Respiratory Viruses

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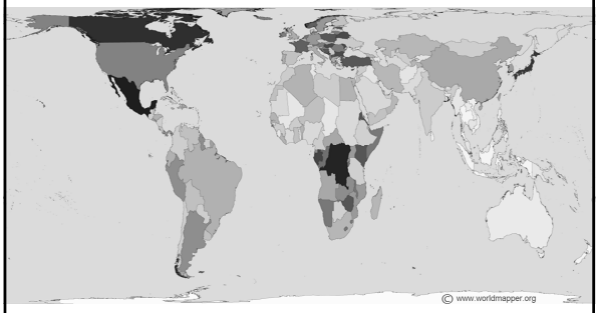
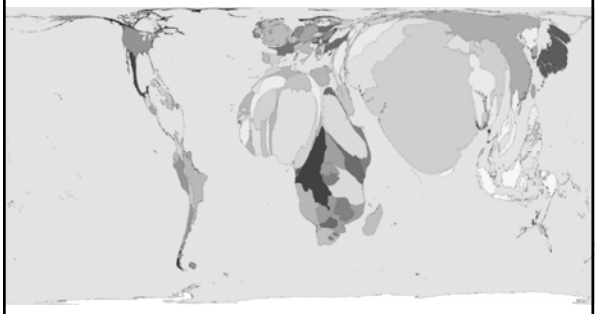
Viral respiratory illness

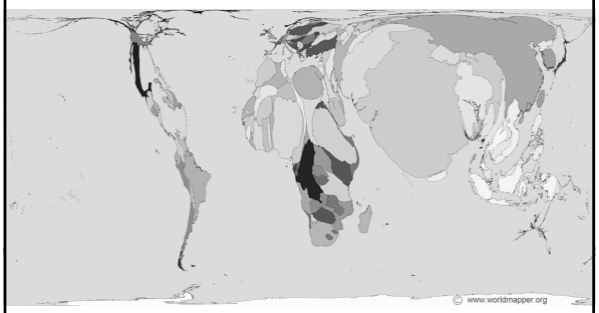
- Exceedingly common causes of disease throughout life
  - Frequently seasonal
  - Often mild/self limited
  - Tremendous economic cost
  - Contribute to burden of antibiotic resistance (inappropriate prescribing)
- Covering two of the most important here:
  - Influenza (seasonal and pandemic)
  - Respiratory syncytial virus (RSV)
- Many other causes of viral respiratory disease
  - Parainfluenza
  - Rhinoviruses
  - Human metapneumovirus
  - Coronaviruses (including SARS coronavirus)
  - Adenoviruses
  - Enteroviruses



Childhood respiratory infection deaths



Poverty



Respiratory syncytial virus (RSV)

- Ubiquitous infectious disease
  - essentially all children infected by age 2
  - world-wide epidemics
  - marked seasonality
  - risk for severe disease in:
    1. very young infants
    2. prematurity
    3. immunocompromised states
    4. congenital heart or lung diseases
- 1-2% of healthy infants are hospitalized for RSV
  - >50,000 childhood hospitalizations/yr (U.S.)
  - most common cause of viral respiratory infection in childhood

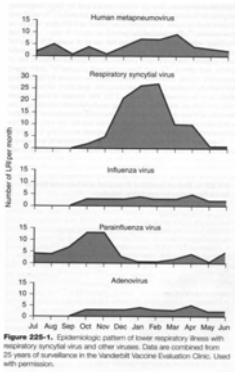
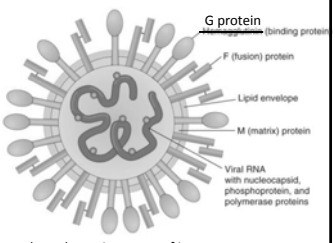


Figure 225-1. Epidemiologic pattern of lower respiratory illness with respiratory syncytial virus and other viruses. Data are combined from 25 years of surveillance in the Vanderbilt Vaccine Evaluation Clinic. Used with permission.

