

The ratio of deaths to population varied from 1.9 per thousand in Spartanburg to 6.8 in Maryland towns. The death rate was by no means parallel to the influenza attack rate, but was correlated closely with the pneumonia rate. In other words, the case fatality of pneumonia tended to be fairly constant, around 30 per cent., except in San Antonio, where it was only 18.5 per cent. The death rate was notably high in children under 1 year old, in adults from 20 to 40, and in persons over 60; higher in males than in females of comparable ages; higher in the white than in the colored.

The case fatality was likewise higher in these age groups: under 1 year, 20 to 40, and over 60 years; and it is this fact, rather than the incidence rates, which determines the death rates in different age groups.

Chart 6 shows the attack rates, death rates and case fatality rates in various age groups.

#### THE IMPORTANT QUESTION OF IMMUNITY

Concerning the important question of the immunity conferred by an attack of influenza, the evidence is not conclusive, chiefly because of the uncertain differentiation between influenza and other infections. Parsons, from his study of the last epidemic,<sup>1</sup> inclines to the view that an attack of influenza in the earlier years of the epidemic conferred a considerable but not absolute immunity in the later outbreaks.

In Baltimore, where our first canvass of 33,776 people was made between Nov. 20 and Dec. 11, 1918, a second canvass of the same population was made in January to determine the extent of the recrudescence reported in December. Among 32,600 people included in this canvass, 724 cases of influenza were found to have occurred since the previous survey. Of this number 121 cases were reported as second attacks, but on investigation through the attending physicians or by a medical officer, the clinical diagnosis of both attacks as influenza was confirmed in only 26 cases, or 0.37 per cent. of the total, and even in these cases the diagnosis is necessarily uncertain. Considering that 23 per cent. of the population had had influenza prior to December 11, the proportion of second attacks should have been much greater if no immunity had been acquired. A second canvass in San Francisco gave generally similar results. The data collected for a study of this question from other angles have not yet been analyzed.

#### GENERAL CHARACTERISTICS OF EPIDEMIC

In general, this epidemic has been quite similar to that of 1889-1890 in its early development, first in mild, scattered outbreaks, later in a severe world-wide epidemic; in the rapidity of its spread, and in its high case incidence. It has been notably different in a much higher frequency of pneumonia and consequently much higher mortality, especially among young adults.

Such evidence as has been collected confirms the conclusion previously reached that the infection is transmitted directly by "contact" in the broad sense. It appears probable, however, that the infection was already widely disseminated in this country some time before a serious epidemic was recognized.

#### PROBABILITY OF RECURRENCES IN THE NEAR FUTURE

The question of most practical and immediate interest is the probability of recurrence in the near future. Recurrences are characteristic of influenza epidemics; and the history of the last pandemic and previous ones would seem to point to the conclusion that this one has not yet run its full course. On the other hand, this

epidemic has already shown three more or less distinct phases and has been more severe, at least in mortality, than the three-year epidemic of 1889-1892, facts which may justify the hope, though not the conclusion, that it has run its course already.

It seems probable, however, that we may expect at least local recurrences in the near future, with an increase over the normal mortality from pneumonia for perhaps several years; and certainly we should be, as far as possible, prepared to meet them, by previous organization of forces and measures for attempted prevention, treatment and scientific investigation.

#### FUTURE STUDY AND CONTROL

As regards preventive measures, the efficacy of those carried out in recent months is not proved, and we can only continue to follow the apparently sound principles already applied. It seems hardly logical to expect that any measure short of effective specific immunization will afford lasting protection to the general population; but we may perhaps hope to delay the spread of infection, thus affording better facilities for treatment of the sick, and this is an achievement well worth while.

With reference to scientific investigations, these should not be conditioned on recurrence of the epidemic. Now is the time to inaugurate comprehensive laboratory and field investigations of influenza and pneumonia, to be continued not for a few months, but for a series of years, since a knowledge of influenza during the intervals between epidemics is essential to the understanding of epidemics. In this connection one of the most essential requisites for a better understanding of the disease is better differential diagnosis of endemic influenza, with more careful observation and recording of the relatively mild, indefinitely diagnosed epidemics of supposed influenza which are noted from time to time in the intervals between definite epidemics. Even in the absence of a definite diagnosis of individual cases, much would be added to the history of influenza by describing such outbreaks more fully and making them matters of more general record.

