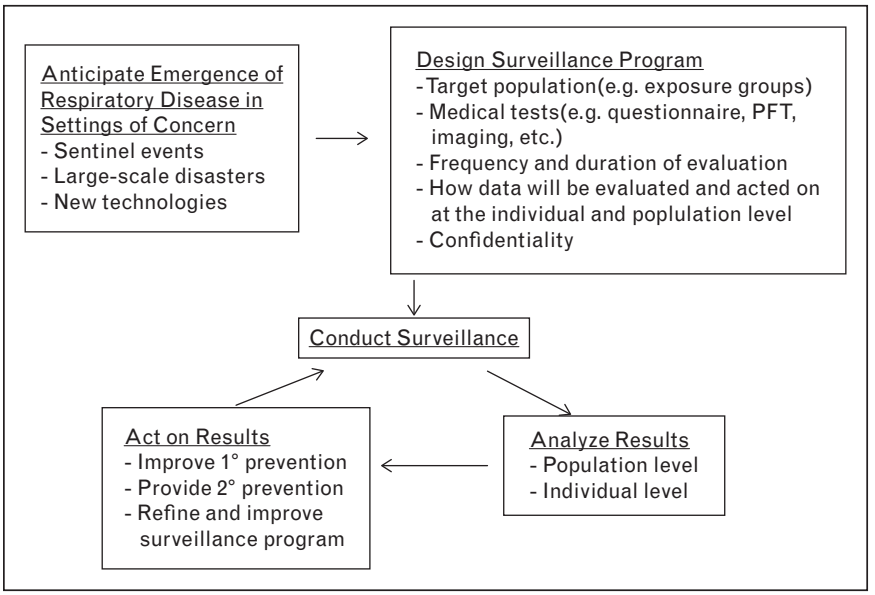

FIGURE 1. General approach to medical surveillance for the emerging occupational and environmental respiratory diseases.

What medical tests should be performed? Respiratory symptom questionnaires can be quite useful in many settings. Objective medical testing will be guided by the type of disease that is anticipated. For example, spirometry may be chosen to monitor a population at risk for airways disease, and chest radiography to monitor a population at risk for pneumoconiosis. It is important to consider how often testing should be performed and over what period of time a population should be monitored. Surveillance must be conducted in a way that protects the individual confidentiality of results and is consistent with the ethical and legal requirements for confidentiality. Controls must be in place to allow the medical surveillance to be conducted and the data analyzed and used, but appropriately limit who has access to the data. A particular concern in occupational settings is protecting the confidentiality of workers' sensitive medical information from their employers.

Individual medical surveillance results should be used to identify the candidates for secondary prevention and also to identify the sentinel cases that provide clues for improvements in primary prevention. It is important that workers be notified of their results and be provided access to guidance. Surveillance results should also be evaluated at the population level to assess whether there are associations of disease with certain work or exposure scenarios, which can guide efforts to improve primary prevention. It is important to act on these results as appropriate, as the desired outcomes of medical surveillance are improvements in primary prevention and secondary prevention. Lessons from the ongoing surveillance can be used to modify the surveillance program and improve it over time. Issues to consider in planning medical surveillance for the emerging occupational and environmental respiratory diseases are as follows:

(1) Does the balance of potential benefit vs. cost justify medical surveillance?
   (a) Challenge: there are many uncertainties in the setting of an emerging disease that make assessment of cost and benefit difficult.
(2) What population should undergo surveillance?
   (a) Challenge: If the causative exposure is unclear and has not been adequately measured, it may be unclear which population is at greatest risk.
(3) What medical tests should be used in the surveillance program?
   (a) Challenge: Performance of medical tests in surveillance for an emerging disease is often unclear.
(4) How frequently should medical surveillance be conducted?
   (a) Challenge: Rapidity of emerging disease development may be unclear.
(5) How long should medical surveillance continue?
   (a) Challenge: Latency of emerging disease development may be unclear.
(6) How should individual data be used for secondary prevention?
   (a) Challenge: Clinicians may be unsure how to respond to some surveillance data (such as a

significant decline in lung function from baseline that is still in the cross-sectional 'normal range').

(7) How should aggregated population data be used to identify problem areas and improve primary prevention?
   (a) Challenge: Aggregated data should be managed in a way to protect individual confidentiality.

