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Influenza surveillance

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The main objectives of influenza surveillance are : to measure the impact of the disease by collection and analysis of epidemiological information on morbidity and mortality, and to anticipate future epidemics and pandemics by the collection and analysis of influenza viruses. The World Health Organization's influenza programme is based on the collaboration of 98 national influenza centres in 70 countries and the 2 WHO Collaborating Centres in Atlanta and London.

Epidemiological information may be based on morbidity figures derived from a variety of sources such as returns from physicians or hospitals; mortality statistics or new claims for sickness benefit; school or industrial absenteeism, etc.

The laboratory aspects of influenza epidemiology are certainly more uniformly covered than the statistical aspects. Since the advent of the A/Hong Kong/1/68 (H3N2) influenza virus A subtype there have been a number of variants with antigenic "drift" but only three succeeded in causing widespread epidemics: A/England/42/72, A/Port Chalmers/1/73, and A/Victoria/3/75. In 1972, the influenza B virus also showed some antigenic "drift", the new variants being characterized by B/Hong Kong/5/72.

Whenever a new variant appears, the degree of protection afforded to the population by the available vaccine is assessed. In the light of these data, WHO publishes annually in the Weekly epidemiological record *recommendations formulated by the WHO Collaborating Centres on vaccine composition.*

The collection and analysis of epidemiological information on influenza morbidity and mortality, makes it possible to measure the impact of the disease, and the collection and analysis of influenza viruses is directed towards anticipating future epidemics or pandemics. The WHO influenza programme is involved with both these objectives and is based on the collaboration of 98 national influenza centres in 70 countries which are in contact with WHO headquarters in Geneva and the two WHO Collaborating Centres in Atlanta, USA, and London, England. The network of national influenza centres covers nearly all parts of the world: 42 laboratories are located in 36 developing countries and 56 laboratories are in 34 industrially developed countries.

In Geneva, all the epidemiological and laboratory information is consolidated and published weekly in the *Weekly epidemiological record*, which is widely distributed to health authorities, influenza centres, and other interested institutions and persons.

EPIDEMIOLOGICAL SURVEILLANCE

Morbidity figures are derived from a variety of sources, such as sickness benefit claims covering the adult working population and the returns of general practitioners concerning

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cases of influenza (in the United Kingdom), telephone surveys or emergency-room visits in large city hospitals (in the United States of America), the numbers attending polyclinics with acute respiratory disease (in the Soviet Union), reports of influenza from sentinel stations (in the Netherlands), or notifications by public health officers in Czechoslovakia, Hungary, and Sweden. Mortality figures may be expressed as the weekly number of deaths attributed to influenza or to acute respiratory infection including pneumonia and bronchitis or as excess mortality.

These indices have been clearly demonstrated to correlate with the presence of influenza viruses in the community and can measure the impact of the disease in relation to a baseline, with seasonal variations, estimated for nonepidemic years.

In the United Kingdom, a collaborative programme of surveillance has been in progress for some years.[a] This is based on data collected each week throughout the winter months from sources that have been confirmed as accurate and reliable. These are: (1) general practitioner consultation rates for acute respiratory illness, (2) mortality statistics, and (3) new first claims for sickness benefit (Fig. 1).

In the USA, additional information on influenza morbidity is obtained from sentinel physicians, industries, schools, and counties. The number of influenza-like illnesses and the total number of bed-days associated with such illnesses per week are provided as part of the Health Interview Survey, which includes a weekly probability sample of households. Pneumonia and influenza mortality data are reported weekly for 121 cities and are used to monitor excess mortality.

In the USSR, an epidemiological model has been developed to enable the monitoring of increase in *daily* morbidity of influenza and other acute respiratory infections.

These indices are related to the number of influenza virus isolations and together allow a fair estimation and comparison of the annual impact of influenza.

In many countries, national morbidity and mortality figures are simply not available. However, where such statistics are available, the procedures adopted for their collection, analysis, and dissemination vary according to the type of information and source. Epidemiological surveillance would be much improved if all the data from a given country or geographical area were standardized and could be collected by a central sorting office for analysis and distribution.