### BACTERIOLOGY OF RECENT PANDEMIC OF INFLUENZA AND COMPLICATING INFECTIONS \*

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When the recent outbreak of influenza appeared, it was assumed by all that it was probably due to the same cause as that of 1889. Health officials, epidemiologists and bacteriologists, already overwhelmed by the demands of the war, were called on to investigate and combat the infection.

The first appearance of the epidemic was in Europe. Bacteriologists, while keeping an open mind, naturally first sought for the influenza bacillus isolated by Pfeiffer from endemic cases of influenza-like infections some two years after the 1889 epidemic.

He had established a relationship between this bacillus and infections of the respiratory tract and had assumed that it was the primary agent in the great

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pandemic. Investigations since then have thrown considerable doubt on this assumption, and many have now come to consider the bacillus as only one of several varieties of bacteria which have a special selective tendency to attack the mucous membranes of the upper respiratory tract.

The reports from different investigations in Europe have been most conflicting. Influenza bacilli were found in some localities to be present in nearly every case, while in others bacteriologists isolated them from only a small minority of the patients.

In their place, pneumococci, streptococci and gram-negative micrococci were found. Frequently, several varieties occurred together. A few observations in France and England indicated that a filtrable virus was present in at least some of the cases. As a filtrable virus had already been demonstrated in outbreaks of common colds, when no epidemic existed, this information, in spite of its great interest, simply added one more line of investigation.

The possibility that more than one epidemic of an influenza-like disease was prevailing in Europe makes it advisable to concentrate our attention on the results of the bacteriologic findings in this country. Here, the unity of the epidemic which swept over the land was unmistakable.

#### NECESSARY PROOF

To identify a micro-organism as the cause of a widespread epidemic, the germ must be capable of producing the type of disease under investigation; it must be present in the advancing area in all cases at the beginning of the infection, and in any outbreak it must have the same characteristics when freshly isolated from different patients. The repeated transfer of a pathogenic germ from patient to patient allows the most characteristic forms to increase, so that until an epidemic is on the wane we find that isolations from different cases from different localities are practically identical. When the different cultures are grown in artificial mediums, under suitable and similar conditions, the isolations from different sources will continue to hold their characteristics sufficiently to be studied and compared.

Even well trained bacteriologists frequently fail to realize that an epidemic strain is alike everywhere in cases belonging to the epidemic.

Before considering the results so far obtained and drawing our conclusions, let us consider for a moment the special problem before us. Epidemic influenza is a disease primarily attacking the respiratory passages. The symptoms during life and the lesions in the dead, although fairly distinctive in the cases at the height of the epidemic, are by no means so in those occurring after it has passed. Whatever the primary infecting micro-organism may be, there is no doubt that in most cases other pathogenic bacteria are decisively associated. Many of these produce very similar symptoms and lesions. It is perfectly possible that a strain of any one of these bacterial varieties may have increased in virulence to an extent enabling it to initiate an epidemic. The micro-organism responsible for the epidemic may either be a microbe hitherto unknown to us or to a new and more virulent strain of some known form. Even if we assume the latter alternative, we have a difficult problem to obtain the proof, for we must discover how to identify it as a new strain. Supposing that we had found pneumococci in all cases, but that in some we had isolated only Type I and in some only

Type II. Instead of this being evidence for a pandemic pneumococcus strain, it would be just the opposite, for two different strains cannot be responsible for one epidemic.

For our purpose, the two types are as distinct as if they were diphtheria and tubercle bacilli; and if either is the pandemic strain, it must occur in all the cases.

Suppose we find in every case a Type II pneumococcus. This is very suggestive, but it is really no proof unless we can show some peculiarity different from that in the cases of respiratory infections before the epidemic. Only then have we probably obtained the culprit. Because of the lack of this evidence, Pfeiffer made his hasty conclusion.

