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The Role of Radiology in Influenza: Novel H1N1 and Lessons Learned From the 1918 Pandemic

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Abstract

The pandemic of swine-origin H1N1 influenza that began in early 2009 has provided evidence that radiology can assist in the early diagnosis of severe cases, raising new opportunities for the further development of infectious disease imaging. To help define radiology's role in present and future influenza outbreaks, it is important to understand how radiologists have responded to past epidemics and how these outbreaks influenced the development of imaging science. The authors review the role of radiology in the most severe influenza outbreak in history, the "great pandemic" of 1918, which arrived only 23 years after the discovery of x-rays. In large part because of the coincidental increase in the radiologic capacity of military hospitals for World War I, the 1918 pandemic firmly reinforced the role of radiologists as collaborators with clinicians and pathologists at an early stage in radiology's development, in addition to producing a radical expansion of radiologic research on pulmonary infections. Radiology's solid foundation from the 1918 experience in medical practice and research now affords significant opportunities to respond to the current H1N1 pandemic and future epidemics through similar interdisciplinary strategies that integrate imaging science with pathology, virology, and clinical studies. The broad range of current imaging capabilities will make it possible to study influenza at the cellular level, in animal models, and in human clinical trials to elucidate the pathogenesis of severe illness and improve clinical outcomes.

Keywords

Radiology; infectious disease imaging; influenza; great pandemic of 1918; epidemic; chest CT; plain film; chest radiograph; history; pulmonary infection

INTRODUCTION

The novel H1N1 influenza virus that emerged in early 2009 has spread throughout the world, causing large numbers of mild illnesses and a much smaller, but still significant, number of fatal cases. Radiologists have responded to the outbreak through efforts to

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characterize pulmonary changes that accompany severe infection [1-4]. In considering how radiology might contribute further to the medical response, and what impact the pandemic could have on the future development of imaging science, it is useful to look back at the most severe influenza outbreak in history, the pandemic of 1918 to 1919.

Even though it occurred nearly a century ago, the “great pandemic” is still remembered for its extremely high death toll of 50 million people and the unexpected concentration of deaths among young adults [5,6]. Less well recognized is the stimulus the catastrophic outbreak gave to medical research and practice, particularly to the young science of radiology. The present review demonstrates that the 1918 pandemic strengthened radiology’s role as an integral component of clinical practice and research at a time (only 23 years after the discovery of x-rays) when radiologic capability was still highly undefined, resulting in widespread acceptance of chest radiography for managing pulmonary disease. Using this historical precedent from 1918, we consider the question of how the 2009 pandemic could potentially affect the future development of radiology and radiology’s response to epidemics. After reviewing the status of radiology in medical practice before, during, and after the 1918 pandemic, we consider how the new influenza outbreak may stimulate further progress in imaging science for pulmonary infection.

RADIOLOGY AND RESPIRATORY INFECTIONS BEFORE 1918

Although radiology is an integral part of contemporary clinical medicine, the role of radiology was quite undefined a century ago. Given Roentgen’s background as a physicist, there was initial debate over whether the discovery and development of x-rays would be primarily the domain of physics or find more translational applications in medical practice [7]. Similarly, there was speculation about the role of x-rays in the practice of medicine during the early 1900s. Some suggested that x-ray imaging could potentially supplant physical examination by establishing a unique image pattern for each disease, whereas others argued that the technology merely provided pictures of abnormalities that could readily be diagnosed by history and physical examination [7,8]. Even the eminent clinician Sir William Osler claimed that radiology offered little that could not be learned through physical examination [8,9].

Significant inquiry into the value of radiology focused on the role of the chest radiograph in clinical diagnosis. Less than a year after Roentgen’s discovery, radiographic examination of the lungs had revealed air bronchograms, and the first images of pneumonia were published in 1903 [10-14]. These clinical observations were supported by technological innovations from 1901 to 1918, such as the Coolidge tube in 1913, which improved radiographic imaging, and the Bucky grids developed from 1913 to 1920, which reduced scatter. Given such rapid progress, it was hoped that radiology could help turn the tide against the major scourge of the early 20th century, tuberculosis, which led to the Trudeau group in 1916 establishing radiographic criteria for diagnosing pulmonary tuberculosis. Although physicians could recognize advanced cases of tuberculosis, it was clear that effective treatment would require earlier detection, which imaging might provide. However, experience and data from a wide range of infections was still scarce and anecdotal at that time [8].