To this end, since 1970, WHO has conducted a collaborative study on the use of " excess mortality " from respiratory diseases in 13 different countries as a means of determining the severity of influenza epidemics. The study has already demonstrated that an excess in the observed over the expected number of *total deaths* does not necessarily indicate an excess in deaths from influenza, and therefore it is preferable to limit the use of excess mortality to respiratory diseases. The collaborative study is continuing and provides weekly surveillance to countries where weekly returns are available. The computer-produced seasonal baseline curves are distributed to participating countries so that they may plot their observed data.

In countries where no statistics are gathered, other means of obtaining a measure of the incidence of influenza should be investigated. This could perhaps be done best through the national laboratories by the use of serological methods as an extension of their present duties in isolating and identifying virus strains.

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[a] PUBLIC HEALTH LABORATORY SERVICE STANDING ADVISORY COMMITTEE ON INFLUENZA. Influenza surveillance 1972-75. *Journal of hygiene, Cambridge*, **78**: 223-233 (1977).

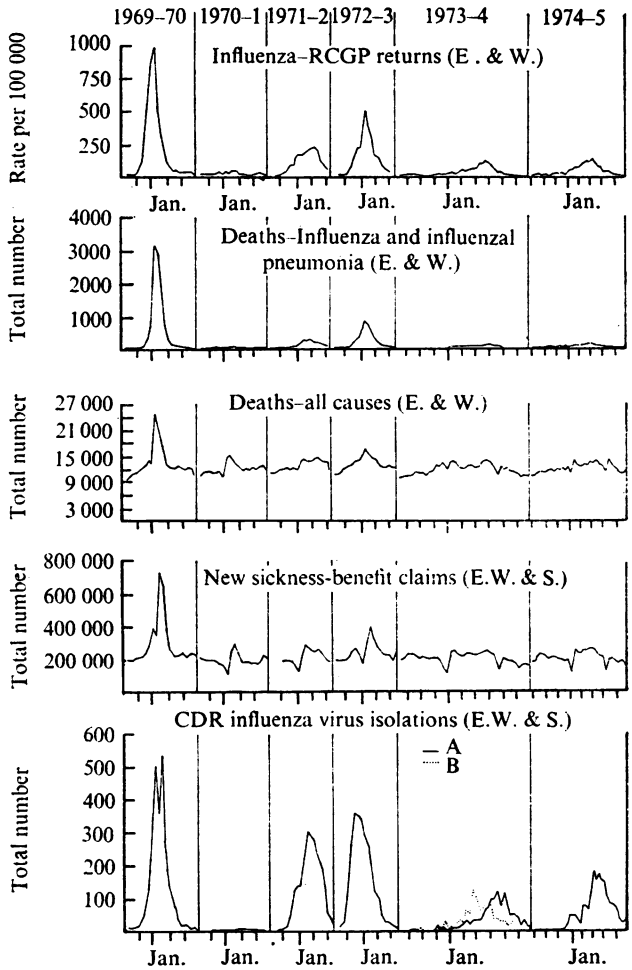

Fig. 1. Indices of influenza morbidity—United Kingdom Influenza Surveillance Programme.

LABORATORY SURVEILLANCE

The laboratory aspects of influenza epidemiology are certainly more uniformly covered worldwide than the statistical aspects. However, it is still necessary to increase coverage of some parts of the world and to encourage workers who have difficulties in obtaining materials from which viruses might be isolated. For this purpose the establishment of " spotters " in either private medical practice, health centres, or schools, has proved invaluable and has ensured the regular taking of swabs from patients with acute respiratory illnesses.

The present methods for isolating influenza viruses require simplification, as the use of embryonated eggs, although well-tried and undoubtedly reliable, has disadvantages of several kinds. The use of rhesus monkey kidney cell cultures for the isolation of respiratory viruses, in particular influenza virus, has been very successful in countries such as the United Kingdom. However, this type of culture is expensive and its use is indefensible

where a species of animal is being depleted and the WHO Scientific Group on Virus Diseases recommended, in 1975, that an alternative cell system should be sought.