The most delicate test that we have for identity of strains is that animals injected with them produce identical antibodies.

The resemblance between the agglutinins produced is usually selected as the best evidence of identity or dissimilarity. With the filtrable viruses we have to depend on finding some susceptible animal, or revert to human volunteers and if successful in producing infection, test for specific immunity.

#### RESULT OF RECENT INVESTIGATIONS

The pandemic of 1918 is over. The difficulty of being certain that any suspected cases are due to the pandemic virus is gradually increasing. It is probable that if we have not at the present time gathered sufficiently convincing evidence to convict some germ we shall have to wait for another epidemic to solve the problem. It will be well to summarize very briefly some representative investigations.

Keegan made cultures from a number of cases in the virulent outbreak at the First Naval District at Chelsea, Mass. Cultures from twenty-three cases gave influenza bacilli in nineteen, and in some no other bacteria were found. In four cases he considered a streptococcus of the hemolytic variety the dominant organism and in seven cases the influenza bacillus. The earlier the cultures were taken, the greater was the percentage of influenza bacilli.

Spooner, Scott and Heath found evidence that the cases reacted to the influenza bacillus invasion by the production of antibodies. At the end of the first week agglutinins appeared sufficiently in the blood of some cases to agglutinate influenza bacilli when in a 1:50 dilution. In five weeks the serum of some agglutinated when in a dilution of 1:800. They found no evidence of strains of influenza bacilli. They did not use the more delicate and accurate absorption methods in their tests. These investigations afforded evidence that in that extensive outbreak the influenza bacilli played an important part either as the primary agent or as a secondary invader. In four cases a hemolytic streptococcus was shown to play an important and even decisive part.

In the Central West, in twenty-three cases of acute influenza in the early stage, Opie, Freeman, Blake, Small and Rivers subjected the patients to examination and obtained influenza bacilli from all. The examination of the sputum from sixty-nine cases of pneumonia revealed influenza bacilli in forty-three.

Pneumococci were found in every case, but were of different types. The men named agree with Keegan as to the etiologic importance of the influenza bacillus in this epidemic. They place the sequence of events as follows: At the time of infection, *B. influenzae* descends into the bronchi; later, pneumococci may

invade the inflamed bronchi, enter the lung and produce either lobar pneumonia or bronchopneumonia. Hemolytic streptococci may at any time descend and infect the pneumonic lung.

Although Keegan, Opie and their associates believe that the influenza bacilli are the causative agent, they present no real evidence. Opie demonstrated in some groups of healthy soldiers, that 50 per cent. could be shown to harbor influenza bacilli. No proof was obtained that these bacilli differed in any way from those isolated from the patients. Their evidence is as strong that the bacilli are secondary invaders as that they were the primary ones.

In 278 cases occurring in New York, Williams found influenza bacilli as shown in Table 1.

TABLE 1.—EXAMINATION FOR INFLUENZA BACILLI

Group	Influenza Bacilli Per Cent. Present
Hospital cases	80
Marines*	100
Home for children	98
Material examined:	
Lungs	80†
Tracheas	96
Heart's blood	10

\*The marines came from different vessels.

†Seventeen per cent. in fine cultures.

We found that the best site for the material selected, the use of the best mediums and long training in the study of influenza colonies were important in finding the bacilli.

In 100 cases, among civil and soldier patients in Chicago, Nuzum, Pilot, Stangl and Bones found the results given in Table 2.

TABLE 2.—BACTERIA FROM SPUTUM, NASOPHARYNX  
AND TONSILS

	Pneu. %	B. Inf. %	St. Hem. %	Mic. Cat. %
Washed bronchial sputum	70	4	20	5
Cultures from nasopharynx	38	0	7	5
Cultures from tonsils	74	0	37	7

Five healthy persons volunteered to be inoculated in the nostrils with the filtrate from infected mucus. A very slight coryza in one and a moderate attack in another resulted. They think the results insufficient to indicate the pandemic to be due to a filtrable virus. They believe that in their cases pneumococci of unusual virulence were the most important early secondary invaders. Influenza bacilli were less important than many other bacteria.