RADIOLOGY IN WORLD WAR I AND THE PANDEMIC INFLUENZA OF 1918

The entry of the United States into World War I had a significant impact on the development of radiology and coincidentally set the stage for radiology to play a large role in the concurrent influenza epidemic. Radiology was adopted as an integral part of the US military’s medical establishment and mobilization for war in 1917 and 1918 (Figure 1). When the United States declared war on Germany and began to mobilize a large

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expeditionary force, the Army Medical Department decided to include radiology detachments in its units. As described in a 1923 report from the US government [15]:

> Prior to the war, only the larger of our military hospitals were equipped with X-ray apparatus. As these larger hospitals were comparatively few in number, there was no organized effort to maintain selected group of officers whose sole or principal specialty was roentgenology …. In May 1917, the officer in charge of the supply division of the Surgeon General's Office recommended that an officer familiar with roentgenological requirements be assigned to the Surgeon General's Office for general supervision of the whole X-ray problem, including the purchase, distribution, and installation of X-ray apparatus …. A committee was appointed by the Council of National Defense for the purpose of standardizing X-ray apparatus and supplies.

Although it was evident that radiographic examination could help manage battlefield casualties, the provision of radiographic equipment was not limited to units embarking for Europe but also included training camps throughout the United States, where the experience of past wars indicated that respiratory infections and pneumonia would be significant threats [16,17]. For example, measles killed >3000 recruits during the winter of 1917 to 1918, with secondary bacterial pneumonia as the major cause of death. Military physicians also hoped that chest radiographs could help screen recruits for their fitness for combat [18].

The wealth of funds provided by mobilization made it possible for the War Department to purchase up-to-date radiographic instruments, including a "portable X-ray apparatus … devised by the General Electric Co, found superior to anything … up to that time" [15]. Bulk purchases of equipment facilitated the standardization of technical procedures and imaging protocols. In addition, the US military initiated an ambitious training program to provide the radiologists and technicians needed for staffing the numerous Army camps and hospitals [15]. The first edition of the *United States Army X-Ray Manual* appeared in 1918, and numerous schools were established to produce 120 new radiologists and technical personnel per month.

Considering the medical community's ongoing uncertainty regarding the utility of imaging in clinical patientcare, the War Department's massive enhancement of its radiologic capability was a bold and ambitious strategy. However, the decision was fully vindicated when a virulent strain of influenza virus emerged in 1918. By fall, it was sweeping through Army training camps, and it soon reached the battlefields of Europe (Figure 2). By the end of the pandemic in 1919, it is estimated that >50 million people had died of the disease. Ironically, the number of soldiers who succumbed to influenza accounted for >40% of American military deaths in World War I.

Because US Army units had been equipped with trained teams of radiologists, up-to-date instruments and standardized protocols, the great pandemic provided the first large-scale test of implementing radiology for severe respiratory tract infections during an epidemic. Experience with radiographs demonstrated that influenza patients with mild clinical symptoms either had normal chest radiographs or displayed enlarged hilar structures without parenchymal lung opacities [19-22]. In severe cases, however, radiologists published papers describing a pattern of "patchy density," often labeled "peribron-chial" and considered to be bronchopneumonia (Figure 3). The distribution of these patchy densities described in published reports is variable, with some labeled as peripheral, "appear[ing] at the periphery and progress[ing] inward, forming a triangle or truncated cone" [23], while others showed a central distribution that expanded outward, "commenc[ing] at the hilus, the lesion spread out from the root as a pivot … like an advancing film of smoke" [24]. Nevertheless, authors generally agreed that patchy opacities represented the most common pattern in chest radiographs, with a consensus that the less frequent lobar consolidations, empyemas, and effusions likely represented complications of bacterial infection in the most severe cases [25-29]. The common finding of bronchopneumonia on chest radiographs agreed with the observations of pathologists and microbiologists that most fatalities resulted from superinfection by pneumococci, streptococci, and other bacteria [30].

Despite the hope that radiography could provide a specific diagnosis of influenza, the appearance of severe cases by chest radiography was sufficiently similar to that of other entities to raise diagnostic dilemmas. For example, many authors from 1918 to 1920 noted that influenza could be confused with tuberculosis [26,31-36]. Such findings challenged the chest radiographic criteria for tuberculosis that had been established by the Trudeau group in 1916 [7] and required a reassessment of how radiologic findings should be applied to patients with mycobacterial infection[14,37,38]. Given the high prevalence of tuberculosis at the time, there was also controversy about whether influenza survivors were at increased risk from mycobacterial disease and whether influenza patients should be isolated in tuberculosis sanitariums [36,39,40].

