PRESS KIT
SEASONAL INFLUENZA

Sanofi Pasteur – world’s leading influenza vaccine manufacturer

CONTACTS:
Global Media Relations
Alain Bernal
T. +33-(0)4-37-37-50-38
alain.bernal@sanofipasteur.com
www.sanofipasteur.com

U.S. Media Relations
Marisol Peron
T. +1-570-957-0717
marisol.peron@sanofipasteur.com
www.sanofipasteur.us
INFLUENZA IS A COMMON BUT POTENTIALLY SEVERE DISEASE

Seasonal influenza is an acute viral infection that spreads easily from person to person and that circulates year-round worldwide.\textsuperscript{1,2} Uncomplicated infection is accompanied by the abrupt onset of fever, sore throat, headache, muscle pain, chills, anorexia, fatigue and severe malaise (feeling unwell).\textsuperscript{1,2} Fever lasting 3-5 days, unproductive cough and a runny or stuffy nose are all common.\textsuperscript{1,2} Illness usually improves after 1 week, but cough and malaise may persist.\textsuperscript{2} However, these symptoms are non-specific and can also be caused by other respiratory tract infections. As a consequence, influenza is often mistaken for the common cold or other benign respiratory tract infections; actually, unlike the common cold, flu may cause mild-to-severe illness and can also induce life-threatening complications, such as viral or secondary bacterial pneumonia and the aggravation of underlying medical conditions, including congestive heart failure and diabetes.\textsuperscript{1,2,3}

Influenza illness affects people of all ages, but adults aged 65 or older and children younger than age 2 are particularly vulnerable, as well as those with certain medical conditions (such as chronic heart, lung, kidney, liver, blood diseases, diabetes) or illnesses that weaken the immune system.\textsuperscript{1} Catastrophic disability resulting from influenza-related hospitalizations represents a significant burden in the elderly population\textsuperscript{4,5} due to their weaker immune system and to the increased frequency of chronic conditions in this age-group.\textsuperscript{6} In addition, more than 90% of deaths associated with influenza occur in the high-risk groups and in the elderly.\textsuperscript{1,7,8}

In adults, the risk of dying from influenza and related complications increases from the age of 50.\textsuperscript{9}

AS A MAJOR CAUSE OF COMPLICATIONS AND DEATH, INFLUENZA REPRESENTS A GLOBAL PUBLIC ISSUE

Influenza is a serious public health problem that causes severe illness, hospitalization and death mainly among high-risk groups (the very young, elderly or chronically ill).\textsuperscript{1,3} According to WHO’s estimates, as much as 5 to 15% of the population are affected by upper respiratory tract infections, in annual influenza epidemics, each year\textsuperscript{10} (influenza annual global attack rates are estimated at 5-10% in adults and 20–30% in children\textsuperscript{8}).

Worldwide, annual influenza epidemics result in three to five million cases of severe illness, and 250,000 to 500,000 deaths.\textsuperscript{1,10}
INFLUENZA IS A HIGHLY CONTAGIOUS ACUTE VIRAL DISEASE

Influenza is a highly contagious disease that often reaches epidemic proportions. Influenza epidemics occur yearly during autumn and winter months in temperate regions. Influenza viruses are very infectious and are easily transmitted from person to person through air droplets projected by coughing and sneezing. The virus can also be spread by shaking hands or touching surfaces contaminated with the virus.

The incubation period averages 2 days (range 1-4 days). Infected adult individuals are contagious from the day before symptoms appear until 5 days after onset of the illness, and severely immuno-compromised persons can shed the virus for weeks or months.

Children can be infectious for more than 10 days after the onset of symptoms. Day-care and primary school children often spread the virus into homes and communities, as children are efficient transmitters of influenza viruses. Children 5–9 years of age typically manifest the highest rates of infection and illness.

Up to 59% of healthcare workers experience flu infections without classic symptoms and can transmit the virus to patients.

INFLUENZA POSES A SIGNIFICANT ECONOMIC BURDEN

Influenza can cause serious economic problems. Clinics and hospitals can be overwhelmed when large numbers of sick people appear for treatment during peak periods of illness.

In industrialized countries, influenza is associated with a considerable economic burden in terms of healthcare costs, lost days of work or education, general social disruption and workforce productivity losses. Indirect costs of influenza can account for 80–90% of the total costs and stem largely from work absenteeism, disruption of activities and loss of productivity. Annual direct costs of influenza, including costs of hospitalizations, outpatient visits and care, physician visits and drugs, etc. have been estimated at US$ 2.2 billion, and indirect costs at US$ 8.8 billion in the USA, in 2004.

