340.721 Epidemiologic Inference in Public Health I

PRE-Activity Questions:
Experimental Studies: Vaccine Efficacy

The Activities provide experience in applying epidemiologic methods, interpreting findings, and drawing inferences. Activities will be discussed during the LiveTalks. Students are expected to work with their assigned Course Group prior to the start of each LiveTalk.

Prior to each Activity, students are to complete the corresponding set of PRE-Activity Questions. Each set of PRE-Activity Questions consists of 10 graded multiple choice questions. The graded multiple choice questions are to be completed via CoursePlus by the date and time listed in CoursePlus. PRE-Activity Questions prepare you for a productive and collaborative experience during the Activities.

Expectations for the PRE-Activity Questions

1. *Individually, read and attempt to answer all PRE-Activity Questions.*

2. *Meet or communicate with fellow students discuss challenging concepts, questions and compare answers. You may refer to their course materials and are strongly encouraged to collaborate with fellow students to complete the PRE-Activity Questions.*

3. *PRE-Activity Questions are due to Courseplus by the date listed on the syllabus. Although group collaboration is encouraged to complete the PRE-Activity Questions, each student must individually submit the PRE-Activity Questions.* ***Without exception, no credit will be given for submitting the PRE-Activity Questions after the due date****. The lowest PRE-Activity grade will be dropped when calculating the overall course grade.*

Motivation
In this assignment, you will evaluate two experimental studies related to vaccine efficacy and effectiveness. Some motivating questions to think about are: How do you test the effect of an intervention? What is the difference between effectiveness and efficacy? How can bias be minimized in epidemiologic study design?

This assignment corresponds to:
Lectures: Analytic Studies and Clinical Trials
Readings: Gordis text (5th ed.) Chapters 7 and 8

Introduction
The purpose of this problem is to examine the epidemiology of influenza and to illustrate methods used in the design, conduct and the interpretation of an experimental field trial of a vaccine. Particular emphasis is placed on the need for controls, the importance of random allocation of participants to vaccine or placebo group, and the double masked nature of the trial.

Concepts covered:
- Development of the influenza vaccine
- Clinical trial characteristics
- Randomization
- Masking (blinding)
- Use of a placebo
- Calculation of vaccine efficacy
- Efficacy vs. effectiveness
- Generalizability
- Ethics of a clinical trial

Learning Objectives:
1. Describe stages in vaccine development.
2. Identify a study population.
3. Define the intervention group.
4. Define the control or comparison group.
5. Compare the experimental and control groups.
6. Examine adverse reactions to the vaccine.
7. Calculate vaccine efficacy and background rates of disease.
8. Identify features of the randomized controlled trial (e.g., double-masked design, use of a placebo, randomization).
9. Identify advantages, limitations, and appropriate use of randomized controlled trials.

A. BACKGROUND

Influenza is an acute viral disease of the respiratory tract whose primary symptoms include: cough, fever, headache, myalgia (muscular pain), coryza (inflammation of nasal mucous membranes), sore throat and prostration (exhaustion or weakness). Influenza epidemics in the United States occur almost every winter (November – March). The disease can spread rapidly, causing widespread morbidity. Serious complications may result, especially among the elderly and those with pre-existing medical conditions. Clinical attack rates during epidemics are between 10-30% in the general population.

Pandemics of influenza tend to appear at irregular intervals. In the 20th century, pandemics occurred in 1918, 1957 and 1968. In 1933, British investigators Smith, Andrews and Laidlaw showed that a virus caused influenza. During World War II, an influenza vaccine was developed and tested.

Further research showed that the influenza virus mutated unpredictably. Influenza strains were classified into three main groups: A, B and C. Two antigens (proteins that create an immune response) in the outer coat of the virion, the hemagglutinin (H) and the neuraminidase (N), tended to vary from outbreak to outbreak, sometimes with only minor changes (called antigenic drift) and sometimes with major changes (called antigenic shift). Flu vaccines are much less effective when an antigenic shift occurs; since this happens rapidly, the current vaccine is not effective against the new virus, the population does not have immunity from previous exposure, and there is no time to create a new vaccine. Antigenic shift in circulating strains of influenza virus can lead to an influenza pandemic.