The overlap in the radiographic features of tuberculosis, influenza, and other pulmonary conditions reported in the literature from 1918 into the 1920s strengthened the view that imaging usually could not offer one specific diagnosis for each patient but instead provided a differential diagnosis that could be integrated with clinical information to make patient care decisions. This pattern, reinforced by thousands of influenza patients, strengthened the role of radiologists as collaborators with clinicians. For example, radiologists during the 1918 pandemic had high levels of accuracy in identifying complications of influenza that benefited from rapid intervention [41]. Thus, numerous publications showed that empyema could readily be diagnosed by imaging[19,20,25,29,32,40,42-50] and that radiography could also visualize spontaneous pneumothoraces and associated subcutaneous emphysema, which benefited from early treatment [49,51]. Interestingly, radiographic associations between pneumothorax and subcutaneous emphysema contradicted contemporary theories that gasproducing microbes were responsible for subcutaneous emphysema in influenza [21,32,52-54]. Because pneumothoraces were often clinically inapparent and had poor outcomes if left untreated, the ability to detect them was a major advance for radiology [32]. Pericarditis and bronchiectasis were two other complications of influenza that previously had been recognized principally at autopsy but could now be detected in vivo by chest radiography. The former was characterized by enlargement of the cardiac silhouette [19,55,56], while evidence of the latter was provided by inflammatory enlargement of plugged airways [40,57].

In addition to contributing to medical therapy, research was recognized to be a major component of the radiologic enterprise during the 1918 pandemic. As noted at the time [26,27],

> the opportunity to study influenza from a roentgenological point of view has been exceptional …. In the epidemic of 1918 a very unusual opportunity was given to study the pulmonary changes from the earliest moment of onset to final changes that resulted in the death of the patient.

Another author [37] observed that

> in the recent World War, the soldiery was rapidly invaded with influenza, and the economic problem of looking after them enabled the medical profession to obtain accurate data which have been secured in no other way. Hundreds of thousands were thus tabulated and the careful studies made give us unquestioned facts upon which we can rely.

Military and civilian radiologists published numerous articles during the pandemic, contributing to a significant increase in the volume of the radiologic literature recorded in Index Medicus. Many reports were written by clinicians and radiologists at US Army training camps, where large numbers of patients were treated, such as Camp Dodge, Camp Lewis, Camp Lee, Camp Jackson, the US Naval Hospital in Philadelphia, Camp Devens, Walter Reed General Hospital, US Army General Hospital No. 16 and No. 1 (Columbia War Hospital), US Army Base Hospital at Fort Riley, and the Surgeon General of the US Army, among others [19,24,26,32,44,46,52,58-62]. In many of these studies, influenza patients were imaged on a daily or even hourly basis, documenting the progression of infection and correlating premortem observations with findings at autopsy [62]. It is unclear from the literature of that time period whether the imaging consistently affected patient outcomes because the published studies mainly investigated the correlation between radiology, clinical features, and autopsy-based pathology as a way of understanding the pathophysiology and natural history of the infection. However, the contribution of this approach was to demonstrate that imaging could provide an in vivo method of following disease progression and monitoring for complications.

The great pandemic also reinforced the role of radiologists as clinical collaborators in patient care. For example, one author wrote, “The interpretation of the [radiographic] plate is not easy, and the roentgenologist must be a physician and one who can interpret his findings in conjunction with the clinical findings presented by the internist” [32,43]. As noted above, this view was supported by the unexpected difficulty of interpreting chest radiographic images, which mandated an integrated approach to patient management [26,31-33,35,40,63]. Reviewing lessons learned during the first year of the pandemic, one writer observed [32],

> There has been no greater proof of the value of cooperation between the clinician and surgeon and the roentgenologist than in the study of the cases of thoracic manifestations of the [influenza] infection and the complications. In many instances, appearances were so unusual or puzzling that a combined clinical and roentgenological study of the cases was essential for an accurate interpretation.

As the pandemic receded, the large number of trained radiology personnel and the accustomed use of imaging by military surgeons and internists combined to maintain radiography as a standard clinical practice. At the same time, soldiers coming home from World War I who had been examined in the radiology suites of Army hospitals now expected that a visit to the doctor would include radiographic imaging [18]. Reflecting on this transformation, Hickey [18] wrote in 1923,

> We can safely say that the average internist, during his military service, became rapidly educated to seek the assistance of the roentgenologist-…. Not only did the military surgeon become rapidly accustomed to a more liberal employment of these examinations, but the returned soldier, when confronted by illness himself or of his family frequently suggested the use of x-rays to which he had become accustomed during his time of military service.

