Influenza has long been recognized as a problem in both industrialized and developing nations. During an ordinary epidemiological season, about 10% of the world’s population catch influenza, i.e. some 500 million people.

Influenza epidemics may spread from one end of the world to another within a few months. The spread is highly favoured by the increasing speed and proportions of modern intercountry travel. Once an infection has been implanted in a receptive population, factors such as humid and cold weather, indoor life and crowded public transport (which intensify the frequency of contacts) may trigger the epidemic wave.

The cost of influenza

Influenza A infections are a predictable cause of excess mortality. For example, in the United States of America in 1957 the Asian strain of influenza virus caused an estimated 70 000 deaths; the Hong Kong virus that appeared in 1968 caused about 30 000 deaths in the United States alone (1). Even without the appearance of a new virus, each year many people die as a result of influenza infection.

Deaths from influenza may result from the destruction of lung tissue in influenza pneumonia, but can also be due to cardiopulmonary or other chronic diseases that are exacerbated during influenza infection. At least 10 000 excess deaths have been documented in the United States during each of 18 different epidemics registered from 1957 to 1985. Between 80% and 90% of the excess deaths attributed to pneumonia and influenza during epidemics occur among persons 65 years of age or more.

During the 1957 influenza outbreak in the United Kingdom, influenza and pneumonia were responsible for the death of about 7 700 people, most of them in the age group over 70.

However, influenza affects all age groups and the age-specific incidence rate is actually highest in children between 1 and 14 years and nearly 4 times (37%) that estimated for the population aged 60 years or more (10%) (1). Hospitalization rates are relatively uniform for ages 5-44 and highest in age groups <5 and >65. The death rate is low in children (2.7 per 100 000) and highest in the over-65 age group (75.9 per 100 000) (2).

Days lost from school and work, and hospitalizations required for complications of influenza infection, result in a very high cost to society. In the United States, for example, hospitalization rates for adults with high-risk medical conditions increase two- to fivefold in different age groups during major epidemics, reaching a maximum rate of about 800 excess hospitalizations per 100 000 high-risk persons (1, 2); hospitalization costs exceed US$300 million for each epidemic.

According to 1985 estimates of disease-burden value and costs associated with treatment, the cost of influenza was between 4 and 50 times higher than other common infectious diseases (1).

It has been estimated in the United States that about 70 million people catch influenza at a cost of about US$4.5 billion during an influenza outbreak (1). Vaccination could have prevented 80% of these infections and saved about US$2.5 billion.

The 1974-1975 influenza epidemic in the United Kingdom was not one of the more severe in recent decades, but its estimated cost in loss of productivity was £100 million (4).

The use of influenza vaccine

In spite of influenza infection being a widespread problem in many industrialized and developing countries, the existing influenza vaccines are among the least utilized. The need for annual revaccination, misconceptions about the capabilities of the vaccine — many recipients expect them to prevent all respiratory infections — and unanswered questions about their efficacy in high-risk persons and populations have led many physicians to conclude that vaccination against influenza was not worth the effort.

The needs and means of influenza control were discussed at a WHO meeting in 1986 (5) which stressed that influenza remains an important disease, causing high levels of morbidity at unpredictable intervals, usually every few years. It was recognized that the vaccine cannot prevent epidemics, largely due to the emergence of antigenic variants. However, it was recommended that studies designed to assess vaccine efficacy should include their ability not only to protect the vaccinees but also to reduce the impact of influenza epidemics in the community.

There is no dearth of data available on the efficacy of influenza vaccine to prevent morbidity and mortality (4). Studies of a large metropolitan population of non-institutionalized ambulatory elderly persons during several recent influenza epidemics in the United States have consistently shown a reduction in morbidity of approximately 70% among vaccinees when the virus inducing the outbreak and the virus used for the production of influenza vaccine are immunologically closely related.

It has been estimated that 60% of residents in United States nursing homes may be affected during an outbreak, and up to 25% of patients die or develop life-threatening complications. A series of some

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20 published and unpublished observational studies of influenza outbreaks showed evidence of vaccine efficacy (4). Some of these studies indicated that “herd immunity” may be an important phenomenon worthy of consideration in determining the spread of influenza virus in the institutional setting. In one study nursing homes which experienced sustained spread of influenza were compared with nursing homes in which only sporadic cases occurred (5). It was found that the former had significantly lower levels of vaccination (median of 51% and 81% of residents vaccinated respectively). This suggests that herd immunity may be achieved with institutional vaccination rates in the vicinity of 80%.