Lamb and Brannin, at Camp Cody, Deming, N. M., found in pneumonia, in sputum specimens, the bacteria as shown in Table 3.

TABLE 3.—BACTERIA PRESENT IN PNEUMONIA\*

	Cases	Per Cent.
Pneumococcus (all types, but chiefly Type IV)	310	89.1
Streptococcus (one third hemolytic types)	222	63.3
B. influenzae	89	23
M. catarrhalis	21	6

\* Blood agar was used for platings.

A careful survey of all the literature leaves the same impression as that left by the brief summary of the few representative investigations I have just given.

There is no proof that any one germ is present in all cases. The influenza bacillus has the lead among the possibilities, partly because of its historical position and partly because, as it requires much training to isolate it from a mixture of other bacteria, the thought remains in the minds of many that the failure to obtain it in some outbreaks is due, not to its absence, but to lack of training in the bacteriologist seeking it.

If isolations from a number of cases proved to have identical characteristics, the probability that the influ-

enza bacillus was the cause of the epidemic would be great, while if many strains were found it would be slight. Williams and I decided, therefore, to test the immunologic reactions of isolations from more than 100 cases. We also tested great numbers of isolations from a few cases. Miss Valentine and Miss Cooper carried out the tests with the utmost care. They used, for every strain, direct and absorption methods.

#### DIFFERENT STRAINS

It was found that from the same case either all or the great majority of isolations were identical in their reactions, but that the majority of the isolations from different cases differed from each other either completely or essentially. The results seemed to show that influenza bacilli, like pneumococci, have gradually through the years altered on the mucous membranes of healthy carriers into many strains which, while having many essential characteristics in common, are still different in their susceptibility to specific immune substances and perhaps in other reactions.

In order to test the stability of the strains, we passed several strains through a series of animals, and others were grown for many generations on different mediums, but without causing any appreciable change. An interesting observation was made during this work that when a plate culture is made from material containing several strains, apparently pure colonies will not infrequently yield two different strains. The resultant mixed culture will agglutinate with each of the two serums. Even further plating may fail to separate them. If thoroughly shaken before plating, pure cultures of each strain can usually be isolated from the majority of the colonies.

An important point was whether the infecting strain could be depended on to produce the major part of the organisms in a case. If it did, isolations from the plates made from nasopharyngeal cultures could be considered as belonging to the infecting strain.

Some of our laboratory findings are instructive: One of the workers developed an acute bronchitis. Cultures revealed abundant influenza bacilli. Fifty fishings of colonies from the plates were found on testing to give forty-nine identical organisms and one that belonged to a different strain. Another bacteriologist, by accident, received an infection from a freshly isolated culture. About thirty colonies were fished from the plate cultures, and all proved to have identical characteristics. Other tests gave the same results.

#### PRIMARY AND SECONDARY INVADERS

It seems right, from the results mentioned above, to assume that the infecting strain is in great excess during an infection and that in nearly every case the colony tested will represent the infecting strain and that the proof that the patients are infected by different strains indicates almost certainly that bacilli were present before and that some other virus created conditions permitting the latent bacilli to attack the tissues.

It is perhaps well to state that not only did Miss Valentine and Miss Cooper subject themselves to the most careful controls, but that they also tested the strains with marks of identification that left them in ignorance of the origin of the cultures.

There was no question in our minds of the essential accuracy of the results.

These results appear to us to throw the influenza bacilli in the cases studied as clearly into the class of secondary invaders.

We believe that the other micro-organisms, such as certain streptococci and pneumococci which are under suspicion in different localities will be found after subjection to similar severe tests not to possess the necessary identity of characteristics to allow them to remain under serious consideration as the primary agent in this epidemic, but rather like the influenza bacillus, to be reckoned among the most important of the secondary invaders.

Our final conclusion is, therefore, that the micro-organism causing this epidemic has not yet been identified.