Current work in the United Kingdom indicates that a continuous cell-line (MDCK) treated with trypsin will give results comparable with monkey kidney for the isolation of influenza viruses and if this is supported by further field work, it is hoped that this simple tissue culture system will lead to a much larger yield of virus strains for analysis. This could be a particularly useful extension of the widespread use in some countries of immunofluorescence for the direct diagnosis of influenza infection, as this procedure has at present the great disadvantage that the viruses themselves are not grown and are therefore not available for further study.

Recent progress in laboratory techniques now allows characterization of the influenza strains by an immuno-double-diffusion test, and strains are compared quantitatively by single-radial-diffusion tests which may be combined with quantitative antibody absorption.

Variant influenza viruses of potential epidemiological importance may appear early in one season, as a very small proportion of the total isolates, and not spread widely until the next influenza season. Early detection of such variants thus depends on the examination of large numbers of strains. Since the appearance of the A/Hong Kong/1/68 subtype of influenza A, the two WHO Collaborating Centres for Reference and Research on Influenza, in Atlanta and London, have received 400–600 or more isolates annually for characterization. Thus they were able to study rapidly the successive antigenic " drifts " from A/Hong Kong/1/68 that were characterized by the variants: A/Hong Kong/5/72, A/England/42/72, A/Port Chalmers/1/73, A/Porto Rico/1/74, A/Scotland/840/74, A/Victoria/3/75, A/Tokyo/1/75, and A/England/864/75. The variant A/Victoria/112/76 is apparently related to A/Victoria/3/75, while the recently isolated A/Texas/1/77 is antigenically closer to A/England/864/75.

In 1972, the influenza B virus also showed some antigenic " drift " from the strains predominant in 1967–71; the new variants were characterized by B/Hong Kong/5/72.

New methods for serological surveillance should also improve the amount of accurate information available from many countries. Single-radial-diffusion is perhaps too expensive for routine use as it requires a high concentration of antigen. Single-radial-haemolysis is, however, in many ways an easier and cheaper test and its use would be appropriate in laboratories where a source of receptor destroying enzyme is not readily available for conventional haemagglutination inhibition tests. Either of these tests could usefully be employed to provide regular information on the current level of antibodies to the prevalent antigenic variants of influenza.

National influenza centres, particularly in countries where epidemiological data is not available, should consider collecting and storing serum samples from a local hospital laboratory where blood specimens are taken for medical reasons. These could then be tested at appropriate intervals to obtain a measure of the impact of any influenza epidemic on the population.

RECOMMENDATIONS FOR INFLUENZA VACCINES

Unquestionably, WHO's most important contribution is to help national health services obtain early and accurate information on changes in the strains of influenza viruses, thus enabling them to develop and apply appropriate control measures. Whenever a new variant is detected, the two WHO Collaborating Centres test homologous and heterogeneous

antibodies in the population, as well as the degree of protection, in terms of percentage and titre, afforded by the previous formulation of influenza vaccine. These data are now collected each year in order to recommend the antigenic composition of vaccines. These recommendations are published in the *Weekly epidemiological record.*

INFLUENZA IN THE WORLD IN THE LAST FIVE YEARS 1973–77

Influenza in 1973–74

Influenza A

In October 1973, influenza A viruses began to circulate once again in the Northern Hemisphere. The strain A/England/42/72 was replaced entirely (except in Bulgaria, the German Democratic Republic, and the USSR where it was still reported) by another variant, A/Port Chalmers/73 had been causing smaller outbreaks in the Northern Hemisphere immediately before. In the United Kingdom, the A/England/42/72 virus did not appear again although half the population did not possess antibodies to it.