Who should be vaccinated?

Influenza vaccines are in routine use in many countries and mainly recommended for persons with chronic disease and at increased risk of influenza complications. However, only a small percentage of the high-risk groups are vaccinated. For example in the United States, 43 million persons are at risk of death from influenza by virtue of underlying illnesses. In reality, only 8 million receive the vaccine. In the United Kingdom, the high-risk groups include 10 million people but again, only a small proportion is vaccinated each year.

It is not realistic to expect influenza vaccines to prevent the spread of the disease in the community as vaccines against measles and poliomyelitis do, but the impact of influenza epidemics can be reduced by vaccines made from the appropriate strains of influenza viruses and used at the right time.

The priority group for influenza vaccination are those at greatest risk of influenza-related complications: adults and children with chronic disorders of the pulmonary or cardiovascular systems requiring regular medical follow-up or hospitalization during the preceding year (including children with asthma); residents of nursing homes and other chronic-care facilities housing patients of any age with chronic medical conditions.

Other priority groups for influenza vaccine are those at moderate risk of influenza-related complications: other healthy persons >65 years old; adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, haemoglobinopathies or immunosuppression; children and teenagers (aged 6 months to 18 years) who are receiving long-term aspirin therapy and, therefore, may be at risk of contracting Reye’s syndrome after an influenza infection.

In addition, groups potentially capable of nosocomial transmission of influenza to high-risk persons: physicians, nurses and other personnel who have extensive contact with high-risk patients (e.g. primary-care and certain specialty clinicians and staff of chronic-care facilities); neonatal intensive-care units, particularly those of smoking parents. Providers of home care to high-risk persons (e.g. visiting nurses, volunteer workers) as well as all household members of high-risk persons, including children, whether or not they provide care.

Among the general population, influenza vaccine should be administered to all persons who wish to reduce their chances of acquiring influenza infection. Persons who provide community services may be considered for vaccination to minimize the disruption of essential activities during severe epidemics.

Vaccine types

Both inactivated and live attenuated virus vaccines are available for influenza prophylaxis (4). Inactivated vaccines are in routine use in many countries. In most of these countries the vaccines are recommended for risk groups, but in some countries vaccination is extended to mass campaigns of healthy adults or children. Cold-adapted (ca) recombinant live attenuated virus vaccines were recently developed in several countries. Clinical studies suggest that these vaccines can afford good protection in healthy children and in adults (4). Such a vaccine is used for mass immunization of adults and schoolchildren in the republics of the former USSR.

Comparative studies of the efficacy of inactivated and ca live virus vaccines showed a greater efficacy of the inactivated vaccine in adults and older children, while among young children the live virus vaccine was more effective (6).

Biological mechanisms of protection

The strategy for influenza control must be based on the mechanisms of immunity to influenza in humans. At present, most information on these mechanisms has been obtained in animal models. It is clear that previous infection of humans with an identical strain of virus confers immunity upon later challenge and that this immunity can be both solid and long-lasting, as shown by the resistance of the population over 20-25 years to H1N1 influenza virus infection on the reappearance of this subtype in 1977, 20 years after the last H1N1 outbreak.

High titres of haemagglutinin-inhibiting antibody are associated with protection against a virus with a closely related haemagglutinin (HA). Resistance to influenza infection in humans has been correlated with HA antibody in nasal washings also in the absence of serum antibody (7). On the other hand, studies of maternally transferred antibody in neonates have shown that serum antibodies alone may contribute to resistance.

Cell-mediated immunity appears to be responsible for the recovery process from influenza infection (8). Since local and serum antibodies and also cytotoxic T-cells (Tc-cells) appear to be mediators of immunity to influenza infection, it is important that influenza vaccines induce all these components of immunity.

