

WORLD HEALTH ORGANIZATION: MONOGRAPH SERIES

INFLUENZA

A Review of Current Research

by

VARIOUS AUTHORS



WORLD HEALTH ORGANIZATION
PALAIS DES NATIONS
GENEVA

1954

INFLUENZA

A Review of Current Research

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The World Health Organization (WHO) is a specialized agency of the United Nations and represents the culmination of efforts to establish a single intergovernmental health agency. As such, it inherits the functions of antecedent organizations such as the Office International d'Hygiène Publique, the Health Organization of the League of Nations, and the Health Division of UNRRA.

WHO had its origin in the proposal made at the United Nations Conference held in San Francisco in 1945 that a specialized agency be created to deal with all matters relating to health. In 1946, representatives of 61 governments met at the International Health Conference, New York, drafted and signed the WHO Constitution, and established an Interim Commission to serve until the Constitution could be ratified by 26 Member States of the United Nations. The Constitution came into force on 7 April 1948, the first World Health Assembly met in Geneva in June 1948, and on 1 September 1948 the permanent Organization was established.

The work of the Organization is carried out by three organs: the World Health Assembly, the supreme authority, to which all Member States send delegates; the Executive Board, the executive organ of the Health Assembly, consisting of 18 persons designated by as many Member States; and a Secretariat under the Director-General.

The scope of WHO's interests and activities exceeds that of any previous international health organization and includes programmes relating to a wide variety of public-health questions: malaria, tuberculosis, venereal diseases, other communicable diseases, maternal and child health, mental health, social and occupational health, nutrition, nursing, environmental sanitation, public-health administration, professional education and training, and health education of the public. In addition, WHO undertakes or participates in certain technical work of international significance, such as the compilation of an international pharmacopoeia, the setting-up of biological standards and of standards for insecticides and insecticide-spraying equipment, the control of addiction-producing drugs, the exchange of scientific information, the drawing-up of international sanitary regulations, the revision of the international list of diseases and causes of death, the collection and dissemination of epidemiological information, and statistical studies on morbidity and mortality.

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NOTE

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INTRODUCTION

In fulfilling its constitutional role as the directing and co-ordinating authority on international health work, the World Health Organization has since its inception devoted considerable attention to the problems of influenza. Its Expert Committee on Influenza has recently been considering* how best to promote international collaboration in the control of this disease, while since 1947 the WHO influenza programme, details of which will be found in an article by Dr. A. M.-M. Payne in this volume, has been developing rapidly. Under this project 54 laboratories in 42 countries have voluntarily co-operated in an international programme of research, which could not be undertaken on this scale in any other way.

It must be recognized, however, that fundamental research and the development of new techniques, at least in their initial stages, are best carried out through private or institutional initiative; almost all significant scientific advances in the past have sprung from such efforts. The role of WHO is to facilitate this work by various means—for example, by collecting and distributing epidemiological information and laboratory findings on an international scale; by promoting the rapid exchange of scientific information among the various workers throughout the world; by providing for the training of specialized workers; and by supplying standard diagnostic reagents and other laboratory needs. All these activities are currently being undertaken by WHO.

The production of this monograph falls within the second category, that of promoting the exchange of scientific information. Many workers have not the time to read the vast literature on influenza, even if they have access to a large well-stocked library, which is not always the case. By bringing together in one volume reviews of various aspects of this complex and fascinating subject, written, at special invitation, by some of the world's leading authorities who through their own work have contributed so greatly to our knowledge, it is hoped to bring to influenza workers the latest information, to show them where further detail can be found, and to stimulate those engaged in routine work to step out into the field of research.

These articles have a practical value. Those on the epidemiology of influenza by Dr. C. H. Andrewes, and on influenza virus vaccines by Dr. T. Francis, jr., will help public-health authorities to understand the

* *World Hlth Org. techn. Rep. Ser.* 1953, 64

problems of the correct use of vaccines. The paper on the causation and treatment of influenzal pneumonia by Professor J. Mulder and Professor C. H. Stuart-Harris will be of value to all clinicians. The article by Sir Macfarlane Burnet on the somatic and genetic aspects of the influenza virus, and that by Dr. P. von Magnus on its morphology, immunology, and kinetics of multiplication, will surely awaken a desire to undertake the fundamental research which is so essential to progress. The laboratory worker will acquire valuable technical information from the article by Professor P. Lépine, and both epidemiologists and virologists will find much to interest them in the paper on influenza antibodies in the population of the USA by Dr. M. R. Hilleman and his colleagues, as well as in the statistical article by Mr. Z. Deutschman. Finally, a classified bibliography has been provided to help workers to explore recent literature. It is not meant, however, to be complete in itself, and is complemented by the reference lists of the individual papers.