The A/Port Chalmers/73 virus was isolated in small numbers in many parts of Europe from October 1973 onwards. However, it was only in the middle of March 1974 that it began to make its presence felt and a sharp increase in deaths attributed to influenza coincided with a sharp increase in the number of virus isolations. This peak towards the end of March then declined slowly and the last strain were detected as late as the beginning of June. In the United Kingdom the proportion of sera with antibody to A/Port Chalmers/73 increased from 17% to 40% during this period of high influenza activity. Other variants, including A/Hanover/61/73, were isolated in several countries in Europe, South-West Asia, and the Pacific, while A/Porto Rico/1/74 was isolated only in Porto Rico.

Influenza B

Influenza B viruses began to circulate at about the same time as the new A/Port Chalmers/73 variant, and in October 1973 both B/Hong Kong/72 and intermediate strains were isolated. The B/England/68 viruses were no longer detected, but the variant A/Victoria/70 continued to circulate in North America and some countries in Europe.

These newer influenza B viruses spread widely, causing many outbreaks of disease among children and young adults in schools and other institutions. In this case, it was unusual that the wave of disease associated with influenza B virus, in general, preceded the wave associated with influenza A virus. Virus A infections were as usual more serious, but in this season relatively few cases with complications were reported and, except in few countries, little excess mortality was noted. In the USA there were indications of an association between influenza B and Reye's syndrome.

In 1974, the influenza A virus circulating in the Southern Hemisphere was almost exclusively A/Port Chalmers/1/73. Influenza B viruses, B/Hong Kong/5/72 and B intermediate, were isolated on only a few occasions. In general influenza activity in 1974 in the Southern Hemisphere was mild.

The incidence began to decline as the number of A/Port Chalmers/73 virus isolations began to increase, but influenza B viruses were still being isolated relatively rarely up to the middle of May 1974. The United Kingdom findings are shown in Fig. 2.

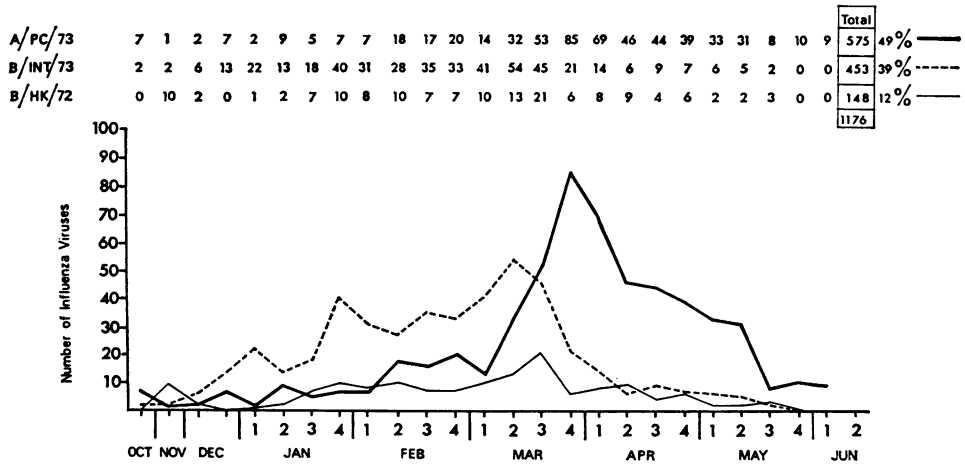

Fig. 2. Influenza viruses in the winter of 1973–74, United Kingdom.

Influenza in 1974–75

Influenza A

As in the previous winters, influenza viruses were first isolated early in the winter, the first cases being detected at the end of November.

In this winter, the A/Port Chalmers/73 virus was not replaced but was accompanied in many countries by two other easily distinguishable variants A/Scotland/74, which was identical with the A/England/635/74 strain isolated the previous winter, and strains intermediate between it and the A/Port Chalmers/73. A few strains of A/Scotland/840/74-like viruses had already been isolated in the Southern Hemisphere in September 1974.

The successive variants have been clearly identified and a progressive loss of reactivity with antisera has been noted in the earlier strains. It has been found essential to include such antisera when new viruses are being identified since, although the differences between consecutive " drifted " variants may be small, the general overall pattern can indicate a significant move away from the parent strain.