RSV: Pathogenesis

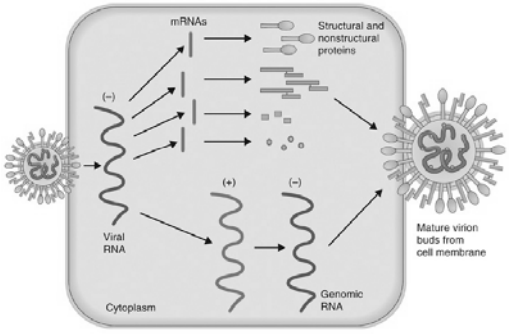
- Member of *Paramyxoviridae*
  - other members include metapneumovirus, parainfluenza, measles, mumps
  - ssRNA, negative-sense, enveloped viruses
  - viral genome encodes 11 proteins
    - N = nucleoprotein
    - P = phosphoprotein
    - L = large polymerase protein
    - M = matrix protein
    - M2-1, M2.2 = regulatory proteins
    - F, G = surface glycoproteins



- Glycoproteins F and G mediate attachment and are the main targets of immune response

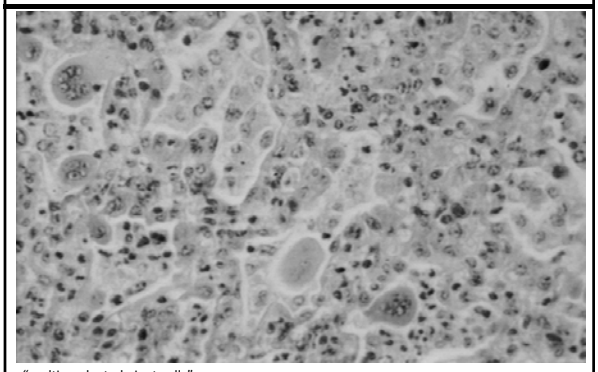
From Schaechter's Mechanisms of Microbial Disease; 4th ed. Engleberg, DiRita & Dermody; Lippincott, Williams & Wilkins; 2007; Fig. 34-1

RSV life cycle



From Schaechter's Mechanisms of Microbial Disease; 4th ed. Engleberg, DiRita & Dermody; Lippincott, Williams & Wilkins; 2007; Fig. 34-2

RSV life cycle: syncytia



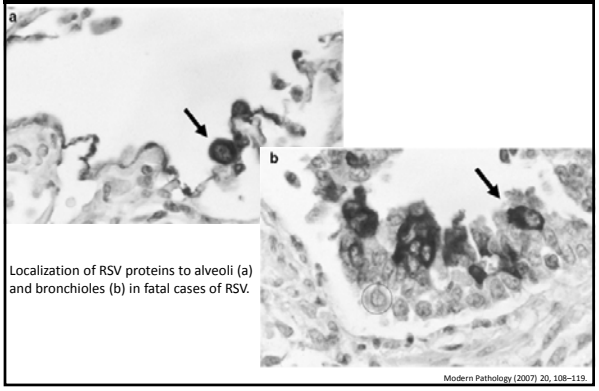
"multi-nucleated giant cells"

pathmicro.med.sc.edu/virol/respsyn.jpg

RSV Pathogenesis

- replicates in cells of nasopharynx
- transmission by respiratory secretions
  - survival on fomites (tabletops, toys, your stethescope)
  - very, very common cause of hospital-acquired infections
- may spread to lower airways (bronchioles, alveoli)
  - most damage in small airways
  - clinical syndrome: **RSV bronchiolitis**
  - may spread to lower airways: **RSV pneumonia**

RSV detection in pathological specimens



Localization of RSV proteins to alveoli (a) and bronchioles (b) in fatal cases of RSV.

Modern Pathology (2007) 20, 108–119.

Clinical signs of RSV

- incubation period = 3-6 days
- duration of uncomplicated RSV = 1-3 weeks
- progression of clinical syndromes
  - upper respiratory tract disease
    - rhinorrhea and congestion ± fever
  - croup (laryngotracheobronchitis)
    - cough, stridor
  - bronchiolitis (about 50% of cases)
    - cough, wheeze; air trapping
    - crackles, wheezes on examination
  - pneumonia
    - more severe respiratory distress, hypoxia
  - otitis media
  - apnea (infants)
- no viremic phase, risk of invasive disease is very low

Immune response to RSV

- Single serotype but two "subgroups" (A and B) exist – unclear significance
- Immunity is incomplete – reinfection is common
- Innate recognition of RSV – surfactant proteins, toll-like receptors
- Cell-mediated immunity
  seems to be important for clearance/resolution – prolonged in compromised patients
- Antibody-mediated immunity is directed at F and G glycoproteins
  reinfection possible even with high antibody titers
- In general, viral replication is low to undetectable during the symptomatic phase of illness. Much of the pathology is due to the immune response.

