





Recent Developments in NIAID Pandemic Influenza Research








The NIAID Pandemic Influenza Preparedness Program supports research in basic biology, surveillance and epidemiology, vaccine development and evaluation, and the development of antivirals against influenza.

Below is an overview of NIAID-supported research and global events dating back to 1997, when the world's first known cases of human infection with avian influenza viruses were documented.



YEAR	RESEARCH DEVELOPMENTS & GLOBAL EVENTS
1997	<div>  <p>- In August, avian influenza (H5N1) infections occur in both poultry and humans in Hong Kong. This is the first time an avian influenza virus has ever been found to transmit directly from birds to humans. The virus kills six out of 18 people infected. All poultry in Hong Kong is culled. (WHO)</p> </div> <div>  <p>- NIAID awards a grant to Baylor College of Medicine (PI, Pedro Piedra) to examine whether vaccinating a large percentage of children can protect a community from a possible influenza pandemic.</p> </div>
1998	<div>  <p>- NIAID awards a contract to Protein Sciences Corporation (PI, John Treanor) for the production of a recombinant H5 hemagglutinin vaccine. Within three weeks, the company produces an investigational vaccine which is tested in NIAID-supported clinical trials. (Related Article)</p> </div> <div>  <p>- NIAID awards the "Influenza Pandemic Preparedness in Asia" contract to St. Jude Children's Research Hospital (PI, Dr. Robert Webster) to:</p> <ul style="list-style-type: none"> • Establish an animal influenza surveillance center in Hong Kong • Determine the molecular basis of transmission of avian flu viruses • Provide characterized viruses suitable for vaccine development • Support training of new laboratory personnel • Produce reagents </div>

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	 <p>- NIAID-supported scientists discover that human influenza A viruses employ the enzyme plasmin to help chop hemagglutinin in two. The discovery may explain what amplifies the disease-causing power of influenza A virus and makes the virus uncommonly deadly. (Related Article)</p>
1999	 <p>- NIAID awards a grant to the University of Wisconsin (PI, Dr. Yoshihiro Kawaoka) to investigate the molecular mechanisms of influenza pandemics. NIAID-supported researchers for the first time succeed in engineering an influenza A virus entirely from cloned genes, a breakthrough that could lead to improved influenza vaccines and new influenza-based gene delivery systems. (Related Article)</p>  <p>- NIAID-supported researchers at St. Jude Children's Research Hospital and the University of Wisconsin demonstrate that a new DNA-based vaccine protects mice from experimental challenge with the H5N1 virus. (Related Article)</p>  <p>- In March, H9N2 infects two children in Hong Kong. Both children recover. (WHO) Meanwhile, in Italy, a two-year H7N1 epidemic begins in the country's bird population. The H7N1 virus, originally of low pathogenicity, mutates in less than a year to a highly pathogenic form. More than 13 million birds die or are culled. (WHO)</p>
2000	 <p>- NIAID's Vaccine and Treatment Evaluation Units (VTEUs) conduct a clinical trial to compare the immune responses of healthy adults who receive either a full dose or a half dose of flu vaccine. (Related Article)</p> <p>- NIAID awards the following three challenge grants to industry partners for vaccine development:</p> <ul style="list-style-type: none"> • NIAID awards a grant to Aviron for the production of a live attenuated vaccine for pandemic preparedness and to develop a cell culture-based flu vaccine (PI, Dr. Shengqiang Li).  