The A/Scotland/840/74 variant, for example, was no longer inhibited by antisera to A/Hong Kong/68 virus and was only poorly inhibited by antisera to the 1972 and 1973 variants. The so-called " intermediate " viruses, although also poorly inhibited by the earlier sera, were clearly still close to the A/Port Chalmers/73 virus.

In the United Kingdom these three variants circulated concurrently from December 1974 to March 1975 with approximately equal frequency (Fig. 3). At the end of this winter the antibody pattern was barely altered.

Influenza B

In the Northern Hemisphere, influenza virus strain B/Hong Kong/5/72 was isolated in very few countries. The incidence and severity of influenza were in general moderate, but varied from one country to another.

The variant A/Victoria/3/75 first appeared in the Southern Hemisphere in 1975 and was widespread in countries in southern Asia and the Pacific; the largest oubreak associated

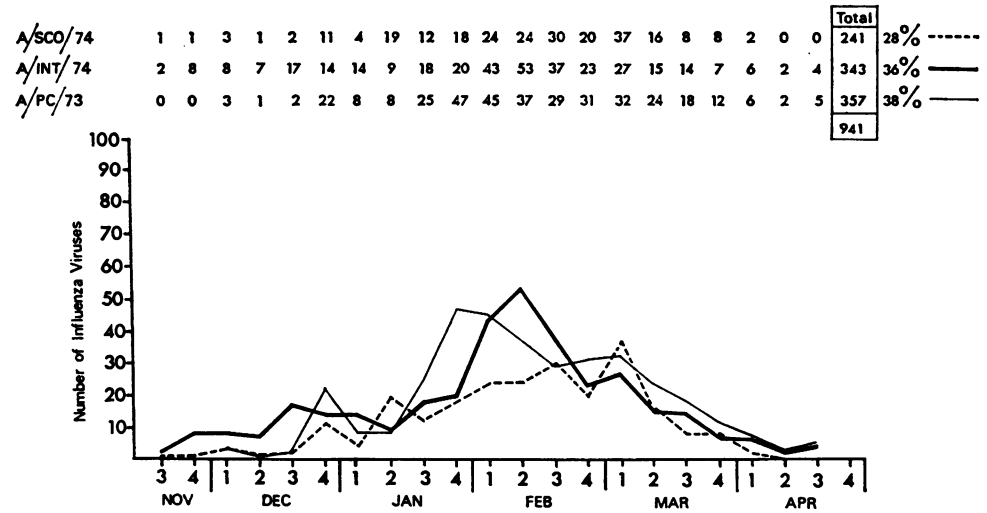

Fig. 3. Influenza viruses in the winter of 1974–75, United Kingdom.

with this strain was in September 1975 in Papua New Guinea. In November, A/Victoria/3/75 was isolated in Chile. Few strains of B/Hong Kong/5/72 were found in the Southern Hemisphere.

Influenza in 1975–76

Influenza A

As mentioned above, during the summer of 1975 reports came of outbreaks of influenza in the Southern Hemisphere associated with a further variant of the A/Hong Kong/68 virus, called A/Victoria/3/75. This virus showed considerable drift from A/Port Chalmers/73 virus and serum surveys indicated that only a small proportion of the population had antibody levels likely to be protective should this new variant come to the Northern Hemisphere. In the event, A/Victoria/3/75 did spread widely in the Northern Hemisphere and caused fairly extensive epidemics.

In the United Kingdom, an influenza A virus appeared as early as November 1975 but was found not to be like A/Victoria/3/75; it had " drifted " in another direction. This variant, called A/England/864/75, was isolated in only a small number of cases until the middle of March 1976. However, the A/Victoria/3/75 strain was eventually found in the last days of December 1975 and immediately spread throughout the country causing widespread outbreaks of illness accompanied by a high mortality rate. The outbreaks reached a peak in middle of February 1976 and declined slowly, ending in the last week of April (Fig. 4). The proportion of sera with antibody to A/Victoria/3/75 virus increased during this period from 7% to about 30%.