Diagnosis of RSV

- Clinical diagnosis
- Viral culture
  Specimens produce cytopathic effect (syncytia formation) within 3-7 days.
- Rapid antigen detection
  Very useful in ER, hospital for infection control
- RT-PCR
  Higher sensitivity than rapid antigen detection but not widely available

Treatment of RSV

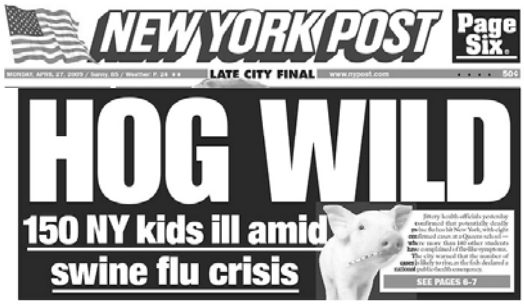
- Treatment is largely supportive: supplemental O2, secretion management, monitoring for apnea, intubation/ventilation if needed
- Bronchodilators in RSV bronchiolitis: controversial
- Steroids in RSV bronchiolitis: no benefit
- Ribavirin: only in severe cases in immunocompromised. Unclear benefit.

Prevention of RSV

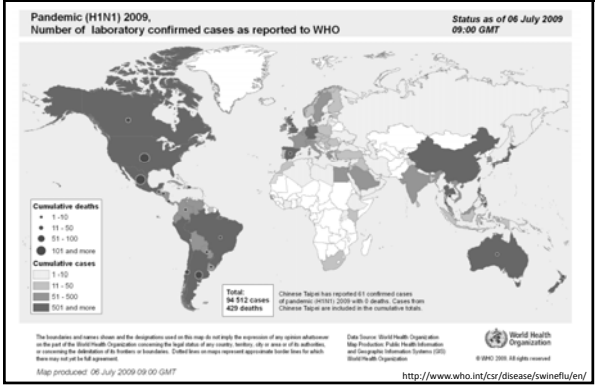
- Infection control
  - o handwashing
  - o cleaning of potential fomites
  - o isolation of cases
- Antibody-based prophylaxis in high-risk infants
  - o Hyper-immune globulin (RSV-IGIV)
  - o Monoclonal antibody (palivizumab)
    targets F glycoprotein
    monthly doses to highest risk population during RSV season
- Vaccine prospects
  - o Traditional approaches have failed: inactivated vaccine gave incomplete immunity (insufficient TLR activation) and led to more severe disease
  - o Live-attenuated vaccine?
  - o Maternal vaccination?

Influenza

- *



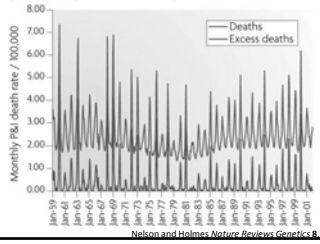
Pandemic Influenza 2009



http://www.who.int/csr/disease/swineflu/en/

Influenza

- Most important viral respiratory disease world-wide
- Annual seasonal epidemics despite effective vaccine
- >36,000 annual deaths, 200,000 hospitalizations in U.S.
- Severe illness in children, elderly, pregnancy, immunocompromised
- Pandemic potential



Nelson and Holmes *Nature Reviews Genetics* **8**, 196–205

Clinical signs of influenza

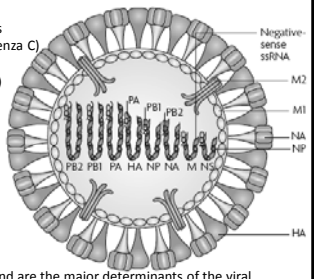
- Fever (may be very high)
- Chills
- Headache
- Myalgias
- Arthralgias
- Dry cough
- Nasal discharge

} "flu-like illness"

- Young children may have atypical course
  "sepsis-like" syndrome, GI symptoms, croup/bronchiolitis, otitis media
- Complications: pneumonia, bacterial superinfection common
  myocarditis, encephalitis, myositis, Reye syndrome rare
- Incubation period = 1-5 days
- Duration of illness = 4-8 days of acute illness, 1-2 weeks convalescence