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	<div data-bbox="245 327 461 386"></div> <ul style="list-style-type: none"> NIAID awards a grant to Aventis Pasteur for the DNA-based generation of avian influenza virus vaccines (PI, Fred Vogel). The project goal is to use a DNA-based system to rapidly produce influenza vaccine candidates, including those against H5 and/or H7 pandemic influenza, which will be tested in clinical trials by NIAID. <div data-bbox="245 548 461 606"></div> <ul style="list-style-type: none"> NIAID awards a grant to Novavax (PI, Dr. Louis Potash) to produce several non-egg-grown influenza vaccines, with the goal being that the most promising will be prepared for use in clinical trials by NIAID. <div data-bbox="237 701 310 785"></div> <ul style="list-style-type: none"> NIAID-supported researchers at St. Jude Children's Research Hospital streamline the use of reverse genetics down to eight plasmids - one for each gene in the virus genomes - making the process simpler and less expensive. (Related Article) <div data-bbox="237 890 310 966"></div> <ul style="list-style-type: none"> NIAID-supported scientists take part in the Options for the Control of Influenza IV Meeting, held in Greece, September 23-28, 2000. The meeting objectives are to review the latest advances in molecular virology and pathogenesis of influenza viruses and relate them to the problems of surveillance, rapid diagnosis and improvement in strategies for the treatment and prevention of influenza.
2001	<div data-bbox="237 1142 293 1215"></div> <ul style="list-style-type: none"> St. Jude scientists and University of Hong Kong (HKU) collaborators detect the re-emergence of H5N1 in live bird markets in Hong Kong. More than one million birds are culled and "market rest day" is instituted. (Related Article). Researchers also identify quail as the mixing vessel for the spread of avian influenza viruses from aquatic birds to land-based poultry. Live quail is banned from live-bird markets the following year. (Related Article) <div data-bbox="237 1331 310 1415"></div> <ul style="list-style-type: none"> NIAID-funded investigators at the University of Wisconsin use reverse genetics to discover that the PB2 gene is key to the virulence of the H5N1 influenza strain. This discovery provides important information that may be useful in understanding the emergence of future viruses that may have pandemic potential. (Related Article) <div data-bbox="237 1551 310 1627"></div> <ul style="list-style-type: none"> In July, NIAID sponsors the Reverse Genetics Workshop (Executive Summary), bringing together an international group of researchers in influenza viruses as well as scientists outside of the influenza field with research experience in other human viruses, biosafety, and public policy. The Workshop discussions are centered on using local biosafety committees to examine the research work that will be done at federally funded universities and to make risk assessments and safety recommendations.

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2002



- St. Jude scientists and HKU collaborators detect the second re-emergence of highly pathogenic **H5N1**. More than 20 farms are found to be infected and more than seven different **H5N1** genotypes are identified in wild aquatic birds. ([Related Article](#))



- St. Jude scientists determine that the H5N1 avian virus that killed six people in 1997 can bypass natural host defenses, which may explain the high lethality of avian strains. ([Related Article](#))



- NIAID awards a grant to the American Registry of Pathology for the complete [characterization of the 1918 influenza virus](#) (PI, Dr. Jeffrey Taubenberger). ([Related Article](#))



- Following an outbreak in May of **H7N2** among poultry in the Shenandoah Valley, Virginia, poultry production area, one person is found to have serologic evidence of infection with H7N2. ([CDC](#))

2003



- St. Jude scientists and HKU collaborators discover that **H9N2** viruses are endemic in land-based birds in China. ([Related Article](#)). It is also discovered that [gene segments of H9N2 flu viruses](#) found in ducks had undergone many changes, with some new combinations coding for antigens that could infect humans. ([Related Article](#))



- In FY 2003, NIAID expands its [Pandemic Preparedness in Asia](#) contract. This expansion supports enhanced animal influenza surveillance sites in Asia, the generation of high-yielding pandemic vaccine candidates, and studies of a newly emerging influenza strain infecting swine in the United States. ([Related Article](#))

- In September, NIAID convenes an international workshop on the [Development of a Clinical Trial Plan for Pandemic Influenza Vaccines](#) ([Meeting Summary](#)) to:



- Review data from earlier trials of pandemic influenza vaccines
- Identify manufacturing and regulatory hurdles
- Prioritize pandemic influenza virus subtypes
- Develop an agenda for the conduct of clinical trials
- Initiate development of a U.S. Pandemic Influenza Vaccine Protocol



- NIAID awards a grant to Stanford University (PI, Dr. Ann Arvin) to study [vaccine-induced and naturally acquired influenza A immunity](#) as a model for in-depth analysis of the innate and adaptive immune response in children and adults.

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- NIAID awards a grant to the University of Maryland to understand the [transmissibility of influenza A viruses](#) (PI, Dr. Daniel Perez). The project's objective is to study the interspecies transmission of avian influenza viruses.