The variant A/England/864/75 was isolated during this winter, but only in a small number of cases in many countries. In Japan, another variant, A/Tokyo/1/75, made its appearance late in 1975 but again A/Victoria/3/75 soon predominated (Fig. 5).

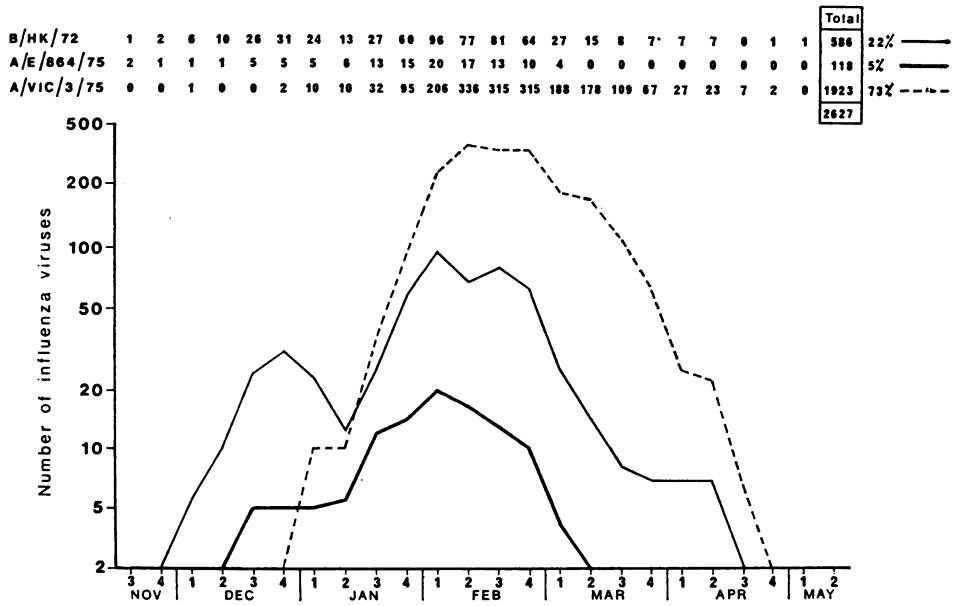

Fig. 4. Influenza viruses in the winter of 1975–76, United Kingdom.

The strain A/New Jersey/8/76 which resembles A/Swine and differs greatly from all other recent variants of virus A, was isolated during an outbreak in a military camp in the United States of America when A/Victoria/3/75 was the predominant strain. Following this limited outbreak, A/New Jersey was found in only a very small number of isolated cases.

A new variant of A/Victoria, typified by A/Victoria/112/76, was isolated in July 1976 from few cases of influenza in Australia, and in August 1976 in the Philippines. These viruses were not involved in widespread outbreaks.

Influenza B

Influenza B viruses were first isolated at the end of November 1975, again associated with numerous outbreaks in schools. This winter most strains were similar to the B/Hong

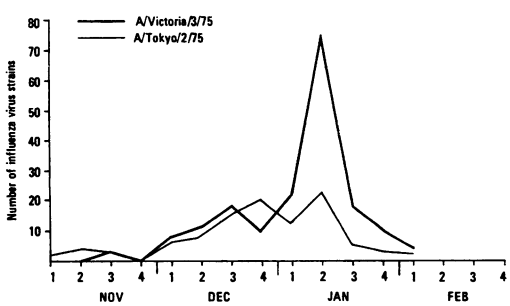

Fig. 5. Influenza viruses in the winter of 1975–76, Japan.

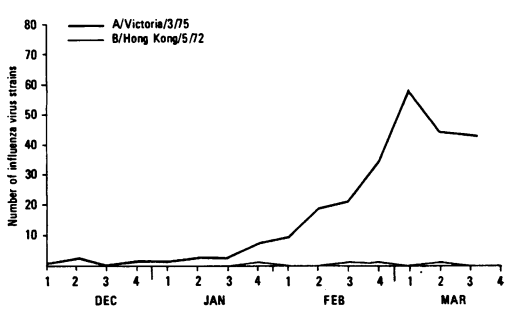

Fig. 6. Influenza viruses in the winter of 1976–77, United Kingdom.