Comparative studies of inactivated and ca live influenza virus vaccines have shown the inactivated vaccine to induce serum IgA and IgG in most vaccinees contrary to the live vaccine. The inactivated vaccines also induced higher titres of serum antibodies than the live vaccine. However, only 38% of vaccinees having received the inactivated vaccines showed a local IgA response compared with 83% of vaccinees immunized with ca live vaccine (7).

Another study showed that pre-challenge local IgA, detected almost exclusively in subjects naturally infected or vaccinated with ca live vaccine, was associated with protection against shedding. Also low levels of nasal IgA (<1.5) were associated with suppression of viral shedding. The effect of nasal IgG was not as clearly
demonstrated but at higher levels (>10^6 PFU) shedding was reduced (7).

The ability of influenza vaccines to stimulate the Tc cell response has not been determined in unprimed humans but ca live influenza virus vaccine induces a primary Tc cell response in mice and sensitizes the lungs for a secondary Tc cell response (6, 7).

Another factor influencing the efficacy of influenza vaccines is the appearance of drift variants of influenza virus. One study indicates decreasing protective effect of repeated vaccinations with inactivated vaccine even when the vaccine viruses matched the prevailing epidemic strains. On the other hand, natural infection with live influenza virus afforded almost complete protection during successive outbreaks involving drift variants for more than 4 years (9). It is possible that the local administration of a live attenuated influenza virus vaccine which would mimic natural influenza infection provides a more long-lasting and broadly reactive immunity than the inactivated vaccine. However, the factors responsible for protection in humans need to be further elucidated before any clear conclusions can be drawn about the efficacy of inactivated vs live virus vaccines.

Antiviral drugs

In addition to vaccines, several antivirals are effective against influenza. Two drugs, amantadine and rimantadine, have shown 70-90% efficacy in protecting against influenza A in controlled studies (10).

Influenza surveillance

Influenza surveillance plays an important part in the control of influenza (11, 12). The main objectives of influenza surveillance are:

- to allow the early detection of influenza outbreaks and identification of the causative agent. The early warning should prompt health providers to prepare for a possible increased demand on health care services and to warn the general practitioners in order that they may carry out vaccinations among persons at risk who have not yet been vaccinated;

- to permit estimates of the impact of the influenza by collection and analysis of influenza morbidity and mortality data;

- to provide influenza virus isolates from outbreaks and sporadic cases for analysis of antigenic characteristics required for the decision about variants to include in influenza vaccines;

- to detect population groups at increased risk of complications from influenza which are not currently specified in recommendations for the use of influenza vaccine.

The true morbidity and mortality from influenza are difficult to estimate in most countries by simply reporting influenza-like illness or acute respiratory diseases. Without laboratory confirmation, illnesses may be erroneously attributed to influenza viruses. On the other hand, diseases and deaths induced by influenza viruses without physician contact or occurring after acute symptoms have subsided will be underreported.

Analysis and comparisons of the impact of influenza and benefit of influenza vaccination in different countries are also difficult because surveillance systems and methods vary from country to country.

The laboratory element of influenza surveillance appears to be globally both more uniform and available than statistical observations. However, both laboratory services and capabilities to isolate and characterize respiratory viruses other than influenza need to be expanded in many parts of the world.

In many countries influenza surveillance is based on groups of physicians (sentinel physicians) volunteering to report weekly on the extent of influenza-like illness. The number of physicians participating in such surveillance systems ranges from about 40 to several hundred. Their interest and experience accumulated over several years result in a high degree of year-to-year consistency despite the range of symptoms presented.

Using patient contacts as denominator and acute respiratory illness/influenza-like illness as numerator, a statistical model can be developed of morbidity baselines which permit the clear demonstration of epidemics that exceed the expected baseline. The approach for statistical modelling is similar to that tested by WHO (13) and used over many years in the United States (14) to assess mortality, and permits the definition of an epidemic threshold.

Laboratory investigation of a subset of patients can be organized by providing the physicians with specimen collection transport kits for throat or nasal swabs to be mailed to a central laboratory. A combination of direct antigen detection and rapid culture methods permit quick and efficient responses to the physicians. About 30-50% of specimens collected by trained surveillance physicians can be positive for influenza and other respiratory viruses including RSV.