This monograph is not intended to replace the textbook : much that can readily be found in the standard works has been deliberately omitted. It is rather both complementary and supplementary to the textbook, covering the most important aspects of recent advances, and offering a range of speculation beyond the province of the orthodox textbook.

EPIDEMIOLOGY OF INFLUENZA

C. H. ANDREWES, M.D., F.R.C.P., F.R.S.

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Director of the National Institute for Medical Research, London, England*

The behaviour of influenza has seemed so erratic as regards its occurrence in both time and space that it has fascinated epidemiologists for many years. Recent work seems to show that the influenza virus is more variable and plastic than are most disease agents, and it may well be that this variability can be held largely accountable for its vagaries. The history of modern research on influenza dates from the discovery in 1933 of the susceptibility of ferrets to the virus. Since then we have been able to say whether or not in any "influenza" outbreak we are dealing with a particular disease agent. As to the influenzas of the 19th century and earlier, and the 1918-19 pandemic, we can guess that we have to do with diseases caused by influenza viruses A or B, but we cannot be sure. In the forthcoming discussion, the assumption is made, for convenience, that most of the influenza of the last century has been due to viruses A or B, or to variants of them.

History of Influenza Epidemics, 1850-1950

The earlier influenzas, of which there were several pandemics between 1820 and 1850, will not be discussed here. We may divide the last century into four periods :

(1) Up to 1889 influenza was at a low ebb and was becoming an almost extinct disease.

(2) A period was ushered in by the pandemic of 1889-90; influenza then became, and has since remained, an important cause of mortality and morbidity in most temperate climates.

(3) In 1918 influenza reached pandemic proportions and is believed to have killed 15-20 million people within a couple of years. Its special character was a tendency towards bronchopneumonic complications fatal to previously healthy young adults. In the years following it gradually became less virulent.

(4) Since about 1933 influenza A has come to many countries in outbreaks every two or three years, with a tendency as time has passed for

the peaks to come less frequently and to attain lesser heights. It is, we may hope, again a waning disease; but we cannot be sure that another lethal pandemic may not be immediately ahead.

The period of abeyance of influenza

Apart from a minor outbreak in 1855, influenza seems to have caused few deaths in Britain in the 40 years preceding the 1889-90 epidemic. Much the same seems to be true of Australia, though some epidemic respiratory infection occurred there in 1860 and 1885. In Britain at the present time deaths from influenza are recorded by practitioners as occurring in years when, in the laboratory, no virus is isolated; very probably wrong diagnosis is to be blamed, for no one can infallibly diagnose influenza on purely clinical grounds. It is not at all unlikely that between 1855 and 1899 influenza was almost or quite absent from Britain. Alternatively, it is possible that it was so infrequent that doctors got out of the habit of using the name in their diagnoses. According to the review by Burnet & Clark ⁶ influenza, though absent from western Europe, caused outbreaks in Russia in 1886 and 1887. They suggest that it had remained endemic somewhere in central Asia, and that its virulence became exalted in Bukhara and elsewhere in May and June of 1889. Other parts of Russia (Tomsk in Siberia, and St. Petersburg [Leningrad]) were affected in October 1889, and western Europe generally in November and December. The particular months may be significant in view of more recent events to be discussed presently.