- NIAID awards three grants to industry partners for influenza product development:



- NIAID awards a grant to the Massachusetts Institute of Technology to investigate [RNA interference of influenza virus infection](#) (PI, Jianzhu Chen) as a new way of preventing and treating influenza infection. ([Related Article](#))



- NIAID awards a grant to Dynavax Technologies Corp. (PI, Gary Van Nest), to find a relatively stable component for use in a new kind of [more broadly protective influenza vaccine](#). The vaccine candidate combines an internal flu protein that is less likely to be altered through mutation, NP, with a bioengineered molecule called an immunostimulatory DNA sequence, or ISS. ([Related Article](#))



- NIAID awards a grant to the University of Colorado at Boulder for the [development of a diagnostic microarray for influenza A](#) (PI, Kathy Rowlen), which may serve as a rapid diagnostic. The project's goal is to develop the "Flu Chip," that will provide information as to whether or not an individual is infected with influenza as well as provide both type and antigenic sub-type characterization of the virus.



- NIAID-supported researchers at the Vaccine and Treatment Evaluation Units at the University of Rochester and Baylor College of Medicine [test an experimental vaccine](#) to protect people against an H9N2 bird flu. Clinical trials are completed and results are expected in early 2005.



- NIAID conducts a Phase II study to evaluate the [first trivalent baculovirus-based recombinant influenza virus vaccine](#). The vaccine, produced by Protein Sciences, was evaluated in healthy elderly subjects and was shown to be safe and well tolerated. The vaccine may also provide a suitable cell culture system for the large-scale production of influenza virus vaccines as a viable alternative to the production of the vaccines in eggs.

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- In February, two cases of avian influenza (**H5N1**) infection occur in a Hong Kong family that had traveled to southern China, resulting in one death. Less than two months later, a widespread outbreak of **H7N7** occurs on poultry farms in the Netherlands, killing a veterinarian. Cases of mild disease or conjunctivitis associated with **H7N7** are reported in more than 80 other individuals during this outbreak. ([WHO](#)) Later the same year in New York, a patient is admitted to a hospital in November with respiratory symptoms, recovers, and goes home after a few week. Subsequent confirmatory tests conducted in March 2004 show that the patient had been infected with an **H7N2** avian influenza virus. ([CDC](#)). In December, Korea reports an outbreak of avian influenza in chickens, verified to be **H5N1**, and more than one million chickens are infected. ([WHO](#)). That same month, a child in Hong Kong is infected with **H9N2** and recovers. ([WHO](#))

2004



- NIAID supports animal influenza training courses in Hong Kong and Japan.

- In 2004, NIAID awards **challenge grants** to six industry partners to develop new diagnostics, therapeutics, and vaccines against influenza virus:



- 1) Shire Biologics, Inc., for the **development of a tissue culture-derived influenza vaccine** (PI, Jonathan Seals).



- 2) Delsite Biotechnologies, Inc., for the **development of an inactivated intranasal influenza vaccine** (PI, Yawei Ni).



- 3) Biota Scientific Management, for the **development of a novel long-acting influenza antiviral drug (neuraminidase inhibitor)** (PI, Jane Ryan).



- 4) Columbia University/Griffin Analytical Technologies for the **development of new diagnostics** (PI, Walter Lipkin) to discriminate between several pathogens including influenza and SARS.



- 5) University of Texas at Austin/Radix BioSolutions for the **development of new diagnostics** (PI, Steven Kornguth) to discriminate between several pathogens including influenza and SARS.

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- 6) BD Diagnostics (PI, Tobin Hellyer), for the development of new diagnostics to discriminate between several pathogens including influenza and SARS.



- **NIAID awards contracts to Aventis Pasteur and Chiron Corporation** to support the production of an investigational vaccine based on a strain of **H5N1** avian influenza. The vaccines will be tested for safety and immunogenicity in Phase I and Phase II clinical trials conducted by NIAID's Vaccine and Treatment Evaluation Units (VTEUs). Studies will test the vaccine in healthy adults first with subsequent studies planned in children and the elderly.



- NIAID awards a grant to Washington University for the **M2 Peptide Based Vaccines Against Influenza** project (PI, Andrew Pekosz). The project's goal is to generate an influenza vaccine with activity against a variety of virus strains using the M2 protein.