It is desirable that the surveillance system provide a measure of severity. A simple measure can be obtained through analysis of weekly mortality reports for an entire region or for major cities. The reports can be either influenza and pneumonia deaths (selected by a trained worker in the office receiving death certificates) or, since influenza epidemics are an almost unique event leading to excess mortality, the total number of deaths. The total number of deaths is often available sooner and more readily. After about 5 years of data collection, statistical baselines can be established and major epidemics of mortality readily detected.

Another possible surveillance system is based on the collection of reports of hospital admissions for respiratory illnesses. As more hospitals install effective computer systems to monitor patient admissions and discharges, such data may be quickly made available without jeopardizing patient privacy.

Other approaches to surveillance used in certain countries include recording the number of emergency hospital bed services, home visits by emergency physicians, statistics on sales of pharmaceuticals, data on social security sickness claims, or absenteeism from schools or work.

WHO influenza programme

The emphasis of the WHO influenza programme established in 1947 is on rapid isolation and char-
acterization of new strains needed for effective vaccines. It is in constant communication with a network of 110 WHO-recognized national institutions for influenza designated by governments in 79 countries, and with 3 WHO collaborating centres for reference and research on influenza. Data on recent influenza activity worldwide collected through the network are published in the Weekly epidemiological record.

National institutions for influenza isolate influenza viruses and send them to the WHO collaborating centres for influenza for analysis of the antigenic characteristics, mainly of the haemagglutinin. The national laboratories make a preliminary identification of current isolates with diagnostic reagents which are updated, produced and distributed by the WHO Collaborating Center for Influenza Reference and Research at the Centers for Disease Control in Atlanta, United States.

Each year, at the end of February, WHO issues the recommendations for the composition of influenza vaccines to be used in the forthcoming epidemiological season. The recommendations (15) are based on various information sources including epidemiological data, antibody prevalence surveys, data from vaccine trials and results of studies of antigenic characteristics of influenza viruses isolated in different countries.

This programme and network of collaborating centres and national institutions on influenza enable WHO to keep its Member States informed on influenza occurrence and antigenic characteristics of any new variant of the virus, and to make new viruses available for vaccine production.

Influenza is not a trivial disease; it kills thousands of people and puts a heavy load on national economies every year, but it can be prevented. Using vaccines and antivirals, it is possible to protect both the individuals in high-risk groups and defined subsets of the population.

**SUMMARY**

Influenza is an underestimated public health problem. Epidemics spread rapidly from country to country and may affect as many as 500 million people across the world in a moderate influenza year. The disease, particularly influenza A, kills and the new influenza viruses which appeared in 1957 (Asian influenza) and 1968 (Hong Kong) are estimated to have caused at least 100,000 deaths in the United States of America. Deaths from influenza also occur in years when there is no new virus; at least 10,000 excess deaths have been documented in the United States during each of 18 different epidemics recorded from 1957 to 1985. Although most deaths are among the elderly, influenza occurs in all age groups with repercussions in schools and work places, and on hospital resources, at a high cost to society.

As many as 79-80% of influenza cases can be prevented when the virus inducing the outbreak and the virus used in the influenza vaccine are closely related. Preventing 80% of cases would correspond in the United States to a saving of US$2.5 billion. People at the greatest risk of influenza-related complications are adults and children with chronic disorders of the pulmonary or cardiovascular systems, residents of nursing homes and of facilities for patients with chronic medical conditions. Other priority groups for vaccination are those at moderate risk of influenza-related complications such as healthy elderly persons, people with chronic metabolic diseases, children and teenagers on long-term aspirin therapy. Groups potentially capable of transmitting influenza to high-risk persons should also be vaccinated. These include all health care personnel who have extensive contact with high-risk patients. Among the general population, influenza vaccine should be administered to all persons who wish to reduce their chances of acquiring influenza infection and to those providing community services, in order to minimize the disruption of essential activities during epidemics.

Both inactivated and live attenuated virus vaccines are available. Comparative studies of the efficacy of two vaccine types showed a greater efficacy of the inactivated vaccine in adults and older children, while among young children the live virus vaccine was more effective.