Influenza: Pathogenesis

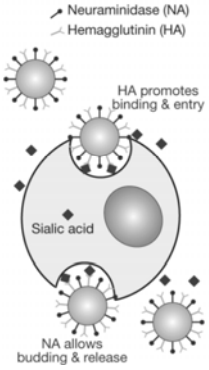
- member of *Orthomyxoviridae*
  - o ssRNA, negative-sense, enveloped virus
  - o viral genome in 8 segments (7 for influenza C)
    - HA = hemagglutinin
    - NA = neuraminidase (influenza A, B)
    - PB1, PB2, PA = polymerases
    - NP = nucleocapsid
    - L = large polymerase protein
    - M1 = associated with NP
    - M2 = ion channel (influenza A only)
    - NS = non-structural proteins



- HA, NA are the immunodominant antigens and are the major determinants of the viral serotype (e.g. H1N1 vs. H3N2).
- Nomenclature: Type/host species (human default)/location/year (HA/NA type)
  Influenza A/California/2009 (H1N1)

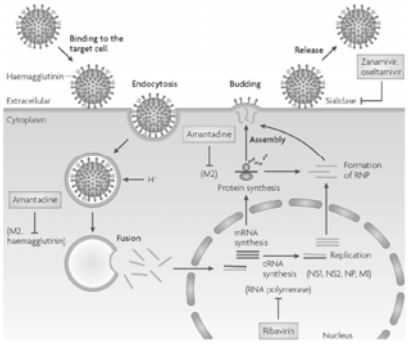
Nature Reviews

Influenza virus life cycle



CSHL PRESS NCSU *Essentials of Glycobiology*

Influenza virus life cycle



Nature Reviews | Drug Discovery

Nature Reviews

Influenza: Pathogenesis

- Influenza virus infects columnar epithelial cells of respiratory tract.
- Replication early (1-3 days), shedding for ~7 days
- Destruction of epithelial cells, increased mucus production, ciliary stasis
- Local cytokine production
- Induces innate and adaptive immune response – both important to clearance. Antibody responses to HA, NA important for future immunity.

Influenza: antigenic shift and drift

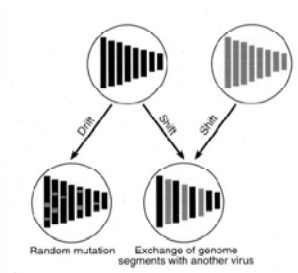


Figure 1.20: Principles of antigenic drift and shift. Colored bars represent novel RNA sequences.

Harper, Molecular virology

Influenza: antigenic shift and drift

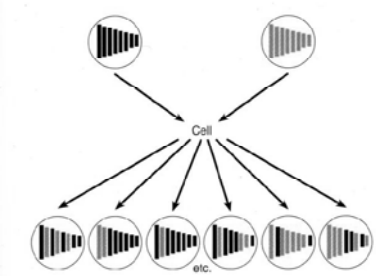
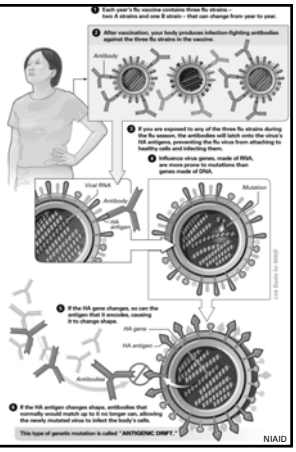


Figure 1.21: Principles of antigenic shift.

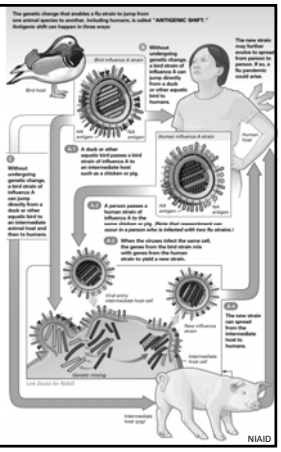
Harper, Molecular virology

Antigenic drift (due to ongoing accumulation of mutations) leads to changes in HA and NA that limit the efficacy of antibody developed in response to prior year's influenza strains.