Influenza circulates at various times throughout the year around the world. To create each year's influenza vaccine, scientists try to forecast the strains that will be circulating during the following flu season. The three most problematic strains predicted to spread the following year (two Type A strains and one Type B) are selected to create a trivalent (3 component) vaccine. These strains are further labeled by the forms of hemagglutinin and neuraminidase contained in their outer coat (*e.g.*, H3N2) and by the location of their isolation (*e.g.*, Panama). The efficacy of these vaccines is limited by the uncertainty over the specific strain of virus that will be circulating in the next season. Typically, these vaccines have been known as the "flu shot," an inactivated vaccine (containing killed virus) that is delivered through a needle, usually in the arm.

Recently, live, attenuated (weakened) influenza virus vaccines (which can be delivered intranasally) have been developed and tested as an alternative to intramuscular injection. In addition to having more appeal because of the delivery method, these vaccines result in infection with live virus strains and may therefore induce a more effective immune response.

This exercise will explore the epidemiologic characteristics of influenza and address findings of a study to assess the safety and effectiveness of live, attenuated influenza virus vaccine (LAIV).

B. Stages in Vaccine Development and Study Design

The development of a new vaccine must go through the following stages of research and field study[1]:

Preclinical Studies. Animal models are used to determine the optimal routes of administration, identify appropriate dosing schedule, and evaluate vaccine safety, which includes making a list of vaccine-induced toxicities. If the potential benefit is deemed to outweigh potential harms, the vaccine proceeds from these animal models to subsequent testing in human studies.

Phase I: Dose Finding and Safety. Early vaccine studies in humans are conducted to evaluate vaccine dose and safety, and to assess whether the vaccine is biologically active. These studies are conducted in healthy, adult volunteers. Childhood vaccines are first tested in healthy adults and older children, prior to testing in infants.

Phase II: Safety and Immunogenicity Trials. The primary endpoints of these studies are safety, benefit and evidence of efficacy. The vaccine is tested in healthy persons representing the population for which the vaccine is indicated.

Phase III: Comparative Efficacy Trials. These studies determine the impact of vaccination on prevention of infection, and begin to assess the feasibility of administering vaccinations in at-risk populations. They are conducted pre-licensure. Involving large numbers of susceptible persons, the primary study design for determining vaccine efficacy is the randomized, double-masked, placebo-controlled trial.

Vaccine Effectiveness and Monitoring Adverse Events. After licensure, vaccines are distributed among various populations at risk of disease who will vary in age, infirmity, access to health care and risk of exposure. At this point, observational studies play an important role in assessing vaccine effectiveness. A significant decline in the overall incidence of disease is one indicator that the vaccine itself and the immunization campaign have contributed to the prevention of disease. Comparative studies continue to collect information on adverse events and additional post-licensure monitoring is achieved through the use of surveillance systems.

[1] Strathdee and Loughlin, "Vaccines". In: Nelson, Williams, and Graham. Infectious Disease Epidemiology, 2000, Aspen Publishing.

C. Effectiveness of Intranasal Influenza Virus Vaccine

Reference: Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults: a randomized controlled trial. Nichol KL, Mendelman PM, Mallon KP et al. *JAMA*. 1999 Jul 14;282(2):137-44.

Objective

"To assess the safety and effectiveness of intranasally administered trivalent, live, attenuated influenza virus (LAIV) vaccine for reducing illness, absenteeism, and health care use among healthy, working adults."

Study Population

"Participants were enrolled from 13 sites across the continental United States between mid-September and mid-November 1997….Persons were eligible if they were 18 to 64 years old, they worked at least 30h/wk outside of the home, they had health insurance, and they were available for follow-up telephone calls."

"Exclusion criteria included a history of acute hypersensitivity to eggs or egg products, previous receipt of the 1997-1998 inactivated influenza vaccine, self-reported pregnancy or unprotected risk for pregnancy within the previous 3 months, and acute febrile illness or upper respiratory tract illness within 72 hours. Because of the placebo-control arm of the study, exclusion criteria also included the presence of any indications for routine vaccination with the inactivated vaccine, such as the presence of high-risk medical conditions or positions of employment that involve significant contact with high risk people."