- NIAID **issues a task order** to Chiron Corporation for the production of an investigational **H9N2** vaccine. Chiron will produce up to 40,000 doses of vaccine with and without the MF59 adjuvant for clinical trials that will be conducted by NIAID, slated for 2005.



- NIAID awards a grant to Innoject, Inc. (PI, Richard Gillespie) for the development of an **auto-injector vaccine delivery system**. Not only could the device be easy to use, but it could be broadly distributed in the event of an influenza pandemic. The clinical trial of the new delivery system, led by Dr. William Barr of Virginia Commonwealth University, will be conducted during the 2005-2006 flu season.



- The Department of Health and Human Services (DHHS) issues the **National Pandemic Influenza Preparedness Plan**, designed to provide guidance to national, state, and local policy makers and health departments for public health preparation and response in the event of pandemic influenza outbreak. As outlined in **Annex 10** of the Plan, the largest body of pandemic influenza research is supported by NIAID.



- DHHS **issues a contract to Aventis Pasteur** to manufacture and store two million doses of avian influenza **H5N1** vaccine.



- DHHS **issues a contract to Sanofi Aventis Inc.**, to secure future egg supply for flu vaccines in the event of a pandemic flu outbreak or future vaccine shortages and to obtain initial investigational lots of pandemic influenza vaccines for clinical trials.



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- NIAID awards a grant to Nexbio, Inc., to develop [novel therapeutics for pandemic and epidemic flu](#) (PI, Fang Fang). This novel class of fusion proteins may be capable of blocking infections by all strains of influenza viruses.



- NIAID awards a grant to the Mount Sinai School of Medicine of NYU (PI, Adolfo Garcia-Sastre) for the [molecular and biological characterization of the "Spanish Flu"](#) to examine the reason behind the high lethality of the 1918 influenza pandemic. ([Related Article](#))



- NIAID awards a grant to the Wadsworth Center entitled "[Discovery of a Novel Promoter in Pathogenic Influenza](#)" (PI, David Wentworth) to further understand the molecular mechanisms of pathogenesis in avian influenza viruses.



- NIAID awards a grant to St. Jude Children's Research Hospital to study [combination chemotherapy for pandemic influenza](#) (PI, Robert Webster) and test the hypothesis that combination therapy with two classes of anti-influenza drugs offers clinical and strategic advantages in the event of an influenza pandemic.



- NIAID launches the [Influenza Genome Sequencing Project](#) that will put influenza sequence data rapidly in hands of scientists, enabling them to further study how influenza flu viruses evolve, spread, and cause disease and may ultimately lead to improved methods of detection, treatment, and prevention. This project is a collaborative effort among NIAID, NCBI/NLM, CDC, St. Jude Children's Research Hospital and others. ([Sequencing Information](#))



- NIAID issues a [notice to the NIH Guide](#) highlighting its interest in receiving grant applications focused on influenza research.



- In January 2003, outbreaks of **H5N1** in Asia were reported by the Global Health Organization. The outbreaks continued ongoing among bird populations in a number of Asian countries and human cases are reported in Thailand and Vietnam throughout early 2004. ([WHO](#)). In Canada, **H7N3** infections in poultry workers in Canada are associated with an **H7N3** outbreak among poultry in February. The H7N3-associated illnesses consist of eye infections. ([CDC](#)). In Vietnam, a 16-year-old girl in Vietnam is infected with **H5N1** in December. The case coincides with several fresh poultry outbreaks reported in southern provinces. ([WHO](#))

2005



- In early 2005, NIAID expands its [Pandemic Preparedness in Asia contract](#) to include surveillance activities in Vietnam, Thailand and Indonesia.

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- In March, NIAID [begins recruitment for a clinical trial](#) to investigate the safety of an H5N1 avian influenza vaccine produced by sanofi-pasteur (formely Aventis Pasteur). Clinical sites, part of the NIAID VTEU network, will test the vaccine's safety and ability to generate an immune response in 450 healthy adults.



- In 2005, cases of H5N1 avian influenza are confirmed in Cambodia, Indonesia, Thailand, and Vietnam. By November 14th, 64 of 126 confirmed cases have been fatal. ([WHO](#))