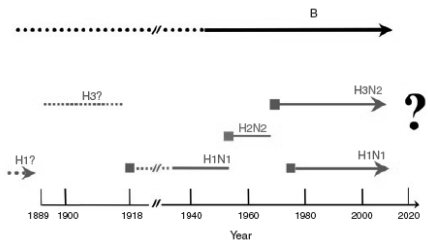
NIAID

Antigenic shift (due to reassortment of influenza genes during simultaneous infection of a single cell with multiple viruses) leads to large changes in the viral genome and may result in novel strains.



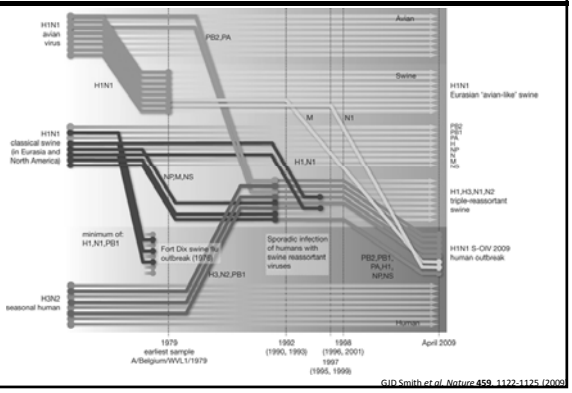
NIAID

From antigenic shift to pandemic



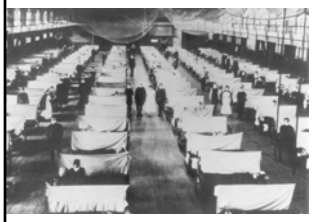
Novel viruses must replicate in human cells, be transmissible between humans, and be associated with little pre-existing immunity in populations in order to have pandemic potential.

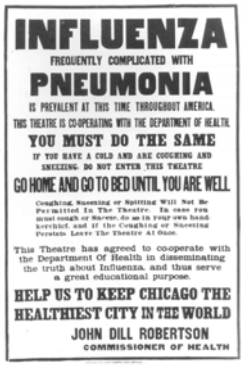
From antigenic shift to pandemic



GJD Smith *et al. Nature* **459**, 1122-1125 (2009)

1918 influenza pandemic





INFLUENZA

FREQUENTLY COMPLICATED WITH

PNEUMONIA

IS PREVALENT AT THIS TIME THROUGHOUT AMERICA.

THIS THEATRE IS CO-OPERATING WITH THE DEPARTMENT OF HEALTH.

YOU MUST DO THE SAME

IF YOU HAVE A COLD AND ARE COUGHING AND SNEEZING DO NOT ENTER THIS THEATRE

GO HOME AND GO TO BED UNTIL YOU ARE WELL.

Coughing, Sneezing or Spitting Will Not Be Permitted In The Theatre. In case you must cough or Sneeze, do so in your own handkerchief, and if the Coughing or Sneezing Persists Leave The Theatre At Once.

This Theatre has agreed to co-operate with the Department Of Health in disseminating the truth about Influenza, and thus serve a great educational purpose.

HELP US TO KEEP CHICAGO THE HEALTHIEST CITY IN THE WORLD

JOHN DILL ROBERTSON

COMMISSIONER OF HEALTH

1918 influenza pandemic

The Influenza-Pneumonia Pandemic in the American Army Camps during September and October, 1918: MAJOR GEORGE A. SOPER. 451

THE pandemic of influenza which has been prevalent in Europe and which swept over the United States in the spring of 1918, causing much suffering and disability in industrial plants and loss of training time in American army camps, reappeared with greatly intensified violence in September and October. Within a month of its recognition it had been reported from nearly every quarter of the United States, civil and military.

CASES OF INFLUENZA AND PNEUMONIA AND DEATHS EACH WEEK AMONG ALL TROOPS IN THE UNITED STATES FOR THE PERIOD, SEPTEMBER 12–OCTOBER 18, 1918

	September		October			Total
	20	27	4	11	18	
Influenza . .	10,094	37,493	88,478	90,303	48,287	274,745
Pneumonia.	758	4,313	8,655	17,882	14,768	46,286
Deaths	96	951	2,275	6,005	5,289	14,616