## THE SYMPTOMATOLOGY AND COMPLICATIONS OF INFLUENZA \*

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To present a paper on this subject at a time when the periodicals are filled with articles of similar title, and to an audience, almost every member of which has had an all too large personal experience with the subject, requires a word of explanation, if not of apology. To be accurate, the title should read "The Symptomatology and Complications of Influenza as Seen in the Army in This Country." No attempt is made to record the manifestations of this disease as they appear in children, in women, or in persons of advanced years; nor as observed in our own, or in other, armies in Europe. Moreover, the statements to be made relate solely to the great epidemic which swept over the country in the autumn of last year. It is interesting to note, however, that in the late winter and the spring of 1918, epidemics of what was regarded locally as influenza appeared in several of the army camps and posts. The symptoms bore a close resemblance to those of the great epidemic six months later, but these local epidemics were distinguished from the latter by the mildness of the symptoms and the rarity of serious complications.

The data on which this paper is based were furnished by reports to the Surgeon-General from seventy-two base and general hospitals scattered throughout the entire country.

In this large number of reports, two features stand out with great distinctness: first, the singularly uniform and clear-cut clinical picture presented by the cases of uncomplicated influenza in the same camp; and, second, the striking agreement by observers in the various hospitals throughout the country as to the characteristic symptoms of the disease. From these reports there can be no possible doubt that, among the soldiers at least, the disease in its march across the country, from the Atlantic to the Pacific, preserved a remarkable uniformity in its clinical picture.

Of forty-seven reports on this subject, thirty-six gave the period of incubation as three days or less. In half of this number it was given as two days or less. In several reports it was stated as being usually not more than twenty-four hours. On the other hand, in several instances, the interval was placed at from three to seven days and, in one instance, at from seven to ten days. In one camp, in the case of five men with whom

the interval between exposure and the onset could be accurately determined, the period in each instance was forty-eight hours. It seems safe to conclude, therefore, that the incubation period is, in general, very short and that the most frequent interval is about forty-eight hours.

In what follows it should be clearly understood that, for the moment, only the symptoms observed in simple, or uncomplicated, influenza are being considered.

### ONSET

There is practical unanimity in the assertion that the onset is abrupt in the great majority of cases. Most reports give the percentage of abrupt onsets to the whole number as from 80 to 90. The initial symptoms were surprisingly constant and uniform, being chilliness, prostration, fever, headache, backache, and pains in the limbs. Somewhat less frequent initial symptoms were an irritating, dry cough and sore throat. To these symptoms must be added a characteristic mental state and a peculiar facies which will be described later.

### SYMPTOMS

*Prostration.*—This was one of the earliest, as well as one of the most constant, symptoms. Frequently extreme, it varied much in its severity and in its duration; but it was characteristic of many cases that the muscular weakness persisted long after the temperature had become normal and all the other symptoms had disappeared.

*Respiratory Symptoms.*—There is general agreement that cough was present at some time in almost all cases, even in most of those classed as uncomplicated. During the early part of the illness it was usually of a hard, dry, racking character, with little or no expectoration, and was commonly associated with a feeling of retrosternal soreness or pain. During the later days of the attack it usually became looser and was accompanied by sputum and by the physical signs of tracheitis or bronchitis. The sputum varied much in character and in quantity. At first scanty, tenacious and mucous, it later became more profuse and mucopurulent. Occasionally, even in uncomplicated cases, it showed streaks of blood and, rarely, blood in considerable quantities.

The frequency of hoarseness as a symptom seemed to vary much. Often the husky voice appeared to depend on the dry, congested state of the pharynx, and on the great prostration, rather than on an actual laryngitis.

Coryza was, in most reports, classed as a frequent manifestation. It was by no means constant, however, and, in some hospitals, seems to have been of infrequent occurrence.

Epistaxis was a striking symptom in many patients. It was present in approximately one fourth of the cases, and sometimes was so severe and persistent as to cause very serious concern. Some observers noted that it seemed to be more frequent in those patients who, later, showed evidences of pneumonia, than in those who did not.

The respiratory rate in simple influenza showed very little disturbance. In relation to the height of the temperature it was notably low. A steady rise in the breathing rate was one of the most trustworthy indications of the existence of a complicating pneumonia. The physical signs of the chest were usually quite normal during the first day or two of the illness, and, indeed, not infrequently throughout the attack. Often,

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