In summary, the 1918 influenza epidemic made a substantial impact on radiology’s development, particularly as the US mobilization for World War I significantly expanded radiology’s capacity for clinical and research contributions. The literature published by radiologists at that time expanded radiology-pathology correlation for pulmonary infections, reinforced routines for radiologists to collaborate with other clinical specialties, demonstrated the imaging features of infectious disease complications (such as bronchiectasis, empyema, pneumothorax, pericarditis, and others), and strengthened the role of chest radiography in managing pulmonary infection. We now turn to the question of how current and future pandemics may advance imaging science and clinical radiology.

RADIOLOGY'S RESPONSE TO THE 2009 H1N1 INFLUENZA OUTBREAK

Ninety-one years after the great pandemic, a novel strain of influenza virus emerged, raising the question of what should be radiology's role in the management of epidemics. In 1918, resources that had been mobilized for World War I were ready for use when influenza unexpectedly appeared, leading to the development of standardized imaging protocols, widespread training of new personnel, a reinforced role of radiologists as collaborators with clinicians, and a large-scale expansion of published radiologic research. Can the vast array of radiologic capabilities developed for oncology, neurologic diseases, and other conditions help improve radiologic response to current and future pandemics, both for clinical care and for basic research? In particular, can imaging help identify the small fraction of influenza patients who will progress to severe or fatal disease in the absence of intensive medical intervention so that they can be triaged appropriately and treated promptly? Answering such questions will require careful observation of hospitalized patients and the integration of knowledge gained from experimental research in the forms of clinical trials and animal studies.

One major advance since 1918 has been the invention of CT, which offers more detailed radiologic-pathologic correlation. Since the novel swine-origin H1N1 virus emerged, several reports have described CT abnormalities in the lungs of severely ill patients [1-4,64]. A characteristic finding has been the presence of multiple patchy ground-glass opacities, often in a peripheral distribution, similar to those described by radiologists during the 1918 pandemic [20,23,25-27,65]. At autopsy, these areas of CT abnormality are thought to correspond to regions of diffuse alveolar damage, but their etiology is still undetermined [3,66]. As severely ill novel H1N1 influenza patients progress toward death, extensive areas of pulmonary consolidation have been observed both on radiographs and CT, apparently corresponding to bacterial pneumonia, which is now thought to have been the cause of death in most cases in 1918 [30,66]. An important means of improving our understanding of influenza's pathogenesis will be the careful correlation of pathology and radiology findings. For example, the relative nonspecificity of ground-glass opacity on CT cases of H1N1 influenza raises an opportunity to better link this radiologic finding with underlying histopathology using CT and advanced viral immunohistochemistry.

The use of molecular imaging to study the pathogenesis of influenza is also a potentially fruitful area of research; 2-[^{18}F]fluoro-2-deoxyglucose PET, which has transformed oncologic practice, is just beginning to serve as a tool for infectious disease imaging. For example, whether the diffuse alveolar damage in viral pneumonia is the consequence of direct injury by the pathogen or is induced indirectly through the release of inflammatory mediators (or both) is a question under investigation. To this end, in vivo imaging studies of infection through probes for viral and inflammatory markers could provide new insights. Such questions might be answered through the variety of techniques under development that visualize and quantify host responses at the molecular level [67]. Although it is unlikely that such methods would soon be introduced into standard medical practice, they could be used in research settings to help explain the origin of structural changes observed by CT and to provide biomarkers for trials of novel therapies.

Because radiology is now a digital specialty, it should be possible to use imaging data to detect and monitor epidemics globally through the collection and sorting of searchable data archives [68]. The major obstacle to introducing this approach lies in the technical infrastructure that would be required to make such a surveillance apparatus functional, flexible, reliable, and secure. The development of a rapid method of collecting and analyzing radiologic information in an outbreak could be critical for identifying disease complications and gaining insight into their pathogenesis. For such a system to be of maximum value, it should integrate the findings of radiologists, pathologists, physicians, surgeons, and other specialists.

A comprehensive system of data analysis is also needed to support evidence-based medical practice, particularly to determine whether novel imaging approaches such as early chest CT can make a difference in clinical outcomes. Past commentaries have pointed out the anecdotal nature of radiology case series published during and after the 1918 pandemic [8], making it clear that future infectious disease imaging research will have to meet rigorous standards for demonstrating a positive impact on patient outcomes. Furthermore, current policy efforts to maximize the cost-effectiveness of imaging warrant evidence-based approaches for radiologic responses to pandemics [69-71].

The arrival of the new H1N1 pandemic has reminded us how little we know of the pathogenesis of seasonal influenza, which even in an average year is responsible for approximately 36,000 deaths in the United States [72]. Clinical studies to enhance the understanding of seasonal influenza might include examination of the natural history of infection by seasonal virus strains and the identification of innate and adaptive immune mechanisms that prevent progression to severe illness. Such research would be greatly enhanced by the application of conventional and molecular imaging that could provide in vivo tracking of the virus with imaging of the host response.