SCIENCE

Friday, November 8, 1918

CONTENTS

THE INFLUENZA PNEUMONIA PANDEMIC IN THE AMERICAN ARMY CAMPS DURING SEPTEMBER AND OCTOBER. 451

Bacterial pneumonia following influenza

MMWR

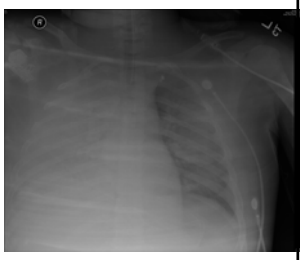
Morbidity and Mortality Weekly Report

Weekly April 13, 2007 / Vol. 56 / No. 14

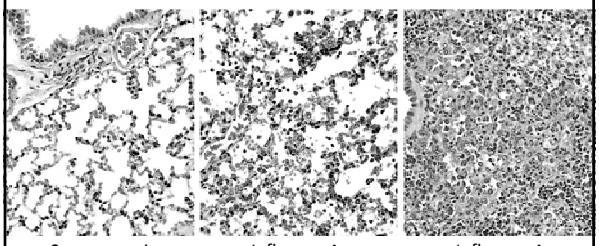
Severe Methicillin-Resistant *Staphylococcus aureus* Community-Acquired Pneumonia Associated with Influenza — Louisiana and Georgia, December 2006–January 2007

MRSA pneumonia following influenza

- 14 year old boy, previously well, unvaccinated against influenza
- Several days of URI symptoms, mild improvement, then high fevers/dyspnea
- To outside ER with severe respiratory distress – influenza A positive
- Failed conventional ventilation, transferred to CHONY for ECMO
- Septic shock, purpura fulminans, death within 24 hrs of transfer
- Post-mortem findings consistent with necrotizing pneumonia, MRSA (USA300 strain) cultured from airway, lungs, pleural fluid.



Synergy between influenza and *S. pneumoniae*



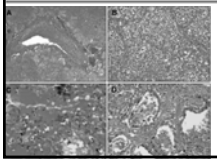
S. pneumoniae | Influenza A | Influenza A + *S. pneumoniae*

McCullers et al. *JID* 2002.

New thoughts about the 1918 flu

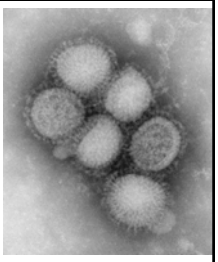
Table 1. Bacterial culture results in autopsy series involving 96 postmortem cultures of lung tissue from victims of the 1918–191 influenza pandemic.

Type of autopsy series	No. of results	No. (%) of cultures from which organism was recovered, by organism: *Streptococcus pneumoniae*	*Streptococcus hemolyticus*	*Staphylococcus aureus*	*Diplococcus intracellulare meningitidis*	Mixed pneumopathogens	*Bacillus influenzae*	Other bacteria	No growth
All military (n = 60)	3515	**855 (24.3)**	615 (17.5)	263 (7.5)	40 (1.1)	707 (20.1)	387 (11.0)	484 (13.8)	164 (4.7)
All civilian (n = 36)	1751	380 (21.7)	281 (16.0)	164 (9.4)	1 (<0.1)	**398 (22.7)**	132 (7.5)	339 (19.4)	56 (3.2)
All military and civilian (n = 96)	5266	**1235 (23.5)**	896 (17.0)	427 (8.1)	41 (0.8)	1105 (21.0)	519 (9.9)	823 (15.6)	220 (4.2)
All higher- quality military and civilian* (n = 68)	3074	712 (23.2)	553 (18.0)	238 (7.7)	21 (0.7)	**828 (26.9)**	144 (4.7)	353 (11.5)	225 (7.3)
Predominance of pneumopathogens not confirmed (n = 14)	1115	209 (18.7)	132 (11.8)	52 (4.7)	0 (0.0)	24 (2.2)	210 (18.8)	**402 (36.1)**	86 (7.7)



Predominant Role of Bacterial Pneumonia as a Cause of Death in Pandemic Influenza: Implications for Pandemic Influenza Preparedness

Diagnosis of influenza

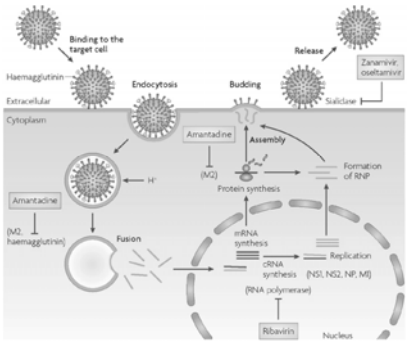


- Clinical diagnosis
  - Useful during epidemic, but important to remember that other respiratory viruses may circulate simultaneously.
- Viral culture
  - Sample respiratory secretions, look for cytopathic effect on tissue culture cells.
- Rapid antigen testing (solid-phase)
  - o Rapid tests for influenza A and B (~15 min)
  - o Very useful in ER, office settings
  - o Sensitivity may only be 50-70%
- PCR testing
  - o Useful for novel H1N1 strain
  - o Not universally available