EXAMPLES OF MEDICAL SURVEILLANCE FOR UNANTICIPATED EMERGING OCCUPATIONAL AND ENVIRONMENTAL RESPIRATORY DISEASES

Flavoring-related lung disease provides an excellent example of the usefulness of medical surveillance in follow-up to a sentinel event [3▪]. The first sentinel event related to respiratory disease caused by butter flavorings occurred in 2000, when an eight-person cluster of severe lung disease in a single microwave popcorn production plant was recognized and reported to the public health authorities. A detailed investigation of the plant followed. Medical surveillance of workers was conducted using respiratory questionnaires and spirometry. Exposure assessment studies were also performed. These studies eventually led to the realization that inhaling of vapors of a chemical used in butter flavorings, diacetyl, caused constrictive bronchiolitis. In addition, greater levels of exposure were related to greater loss of forced expiratory volume in 1 s (FEV_1), and certain jobs and tasks, such as mixing flavors, were found to be associated with greatest risk. Similar medical surveillance in five additional microwave popcorn plants over the next several years identified additional previously unrecognized cases and demonstrated that this was an industry-wide issue. Analysis of the aggregated data documented certain risk factors (e.g. mixing, working near nonisolated tanks of oil, and flavorings) and suggested strategies for primary prevention. Follow-up medical screening in the index plant after exposure controls were put into place documented reduced rate of FEV_1 decline in workers as a measure of effectiveness [3▪,7].

Two more sentinel events related to flavorings occurred in 2004 and 2006, when constrictive bronchiolitis occurred in two workers in flavoring-manufacturing plants in California [8]. These workers were exposed to diacetyl and other flavoring chemicals when they prepared batches of flavoring mixtures. In response, from 2006 to 2009, the California Division of Occupational Safety and Health (Cal/OSHA) and the California Department of Public Health implemented a state-wide program of occupational health surveillance in the flavor manufacturing industry that included medical surveillance and exposure assessment and control. The medical surveillance component included a respiratory health questionnaire and spirometry that was carried out at 3–6-month intervals. Initial cross-sectional medical surveillance identified 18 workers with spirometric obstruction (5 with an FEV_1 that was severely reduced at <50% predicted) [9]. Follow-up rounds of medical surveillance demonstrated the utility of longitudinal spirometry in medical surveillance for this disease. It identified clusters of workers with abnormally rapid FEV_1 decline in some flavor manufacturing companies. FEV_1 decline was greater at companies using at least 800 pounds per year of diacetyl than at those using lesser amounts. One worker was reported with an FEV_1 decline of 1.71 over only 8 months [10▪].

As experience has accumulated about flavoring-related constrictive bronchiolitis, it has become clear that medical surveillance has an important role to play in primary and secondary prevention, that spirometry is a useful medical test for this surveillance, and that surveillance must be conducted relatively frequently because the disease can develop and progress quickly. In 2011, the National Institute for Occupational Safety and Health (NIOSH) issued draft guidelines for medical surveillance of workers exposed to diacetyl and a related alpha-diketone that is also used in butter flavorings, 2,3-pentanedione [11]. Medical surveillance is recommended for all workers who regularly work in or enter areas where diacetyl or 2,3-pentanedione are used or who have had these types of duties in the last year (follow-up should be longer if abnormalities are present). Medical surveillance should include a questionnaire that collects information about demographics, work history, exposures, personal risk factors, health history, and symptoms and spirometry. The recommended frequency of evaluation is every 6 months. However, if a likely case of work-related lung disease is identified in the workplace, the frequency of evaluation for all similar workers should be increased to every 3 months and the workers instructed to report any new or worsening symptoms. This higher frequency is recommended to be maintained until excessive exposures have been corrected and no new cases have occurred for 12 months. Individuals identified as possibly having flavoring-related lung disease should undergo medical evaluation and be removed from exposure pending completion of the medical evaluation. Population data should be evaluated to assess for work-related risk factors based on job,

task, area, and other exposure-related indices to guide interventions as needed.

Sentinel cases of 'indolent constrictive bronchiolitis' continue to be recognized in new occupational settings [12▪]. Examples include among flavored coffee manufacturing workers [13], fiberglass workers [14], and U.S. soldiers returning from Iraq and Afghanistan [15]. The latter exemplifies the challenges in determining appropriate recommendations for medical surveillance in the setting of a poorly understood emerging occupational and environmental respiratory disease. The sentinel event was recognition of a cluster of lung disease in soldiers returning from Iraq and Afghanistan. A total of 80 soldiers were evaluated because of dyspnea on exertion with inability to meet the military fitness standard for a 2-mile run. After evaluation, 49 were referred for lung biopsy. Thirty-eight soldiers had biopsy-confirmed constrictive bronchiolitis. A clear causative exposure was not identified. Medical tests were insensitive, with normal chest radiograph in 97%, normal chest computed tomography scan in 68%, and normal pulmonary function testing in 34% (13 of 38). The only abnormal pulmonary function test abnormality in 19 of 38 was an isolated low carbon monoxide diffusing capacity. Had these soldiers not been recognized to be part of a concerning sentinel disease cluster, it is likely that many would not have undergone biopsy because screening tests would not have suggested the necessity.