The strategy for influenza control must be based on the mechanisms of immunity to influenza in humans. Most information is derived from animal studies but it is evident that in humans previous infection confers immunity upon later challenge with an identical virus and that this immunity can be both solid and long-lasting. It is possible that the local administration of a live attenuated influenza virus vaccine which would mimic natural influenza infection provides a longer lasting and more broadly reactive immunity than the inactivated vaccine. However, the factors responsible for protection in humans need to be further elucidated before any clear conclusion can be drawn about the efficacy of inactivated vs. live virus vaccines. In addition to vaccines, several antivirals are effective against influenza. Two drugs, amantadine and rimantadine, have shown 70-90% efficacy in protecting against influenza A.

Influenza surveillance plays an important part in the control of the disease. The main objectives of influenza surveillance are the early detection of influenza outbreaks and the identification of the causative agent. Surveillance systems should allow for estimates of the impact of influenza on morbidity and mortality data and provide the influenza virus isolates required for deciding on influenza vaccine composition and vaccine production. Surveillance should also help detect population groups at increased risk of complications from influenza which are not currently specified in recommendations for the use of influenza vaccine.

The emphasis of the WHO influenza programme established in 1947 is on the rapid isolation and characterization of new strains needed for effective vaccines. It is based on a network of 110 WHO-recognized national institutions for influenza designated by governments in 79 countries and 3 WHO.
collaborating centres for reference and research on influenza. The national laboratories isolate influenza viruses and send them to the collaborating centres for analysis of the antigenic characteristics. Each year at the end of February, WHO issues recommendations for the composition of influenza vaccines to be used in the forthcoming epidemiological season. The recommendations are based on various information sources including epidemiological data, antibody prevalence surveys, data from vaccine trials and results of studies of antigenic characteristics of influenza virus isolates in different countries.

RÉSUMÉ

La grippe — impact et lutte

On sous-estime la grippe en tant que problème de santé publique. Les épidémies se propagent rapidement d'un pays à l'autre et au cours d'une année moyenne, jusqu'à 500 millions de personnes peuvent être touchées dans le monde par la maladie. Elle peut être mortelle, en particulier la grippe A, et les nouveaux virus qui ont fait leur apparition en 1957 (grippe asiatique) et en 1968 (Hong Kong) ont causé, selon les estimations, au moins 100 000 décès aux États-Unis d'Amérique. Des décès peuvent également se produire les années où aucun nouveau virus n'apparaît; aux États-Unis, on a observé une surmortalité d'au moins 10 000 décès lors de chacune des 18 épidémies enregistrées entre 1957 et 1985. Bien que ces décès frappent surtout les personnes âgées, la grippe touche tous les groupes d'âge avec les conséquences que l'on sait sur la scolarité, l'activité professionnelle et les ressources hospitalières, le coût en étant très élevé pour la société.

Lorsque les virus responsables de la flambée et ceux qui entrent dans la composition du vaccin antigrippal sont très proches, on peut éviter jusqu'à 79-80% des cas de grippe. Aux États-Unis, prévenir 80% des cas reviendrait à économiser US$2,5 milliards. Ce sont les adultes et les enfants porteurs d'infections pulmonaires ou cardio-vasculaires chroniques qui sont les plus exposés aux risques de complications, de même que les pensionnaires des établissements de soins et les malades hospitalisés pour longue maladie. Parmi les autres groupes à vacciner en priorité figurent ceux qui sont exposés à un risque modéré de complications comme les personnes âgées en bonne santé, les personnes souffrant de troubles métaboliques chroniques, les enfants et les adolescents qui suivent un traitement au long cours par l'aspirine. Il faudrait également vacciner les groupes qui pourraient transmettre la grippe aux personnes à haut risque. Il s'agit notamment de tous les personnels soignants qui sont largement en contact avec les malades à haut risque. Dans la population générale, il faudrait vacciner toutes les personnes qui souhaitent éviter la maladie ainsi que celles qui assurent les principaux services collectifs afin de réduire au minimum la désorganisation des activités essentielles pendant les épidémies.

Il existe des vaccins à base de virus inactif et de virus vivant atténué. L'étude comparée de leur efficacité respective montre que le vaccin inactif est plus efficace chez l'adulte et les grands enfants alors que, chez les jeunes enfants, c'est le virus vivant qui est le meilleur.

La stratégie de la lutte antigrippale doit se fonder sur le mécanisme de l'immunité vis-à-vis de la maladie.
REFERENCES