Treatment of influenza

- Adamantanes (amantidine, rimantidine)
  - o effective for influenza A only
  - o target M2 ion channel, interfere with uncoating
  - o resistance common, may develop on therapy
  - o prophylaxis (both) and treatment (amantidine only)
- Neuraminidase inhibitors (zanamivir, oseltamivir)
  - o effective for influenza A and B
  - o resistance emerging, including among novel H1N1 strains
  - o prophylaxis and treatment
  - o early initiation of therapy (< 72 hrs) most important for efficacy
- Ribavirin (rarely used)
  - o severe disease with virus resistant to other agents
  - o combination therapy in immune compromised with prolonged shedding

Treatment of influenza



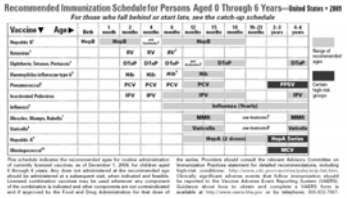
Nature Reviews | Drug Discovery

Prevention of influenza: vaccination

- Vaccine formuations change annually
  - o includes 2 A strains, 1 B strain – prediction based on circulating viruses
  - o efficacy 60-90%
  - o changes based on age of patient, match of vaccine to actual virus
- Trivalent, inactivated vaccine (TIV) – intramuscular
  - o whole influenza virus grown in eggs
  - o formalin-fixed whole virus or "split-virus" formulations
  - o 1 dose/year except for children under age 9 getting first vaccination (2 doses)
  - o immunity in ~1-2 weeks, lasts ~6 months
- Live, attenuated vaccine (LAIV) – intranasal ("the squirty")
  - o 6 genes from cold-adapted virus reassorted with known HA, NA genes
  - o for healthy people 5-49 years old
  - o better acceptability
  - o mild increase in risk of airway reactivity (wheezing) following vaccination
  - o small but finite risk of transmission

Who gets influenza vaccine?

- You! (health care workers)
- Children 6 months – 18 years; adults > age 50
- Contacts of children < 6 months or other high risk people
- Pregnant women
- Chronic medical conditions
- Aspirin therapy
- Chronic care facilities
- Anyone who wants it!


Recommended Immunization Schedule for Persons Aged 0 Through 6 Years—United States • 2009

For those who fall behind or start late, see the catch-up schedule

Vaccine ▼ Age ►	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B[1]	HepB		HepB			HepB					
Rotavirus[2]			RV	RV	RV[2]						
Diphtheria, Tetanus, Pertussis[3]			DTaP	DTaP	DTaP			DTaP			DTaP
Haemophilus influenzae type b[4]			Hib	Hib	Hib[4]		Hib				
Pneumococcal[5]			PCV	PCV	PCV		PCV			PPSV	
Inactivated Poliovirus			IPV	IPV			IPV			IPV	
Influenza[6]						Influenza (Yearly)					
Measles, Mumps, Rubella[7]							MMR		see footnote[7]		MMR
Varicella[8]							Varicella		see footnote[8]		Varicella
Hepatitis A[9]						HepA (2 doses)			HepA Series		
Meningococcal[10]									MCV		

Range of recommended ages

Certain high-risk groups

This schedule indicates the recommended ages for routine administration of currently licensed vaccines, as of December 1, 2008, for children aged 0 through 6 years. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. Providers should consult the relevant Advisory Committee on Immunization Practices statement for detailed recommendations, including high-risk conditions: http://www.cdc.gov/vaccines/pubs/acip-list.htm. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at http://www.vaers.hhs.gov or by telephone, 800-822-7967.

Who shouldn't get influenza vaccine?