In unvaccinated healthy adults aged 50-64 years, influenza illness was shown to be responsible for 39% of all illness-related work days lost and 49% of all days with illness-related reduced “on-the-job productivity”. In the USA, 44 million days of productivity were estimated to be lost due to influenza illness every year.
Estimates from France, Germany and the United States indicate that the total annual cost of influenza outbreaks varies between US$1 million and US$6 million per 100,000 inhabitants.8

Influenza is the most frequent cause of acute respiratory illness requiring medical intervention because it affects all age groups and because it can recur in any individual.11

**VACCINATION IS THE MOST EFFECTIVE WAY TO REDUCE THE BURDEN OF INFLUENZA**

To prevent transmission as much as possible, infected people should cover their mouth and nose with a tissue when coughing or sneezing, and wash their hands regularly.1 Annual vaccination is however still to date considered as the most effective way to prevent influenza infection and its complications and to alleviate its economic burden.1 Vaccination is especially important for people at higher risk of serious influenza complications and for people who live with or care for high risk individuals.1,2,8

The World Health Organization (WHO) therefore strongly emphasizes the importance of raising public awareness of influenza and its complications as well as the beneficial effects of influenza vaccination8 and is working, in close partnership with global health authorities, to strengthen national and regional influenza diagnostic capacities, disease surveillance and outbreak responses.1,20

In 2003, the World Health Assembly urged Member States with influenza vaccination policies to increase vaccination coverage in all people at high risk, including the elderly and persons with underlying conditions (with a low-end goal of 75% coverage for the elderly).8,20,21 The approach to influenza control typically aims at reducing severe influenza-related outcomes largely by vaccination of the elderly, who are at highest risk for influenza-related deaths,22 and, indeed, among the elderly, the vaccine reduces severe illnesses and complications by up to 60%, and deaths by 80%.1

Influenza vaccination offers approximately 70-90% protection against clinical disease in healthy adults aged 18-59, provided there is a good match between the vaccine antigens and circulating viruses.1,8,23 The benefits of influenza vaccination in this healthy adult group23—including health-care workers—justify the economic costs involved since vaccination prevents absenteeism and loss of productivity while reducing illness rates and the burden of disease.23,24
SAFE AND EFFECTIVE INFLUENZA VACCINES ARE AVAILABLE AND ARE TO BE ADAPTED EVERY YEAR

Inactivated influenza vaccines have been available and in use for more than 60 years and are safe and effective. Sanofi Pasteur’s influenza vaccines contain inactivated split viruses that cannot cause influenza, but induce an immune response that protects against the disease or complications from the illness

Influenza virus infection induces humoral and cellular immune responses, both elements playing a role in viral clearance and in the prevention of infection. The protective role of antibodies-elicited either in the natural course of influenza infection or following vaccination and directed against haemagglutinin (HA) and neuraminidase (NA)-has been widely demonstrated.

Seasonal influenza vaccines are formulated every year, based on the WHO seasonal recommendations and contain the HA and NA antigens of two influenza A virus subtypes (H3N2 and H1N1) and those of one influenza B virus. Flu viruses are, indeed, capable of evading the body’s immune system by undergoing continuous genetic variation and may change from season to season. Individuals are susceptible to new strains despite previous infection by other influenza viruses. People may have limited protection against new circulating viruses. This is why changes in influenza vaccine strains may be needed from one year to another and why annual administration of influenza vaccine may be recommended by authorities.

Influenza epidemics occur yearly during autumn and winter in temperate regions and can seriously affect all age groups. In some tropical countries, influenza viruses circulate throughout the year with one or two peaks during rainy seasons. Every year the WHO Global Surveillance Network analyses thousands of virus samples from around the world and makes predictions about which seasonal strains will likely threaten human health the most in the next season.

The recommendations for the influenza strains to be used in the composition of seasonal vaccines are determined twice yearly (in February for the Northern Hemisphere and in September for the Southern Hemisphere) by the WHO, based on the data reported by collaborating influenza centers throughout the world. Vaccine manufacturers formulate new influenza vaccines every year accordingly.

Immunogenicity criteria for influenza vaccines are well established (see Appendix 1 for the European Medicines Agency’s immunogenicity criteria for influenza vaccines).

* Haemagglutinin (HA) and neuraminidase (NA) are antigenic components of the outer membrane of the virus that can be recognized by virus-neutralizing-antibodies.
CURRENT CHALLENGES TO INFLUENZA VACCINATION

INFLUENZA VACCINES ARE UNDERUTILIZED AND INFLUENZA REMAINS AN UNCONTROLLED INFECTIOUS DISEASE\textsuperscript{17,20,27,28}

Despite the implementation of prophylactic measures and the availability of symptomatic or specific (antiviral) treatments against influenza, and although the quality, availability and use of inactivated influenza vaccine have increased substantially, annual epidemics continue to cause substantial sickness and death worldwide as large numbers of unvaccinated at-risk persons are left vulnerable to infection and its complications, and influenza continues to be a major global health problem.\textsuperscript{2,8,20,29}