Kong/72 virus, but some were poorly inhibited by antisera to B/Hong Kong/72 and appeared to be antigenically different.

Influenza in 1976–77

Influenza A

The impact of influenza this winter in the Northern Hemisphere was minimal, with little increase in absence due to sickness in the working population or in the number of deaths attributed to influenza. Were it not for the continual laboratory surveillance of cases of respiratory illness, it might have been regarded in many countries as one of the rare non-influenza winters. Influenza A/Victoria/3/75 was isolated in a small number of cases all over the world. For example, in the United Kingdom, up to the end of March 1977, A/Victoria/3/75-like viruses were isolated on only 284 occasions compared with nearly 2000 in the previous winter (Fig. 6).

Towards the end of the influenza season, some variants of H3N2 virus, characterized by A/Texas/1/77, were identified in the USA in association with limited outbreaks among military personnel and sporadic cases in the civilian population. These variants form a heterogeneous group which generally resemble the A/England/864/75 strain isolated last year in Europe, southern and western Asia, and the Caribbean.

Small outbreaks were reported in a number of countries in the tropics and in the Southern Hemisphere. A/Victoria/3/75 was isolated in the majority of these outbreaks but in a number of them A/Texas/1/77 was also involved. A/Texas/1/77 was the only virus implicated in limited outbreaks in a few countries in South America and in the Caribbean.

Influenza B

There was a little activity of influenza B/Hong Kong/5/72-like viruses, but in many countries, the activity of influenza A viruses was lower still and influenza B predominated.

Influenza in 1977-78

During the autumn of 1977 and early in the winter of 1977–78 there was very little influenza in the world. A/Victoria/3/75- and A/Texas/1/77-like viruses continued to circulate in several countries. However, in November 1977 influenza A viruses of the subtype H1N1 made their appearance in the USSR and Hong Kong. In the USSR, the outbreaks spread rapidly from east to west but were short lived: they involved mainly children and young adults. The disease was generally mild. In Hong Kong, the outbreaks mainly affected schoolchildren. By the end of December 1977, localized outbreaks associated with an H1N1 virus similar to the A/USSR/90/77 were reported in Finland and Czechoslovakia. A similar virus had been isolated in May 1977 in China, where it was associated with epidemics of influenza from July to October 1977.

The age-specific antibody prevalence rates against A/USSR/90/77 estimated in the United Kingdom and the USA indicate that antibodies are absent in individuals under 20 years of age, whereas antibody titres of $\geqslant 40$ are present in approximately one-third of the adult population up to 50 years of age. Less than 10% of those over 50 years of age have antibody titres at this level.

It is still too early to predict the spread of the A/USSR/90/77 influenza. Increased school absenteeism would seem to be the most reliable index of influenza activity in this case.

RÉSUMÉ

La surveillance de la grippe

La surveillance de la grippe répond à deux objectifs: l'un est de mesurer l'impact de la maladie à partir des données épidémiologiques de morbidité et de mortalité, l'autre est d'assurer la prévision des épidémies ou des pandémies par la collecte et l'analyse des virus grippaux dans divers laboratoires. Le système de surveillance de la grippe, établi par l'OMS dans le cadre du programme de la grippe, obéit à ce souci. Il est fondé sur la collaboration de 98 centres nationaux de la grippe, répartis dans 70 pays, et de deux centres collaborateurs OMS situés l'un à Atlanta et l'autre à Londres. L'information épidémiologique ainsi recueillie est vérifiée puis publiée dans le *Relevé épidémiologique hebdomadaire* de l'OMS.