- Inactivated vaccine (TIV)
  - o Children under 6 months
  - o Anaphylactic reaction to eggs or other vaccine components
- Live-attenuated vaccine (LAIV)
  - o Children less than 5 years or adults > 50 years
  - o Anaphylactic reaction to eggs or other vaccine components
  - o Immunocompromised or other high risk for severe influenza
  - o Currently receiving salicylates (aspirin)
  - o History of Guillain-Barré syndrome
  - o Asthma
  - o Pregnant women

Encourage your patients, colleagues, friends, and family to be vaccinated!

Prevention of influenza: chemoprophylaxis

- People at high risk of complications who are close contacts of confirmed cases of influenza.
- Health care workers who had unprotected close contact exposure to a confirmed case of influenza.
- Because novel H1N1 is resistant to the adamantanes, neuraminidase inhibitors are the only current option for prophylaxis.

Agent, group		Treatment	Chemoprophylaxis
Oseltamivir			
Adults		75-mg capsule twice per day for 5 days	75-mg capsule once per day
Children ≥ 12 months	15 kg or less	60 mg per day divided into 2 doses	30 mg once per day
	16-23 kg	90 mg per day divided into 2 doses	45 mg once per day
	24-40 kg	120 mg per day divided into 2 doses	60 mg once per day
	>40 kg	150 mg per day divided into 2 doses	75 mg once per day
Zanamivir			
Adults		Two 5-mg inhalations (10 mg total) twice per day	Two 5-mg inhalations (10 mg total) once per day
Children		Two 5-mg inhalations (10 mg total) twice per day (age, 7 years or older)	Two 5-mg inhalations (10 mg total) once per day (age, 5 years or older)

CDC

Prevention of influenza: non-vaccine measures

Public health measures: 1918

TREASURY DEPARTMENT
UNITED STATES PUBLIC HEALTH SERVICE
HUGH S. CUMMING, SURGEON GENERAL

MUNICIPAL ORDINANCES, RULES, AND REGULATIONS PERTAINING TO PUBLIC HEALTH 1917-1919

COMPILED BY
JASON WATERMAN, LL. B.
AND
WILLIAM FOWLER, LL. B.
United States Public Health Service

SUPPLEMENT No. 40
TO THE
PUBLIC HEALTH REPORTS

BERKELEY, CALIF.

Influenza—Notification of Cases. (Ord. 609, effective Jan. 17, 1919.)

SECTION 1. It shall be the duty of any and all physicians, surgeons, practitioners, healers, and nurses practicing in the city of Berkeley, upon discovery of any patient afflicted with influenza, in any of its forms, to at once report in writing to the health officer of said city of Berkeley, the name, address, age, and sex of such patient, and the date of onset, to the end that such measures be adopted by said health officer as shall correctly inform the attendants and relatives of said patient, concerning the proper methods whereby the further spread of the same may be inhibited.

SEC. 2. A violation of this ordinance shall be deemed a misdemeanor and punishable by a fine not exceeding $50, or by imprisonment not exceeding 30 days, or by both such fine and imprisonment.

Influenza—Wearing of Gauze Masks Required in Certain Cases. (Ord. 610, effective Jan. 17, 1919.)

SECTION 1. During the period of the epidemic of influenza, which is now

BOONE, IOWA.

Influenza and Pneumonia—Notification of Cases. Measures to Prevent Spread of Influenza. (Reg. Bd. of H., Dec. 5, 1918.)

1. That from and after this date, all schools of the city, all churches, all pool halls, card rooms, theaters, moving picture shows, houses of entertainments and amusements, district court, except for the hearing of equity cases and matters tryable to the court without witnesses, dances, lodges, banquets, social and religious gatherings, and all other public gatherings of every kind and description whatsoever, be closed and prohibited.
2. That all mercantile houses and other places of business of the city, including five and ten-cent stores, shall not permit more than 12 patrons or persons in any store or place of business at any one time, in addition to the regular employees, and no place of business shall remain open between the hours of 7 p. m. and 7 a. m. on any day, excepting only eating houses, hotels, restaurants and the prescription departments of drug stores, and no loafing shall be permitted therein.
3. That all funerals shall be private and that no public funerals shall be held.
4. That no special sales of any kind shall be advertised or held by any of the merchants in said city.
5. That all physicians practicing medicine within the corporate limits of said city shall within 12 hours from the service of notice of these regulations upon him, report to the mayor of said city, or to the clerk thereof, all existing cases of colds, grippe, la grippe, influenza, Spanish influenza, pneumonia, and all similar diseases or ailments within the knowledge as such physicians.