One of the key challenges in influenza prevention is therefore convincing patients to get vaccinated. Some of the main reasons for people not to be vaccinated include lack of education about the real impact of the disease and the necessity to repeat vaccination every year, lack of physician recommendations and mistaken assumptions on the disease or on the vaccine and a misunderstanding of the vaccination process.\textsuperscript{30} Additionally, the current most common mode of vaccination-intramuscular injection—and the fear or the dislike of needles, may represent a potential barrier for all adults—whether healthy or at-risk—who are apprehensive of injections and/or needles\textsuperscript{30} and may keep them from being vaccinated.\textsuperscript{20,28,30} Patients not only need to be convinced of the benefit of being vaccinated, but also reassured about the process of receiving an influenza vaccination.\textsuperscript{20,27,28,30}

IMMUNOSENESCENCE – WEAKENED IMMUNITY IN THE ELDERLY

The natural ageing process has a major impact on numerous physiological functions, including immune function.\textsuperscript{6} Ageing is associated with a decline in the body’s ability to fight infection and mount novel immune responses.\textsuperscript{4,6,8,22,31}

This weakening of the immune system with ageing phenomenon is called immunosenescence.\textsuperscript{22} Changes related to immunosenescence include functional defects and modifications in the concentrations of immune cell type populations, as well as a more inflammatory state. Although ageing affects all aspects of immune function, the impact on T-lymphocytes is well documented.\textsuperscript{2,6} As T-lymphocytes are pivotal to the immune response, the overall function of the immune system is compromised.\textsuperscript{6,8}
With a weakened immune system, individuals aged 60 and over become not only more susceptible to infections and to complications from influenza, but also less responsive to vaccination compared with younger adults. Despite this, it is important to note that vaccination is still of significant health benefit in this population. Influenza immunization was, indeed, demonstrated to be associated with a reduction in the risk of hospitalization for heart disease, cerebrovascular disease and pneumonia or influenza as well as the risk of death from all causes during influenza seasons.

In a 10 month follow-up study conducted in elderly adults, influenza vaccination was proven to be not only strongly associated with a reduction in lung disease-specific mortality, including pneumonia and chronic obstructive pulmonary disease (COPD), but also with reducing all-cause mortality and other major cause-specific mortality, after adjusting for age, sex, and risk status. Vaccination against influenza was indeed shown to reduce mortality due to stroke by 65%, diabetes mellitus by 55% and renal diseases by 60%. These results were even better than those obtained for mortality associated with pneumonia (53%) and COPD (45%). The authors concluded that the influence of influenza vaccination on reducing mortality might be much more extensive than stated in previous reports that focused mostly on respiratory diseases.

While influenza vaccination, by preventing influenza infection and complications including hospitalization and death, is of great benefit in adults aged 60 and over as well as in patients with compromised immune systems or chronic conditions, there remains a significant need for more effective vaccines for this specific adult populations: enhancing the immune response to vaccination is expected to reduce the morbidity and mortality associated with influenza. Approaches aimed at surmounting the weakness of the ageing immune system and developing age-specific vaccination strategies are extremely important.

OTHER FACTORS AFFECTING VACCINE EFFICACY

Improving the antigenic match and achieving better understanding of the virulence factors of influenza epidemics represent other key challenges of influenza vaccination.
APPENDIX 1: THE EUROPEAN MEDICINES AGENCY (EMA) IMMUNOGENICITY CRITERIA FOR INFLUENZA VACCINES

The immunogenicity of an influenza vaccine is determined by measuring the antibodies against the influenza haemagglutinin in blood samples taken before and after vaccination. This measure is usually performed by a test called haemagglutination-inhibition (HI) test or by a test called single radial haemolysis test (SRH).

Three parameters are evaluated:\textsuperscript{24,34}

The **seroconversion rate**, i.e. the proportion of subjects who acquire or achieve a significant increase in anti-haemagglutinin antibody titer 21 days after vaccination, i.e. a postvaccination titer $\geq 40$ in subjects with a prevaccination titer $< 10$, or a $\geq 4$-fold increase in titer after vaccination in subjects with a prevaccination titer $\geq 10$.

\textit{EMA requested criteria: Influenza vaccines must provide a seroconversion rate of 40% in adults 18-59 years, and 30% in adults 60 years and over.}

The **seroprotection rate**, i.e. the proportion of subjects achieving a post-vaccination antibody titer equal or superior to the protective threshold (HI titer $\geq 40$).

\textit{EMA requested criteria: influenza vaccines must provide a seroprotection rate of 70% in adults 18-59 years, and 60% in adults 60 years and over.}

The **meanfold increase** (MFI) in haemagglutinin antibody titers.

\textit{EMA requested criteria: influenza vaccines must provide a >2.5 fold increase in adults 18-59 years, and >2 in adults 60 years and over.}
Sources:


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