Constrictive bronchiolitis in this population highlights the challenges in developing recommendations for medical surveillance for an emerging occupational and environmental respiratory disease, as was recently done by a working group assembled by the U.S. Department of Defense and the U.S. Department of Veterans Affairs [16▪▪]. Because the causative exposure is unclear, it is not possible to tightly target medical screening. Therefore, it is recommended that all U.S. troops deployed to Iraq and Afghanistan for at least 30 days should be in a medical surveillance program, and all deployed personnel should undergo predeployment and postdeployment respiratory disease surveillance. The recommended components of surveillance include administration of a questionnaire asking about smoking history, pertinent medical history, and respiratory symptoms; spirometry before and after bronchodilator; and exercise capacity evaluation, including 1 or 2 mile run times. Predeployment evaluation provides an important baseline, as many soldiers have 'super-normal' test results at baseline and would have to lose much pulmonary function before dropping to conventional cross-sectional thresholds of abnormality. Criteria have been developed for recommending diagnostic referral based on the medical surveillance results, including changes exceeding certain percentages of baseline values [16▪▪].

EXAMPLES OF MEDICAL SURVEILLANCE FOR ANTICIPATED EMERGING OCCUPATIONAL AND ENVIRONMENTAL RESPIRATORY DISEASES

Identifying the best approach to medical surveillance for anticipated emerging diseases is extremely challenging. An excellent example of an emerging exposure is engineered nanoparticles. A recent report cautioned against rigid definitions, but noted that nanoparticles are often thought of as particles measuring 1–100 nm and exhibiting novel properties related to size [4▪▪]. There are many types of engineered nanoparticles, and new generations continue to emerge that are used in a wide range of products and industries. Examples of established products include ceramic nanoparticles, carbon nanotubes, and nanoporous materials. The economic impact of nano-enabled products in 2015 is estimated to be $2 trillion [4▪▪].

Perhaps, because relatively little time has passed since the widespread introduction of nanomaterials, it is still unclear how exposure to them will affect the burden of respiratory disease in exposed people. Thus, recent NIOSH recommendations for medical surveillance of workers exposed to carbon nanotubes and nanofibers were largely based on the animal toxicology studies showing that some of the tested materials had the ability to penetrate epithelial barriers and from lung into the pleura and circulation, to cause pulmonary inflammation and fibrosis, to interact with mitotic spindles and cause aneuploidy in daughter cells, and to increase the risk of lung cancer in mice co-exposed to a known carcinogen [17▪▪]. The evaluation of need for medical surveillance and how to perform it use this animal health data to anticipate potential human health problems. The recommended elements of surveillance include a baseline evaluation including a questionnaire, physical examination, spirometry, and a chest radiograph. Follow-up includes questionnaire and focused physical examination annually, spirometry every 3 years, and other evaluation as indicated.

Another type of setting in which emerging exposures occur and emerging diseases can be anticipated is after a large-scale disaster such as the WTC disaster. An important lesson in medical surveillance from that disaster was the importance that baseline medical information such as spirometry played in the follow-up of Fire Department of

New York (FDNY) personnel after the disaster. The availability of baseline spirometry and other data (such as smoking history) allowed documentation of the pronounced declines in pulmonary function occurring soon after the disaster that would not otherwise have been possible [18]. Another effort involving medical monitoring, the WTC Health Registry, has enrolled 71 thousand participants, including workers, residents, and others with a high probability of exposure to WTC-related airborne contaminants. It is planned to evaluate them every 3–4 years over 20 or more years. A recent article from the registry described the lessons learned, among them the importance of thoroughly documenting the exposures of the target population as quickly as possible during the disaster [5]. In a recent publication documenting the lessons learned from the Deepwater Horizon response, NIOSH investigators noted the importance of addressing the need for long-term follow-up studies early in a disaster, noting that such studies can be costly and difficult to design. They suggested that general areas of investigation might include etiologic investigations to evaluate the health impact of exposures to novel, under-studied agents; follow-up after exposure to agents with known adverse health effects and for which secondary prevention might be effective; or a combination of the two [19].

CONCLUSION

Medical surveillance is a useful tool in addressing the emerging occupational and environmental respiratory diseases. It can be applied after they are recognized in sentinel events or if they are anticipated as potential problems in people who have had hazardous exposures (Fig. 1). Before implementing medical surveillance, cost vs. benefit should be considered and if medical surveillance is felt to be appropriate, careful planning should determine who should undergo surveillance and how it should be carried out (see list above). Medical surveillance only achieves its full potential for benefit when surveillance information is analyzed and appropriately acted on at the individual level for secondary prevention and population level to improve primary prevention. Lessons from the recent emerging occupational and environmental respiratory diseases such as constrictive bronchiolitis and WTC-associated respiratory disease include the importance of recognizing and acting on sentinel events; the importance of longitudinal follow-up of lung function and having access to baseline lung function measurements; and the importance of quickly identifying subpopulations with exposures, putting them at greatest risk for respiratory disease and thus at greatest potential benefit from medical surveillance.

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Conflicts of interest

D.N.W. is a full-time employee of the U.S. Government and has no commercial conflicts to disclose. The findings and conclusions in this report are those of the author and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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