Imaging of experimental influenza in humans, under approved clinical protocols, should be accompanied by parallel studies in animal models, including nonhuman primates. The inclusion of conventional and molecular imaging in such experiments would revolutionize the study of influenza and other viral diseases by making it possible to follow major parameters of infection in the same animal over the entire course of illness. To succeed, such research will require the integration of imaging, radiotelemetry, and pathology in the setting of a secure biocontainment laboratory; a facility of this type is now under development at the National Institutes of Health [73].

CONCLUSIONS

The devastating influenza epidemic of 1918 strongly affected the development of radiology at an early stage in the specialty's development. The numerous publications of imaging findings during that pandemic with close collaboration among pathologists, clinicians and radiologists constituted a large-scale effort to study the role of imaging in infectious disease management. The 1918 pandemic shows that an outbreak can stimulate significant progress in technical capability, clinical knowledge, and research in radiology. The H1N1 pandemic is providing an avenue for radiology to once again define its participation in the diagnosis and management of current and future infectious outbreaks. Just as the 1918 influenza pandemic helped establish lasting clinical and research patterns of interdisciplinary cooperation among clinicians, pathologists, and radiologists, the current outbreak and preparations for future pandemics provide an opportunity to advance imaging science.

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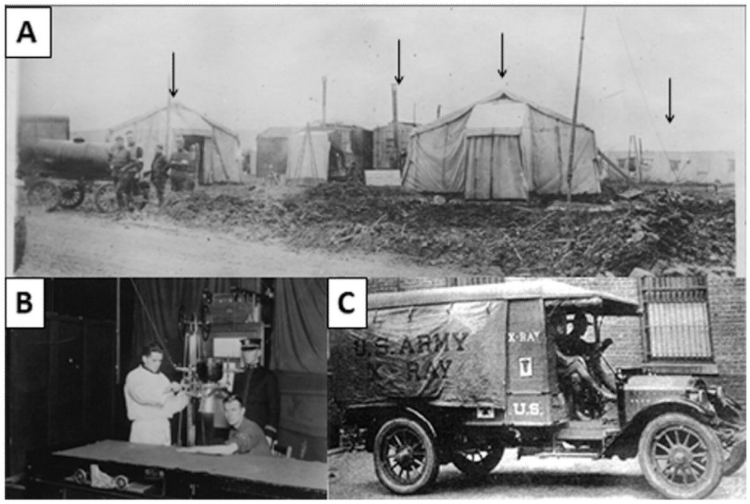

Fig 1.

(A) Military hospital (1914-1918) with radiology station. Mobile Hospital No. 6, Varennes Station, France. Structures shown left to right (arrows): evacuation ward, radiology station, shock tent, postoperative ward. (B) US Naval Hospital No. 1, Brest, France (1914-1918) during World War I; personnel configuring x-ray equipment. (C) US Military Mobile X-Ray Unit, World War I. Source: National Museum of Health and Medicine, Armed Forces Institute of Pathology, Washington, DC.

Fig 2.

Influenza epidemic hospital ward, Camp Funston, Kansas, 1918. Source: National Museum of Health and Medicine, Armed Forces Institute of Pathology, Washington, DC, image NCP 1603 (http://evans.amedd.army.mil/pandemicflu/1918.htm).

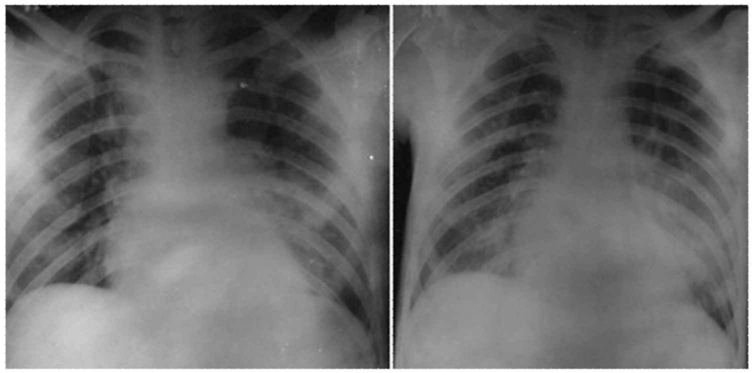

Fig 3.
Chest radiographs of 2 patients with 1918 influenza showing patchy lung opacities. Source: National Museum of Health and Medicine, Armed Forces Institute of Pathology, Washington, DC.