La surveillance épidémiologique se fonde sur deux indices: les données de morbidité et de mortalité. Ces données ont des sources variées suivant les pays. Au Royaume-Uni, elles proviennent *a*) des taux de consultation pour affections respiratoires aiguës, fournis par les médecins généralistes, *b*) des statistiques de mortalité, *c*) des premières demandes nouvelles de remboursement des frais de maladie. Aux Etats-Unis, des médecins désignés, dans l'industrie, les écoles et les comtés, fournissent des données complémentaires utiles sur la morbidité grippale. En URSS, un modèle épidémiologique permet de contrôler l'accroissement de la morbidité journalière due à la grippe ou à toute autre affection respiratoire. Ces indices sont rapportés au nombre de virus grippaux isolés, en vue de permettre une estimation et une comparaison fiables de l'impact de la grippe d'une année à l'autre. Dans beaucoup de pays il n'existe pas de données de morbidité et de mortalité: pour ceux-ci il y aurait lieu de confier aux laboratoires nationaux, outre la tâche d'isoler et d'identifier les souches de virus, celle d'utiliser les méthodes d'enquête sérologiques.

La surveillance par les laboratoires apporte généralement des données plus étendues et plus uniformes que celles fournies par les statistiques, mais dans certaines régions du monde le service d'information présente des lacunes et certains laboratoires ne peuvent se procurer les échantillons nécessaires pour isoler les virus. La désignation de « détecteurs » parmi les praticiens libres, dans les centres de santé ou dans les écoles, s'est révélée utile et a permis d'obtenir régulièrement des échantillons de patients atteints d'affections respiratoires aiguës.

Les méthodes d'isolement des virus grippaux sont susceptibles de simplification et d'amélioration. La méthode classique d'isolement sur œuf incubé présente des inconvénients connus. L'utilisation de cultures de cellules de rein de singe rhésus a donné, au Royaume-Uni, d'excellents résultats, mais elle est coûteuse et à proscrire aux fins d'enquête, surtout quand l'animal utilisé est menacé de disparition. Le système de culture cellulaire continue (MDCK) avec traitement à la trypsine est prometteur et pourrait être utilisé conjointement à la technique d'immunofluorescence pour le diagnostic direct de la grippe. Des recherches plus récentes permettent de caractériser les souches au moyen du test de double immunodiffusion et leur comparaison en série est possible grâce aux tests de diffusion radiale unique qui peuvent être combinés avec les tests quantitatifs d'absorption des anticorps. La rapidité de dépistage des virus variants d'importance épidémiologique potentielle est liée à l'examen d'un grand nombre de souches. Depuis l'apparition du sous-type A/Hong Kong/1/68 du virus grippal A, les deux centres collaborateurs d'Atlanta et de Londres ont reçu quelque 400 à 600 isolats à caractériser. Ils ont pu ainsi étudier sans délai huit dérivants antigéniques du virus A/Hong Kong/1/68 et d'autres virus. De nouvelles méthodes de surveillance épidémiologique devraient améliorer le volume et la qualité de l'information disponible dans plusieurs pays. Tel est le cas de la technique de diffusion radiale unique (toutefois coûteuse en raison de la forte concentration d'antigène requise) et de la technique d'hémolyse radiale unique (plus simple

et moins coûteuse que la précédente). Les auteurs recommandent aux centres nationaux de la grippe, en particulier à ceux des pays dépourvus de données épidémiologiques, de rassembler et conserver les échantillons à partir des échantillons de sang recueillis pour raisons médicales dans les laboratoires des hôpitaux. Le contrôle périodique de ces échantillons pourrait fournir une mesure de l'impact de toute épidémie de grippe sur la population.

De même que l'information épidémiologique, les formulations recommandées du vaccin antigrippal sont publiées dans le *Relevé épidémiologique hebdomadaire* de l'OMS. Elles sont établies sur la base des données recueillies par les deux centres collaborateurs OMS à partir des tests effectués avec des anticorps homologues et hétérologues pour tout nouveau variant du virus: ils permettent de déterminer le degré de protection de la population en termes du pourcentage et du titre.

Le dernier point de l'exposé fait un rapide survol de l'épidémiologie des virus A et B ainsi que de leurs variants, des années 1973 à 1978.