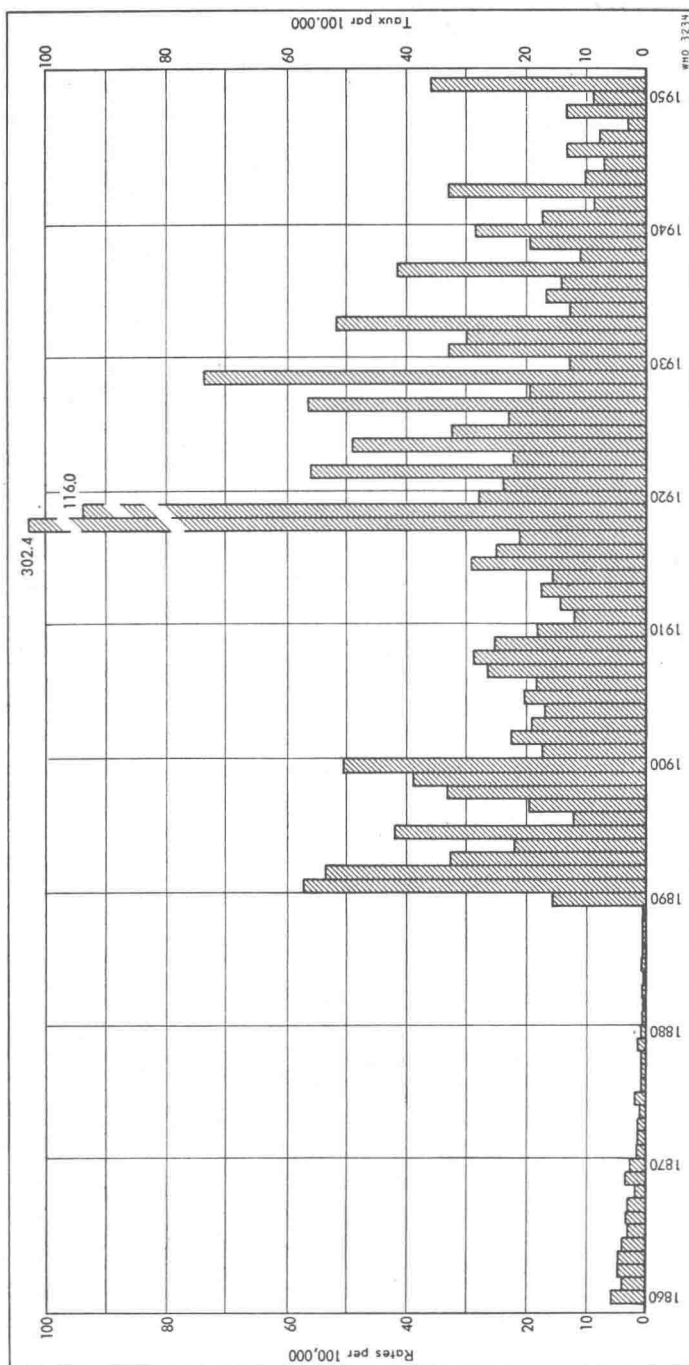
The 1889-90 epidemic and after

The 1889-90 pandemic affected a large part of the world but was not associated with particularly high mortality for young adults. Its chief interest lies in the fact that never subsequently has influenza fallen to the pre-1889 low level. The first wave, in January 1890, was succeeded by others in May 1891 and January 1892, causing progressively higher mortality. There was yet another in December 1893, but, as Burnet & Clark state,

"it would be preferable to consider the third wave as the last portion of the 1889-93 pandemic, otherwise there seems to be no reason whatever to regard it as finished until its continuing reverberations were lost in the vast new disturbance of 1918".

As Greenwood ¹² has put it, "the position lost in 1890 has never been regained". He discounts the idea that the higher level of influenza since 1890 can be accounted for by changing fashions in nomenclature. The striking nature of the change is well shown by fig. 1, depicting the annual death-rate per 100,000 from "influenza" in England and Wales. What underlies this dramatic change is at present a mystery. It is not simply that a "new" disease has now become endemic. As already mentioned, laboratory tests fail to reveal the presence of influenza virus infection

FIG. 1. THE HISTORY OF INFLUENZA IN ENGLAND AND WALES, 1860-1948, AS INDICATED BY THE ANNUAL DEATH-RATE FROM "INFLUENZA" PER 100,000 POPULATION *



* Data based partly on the League of Nations Health Organization's *Annual Epidemiological Reports*

in non-epidemic years—or they show it very rarely. Yet there is some respiratory infection which kills people every year and which was not widely prevalent before 1890. The writer¹ has discussed whether, between epidemics, influenza virus may not persist as a “basic virus” which cannot be recognized as influenza by current laboratory tests. Such a virus could perhaps be held accountable for the “influenza” deaths of “non-influenza” years. Otherwise we must believe either that the statistics are meaningless, or that influenza virus is present but is overlooked in some years, or that some quite different respiratory infection has enjoyed increased prevalence, alongside influenza, since 1890.

The 1918-19 pandemic and after

This, the most lethal pandemic known in history, will not be discussed except in relation to the general theme. According to Frost,¹¹ there had been a steady increase in the mortality from influenza and pneumonia in New York between 1914 and 1918. In view of recent experiences, it is very questionable whether this progressive rise can be ascribed to the activity of influenza A or of any other single virus. We do not, in fact, know at all what led to the catastrophic events of 1918-19. In the early months of 1918 the influenza had no unusual properties, but in June, in Britain, there was some indication that it was beginning to kill young adults. The really virulent form of the disease appeared at about the same time in the United States of America, around Boston, and in France, in Brest—i.e., at ports of embarkation and debarkation of American troops coming to Europe. In the ports of western Europe, too, there were people of many other races. In view of recent work on gene-recombination among influenza viruses it might be argued that a vicious new hybrid virus had been born in that very mixed culture. (Burnet & Lind,⁷ it will be recalled, found evidence that, experimentally, the properties of two influenza viruses could be exchanged, producing a stable variant having mixed attributes.)

The rapid spread of the lethal kind of influenza all over the world is a familiar story. It is estimated that at least 15 million people died as a result. The island of St. Helena in mid-Atlantic is one of the very few places known to have definitely escaped. It seems likely that during the pandemic several different mutants may have arisen, having differing antigenic properties but all still sharing the ability to kill young adults. In such a way we can perhaps account for the fact that, in some English schools and other communities, later waves of influenza might or might not spare the victims of earlier waves.¹² A partial but incomplete protection by one strain against the effects of another could be invoked to explain the varying number of waves which hit different cities in the USA (Pearl²⁶). We may picture a number of virus outbreaks moving around, being deflected from their courses when they met with foci of greater resistance.

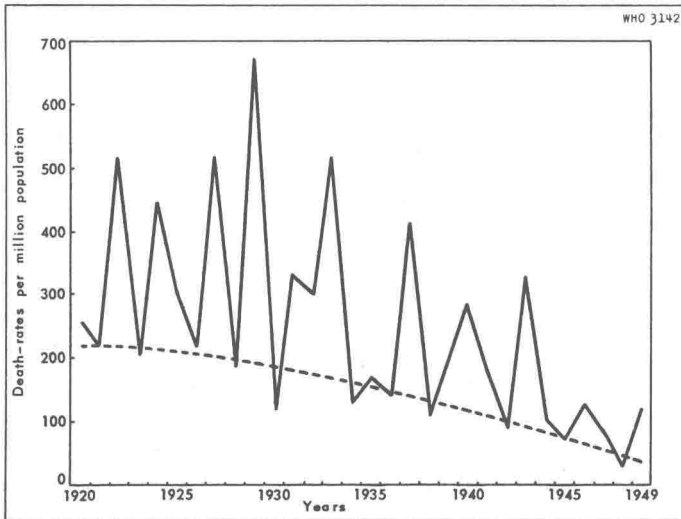
An interesting question of some practical importance is raised by the considerable postponement of the entry of pandemic influenza into Australia: this is claimed to have been due to the imposition of quarantine (cf. Burnet & Clark ⁶). The quarantine was, however, far from complete, and experience with the influenza of these times tells us that many carriers and subclinical cases occur. It is quite likely, therefore, that Australia's immunity up to the beginning of 1919 can be attributed rather to the prevalence there of what we may call a routine outbreak of ordinary influenza in September-October 1918.

After the pandemic years influenza returned gradually to its former habits of killing the old and weak rather than the young and vigorous. This reversion took at least three years in the USA and perhaps a decade in Britain. We may suppose that the 1918-19 influenza, aggressive as it was, lacked some property enabling it to persist between epidemics, so that a less spectacular derivative, or perhaps the resurrected pre-pandemic strain, gradually replaced it.

Recent history

There has, perhaps, been a steady change in the epidemiology of influenza even since the pandemic, but it is convenient to treat "recent history" as being from 1933 when the influenza virus was first transmitted to ferrets. The changing death-rate in England and Wales has been discussed by Martin.²⁴ It seems that, especially since 1933, the mortality

FIG. 2. DEATH-RATES FROM INFLUENZA IN ENGLAND AND WALES, 1920-1949, PER MILLION POPULATION *



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