Intervention

Vaccine: "The LAIV vaccine for the 1997-1998 season included 3 live, attenuated influenza virus strains: A/Shenzhen/225/95 (H1N1), A/Wuhan/359/95 (H3N2), and B/Harbin/7/94-like, in egg allantoic fluid containing sucrose-phosphate glutamate (SPG). These strains were antigenically equivalent to those included in the inactivated vaccine for the 1997-1998 season."

Placebo: "The placebo, which consisted of egg allantoic fluid containing SPG, was indistinguishable in appearance and smell from the vaccine."

"Vaccine and placebo were supplied in single-dose intranasal sprayers. Participants were provided with instructions on intranasal administration of the vaccine and were given the option of self-administration under direct supervision of or administration by a study staff member."

"To allow sufficient time for an immune response to develop before any anticipated influenza outbreaks, vaccine or placebo was administered between September 18 and November 15, 1997."

Randomization and Masking

"Participants were randomized 2:1 to receive the investigational LAIV vaccine or placebo….at the time of vaccination. Each new participant was assigned to the next available sequential allocation number according to the predetermined, computer-generated randomization schedule. The sequential number imprinted on the vaccine label determined the material used for vaccination. Adherence to the predetermined allocation sequence was documented through accountability logs. Both the vaccine and placebo were prelabeled according to the computer-generated randomization schedule…, packaged to be visually identical, and delivered to the study sites by Almedica Service Corp….Blinding to intervention assignment of the study participants and site personnel was maintained until all outcome data had been collected and verified."

Table 1: Characteristics of Study Participants

	Vaccine Group (n = 3041)	Placebo Group (n = 1520)
Age, mean, y	38.3	38.2
Sex, female	1664 (54.7)	825 (54.3)
Race/ethnicity		
White	2576 (84.7)	1269 (83.5)
Black	292 (9.6)	166 (10.9)
Asian	69 (2.3)	38 (2.5)
Hispanic	68 (2.2)	32 (2.1)
Native American	10 (0.3)	2 (0.2)
Other	26 (0.8)	12 (0.8)
Highest level of education		
Up to 12th grade, no diploma	60 (2.0)	30 (2.0)
High school graduate	509 (16.7)	297 (19.5)
Some college or associate's degree	1008 (33.2)	496 (32.6)
Bachelor's degree	944 (31.0)	435 (28.6)
Advanced degree (master's, doctorate, professional)	520 (17.1)	261 (17.2)
Other	0 (0)	1 (0.7)

Table 2: Follow-up Procedures for Evaluating Vaccine Reactions and Vaccine Efficacy

Purpose	Time	Procedures
Ascertainment of vaccine reactions	Evening of vaccination through 7 days thereafter	Participants record daily temperatures with a digital thermometer and check off the presence of respiratory tract symptoms on a symptom card.
	7 days after vaccination	Study personnel call participants to remind them to return their symptom cards.
Ascertainment of serious adverse events	28 days after vaccination	Study personnel call participants to identify the occurrence of any serious adverse events not reported on their symptom cards.
Ascertainment of febrile illness during follow-up	During entire study period (November 1997-March 1998)	Computer-generated telephone messaging system reminds participants to complete and return symptom cards.

*Symptom cards were used to record adverse reactions to the intervention and symptoms of influenza (*e.g.,* headache, runny nose, sore throat, fever)

Table 3: Symptom Data for the 7 Days Following Inoculation for Vaccine & Placebo Recipients

Reaction	Vaccine (%)	Placebo (%)	V – P[1] (%)
Fever	1.0	1.0	
Runny nose	44.3	26.6	44.3 – 26.6 = 17.7
Sore throat	26.6	16.3	
Cough	15.2	12.3	
Headache	41.1	40.5	
Muscle aches	16.6	15.6	
Chills	5.0	4.0	
Tired/weak	26.6	21.3	

[1] V - P is the difference between the percent of participants experiencing the given symptom in the vaccine group and the placebo group.

Table 4: Case Definitions Used by Investigators

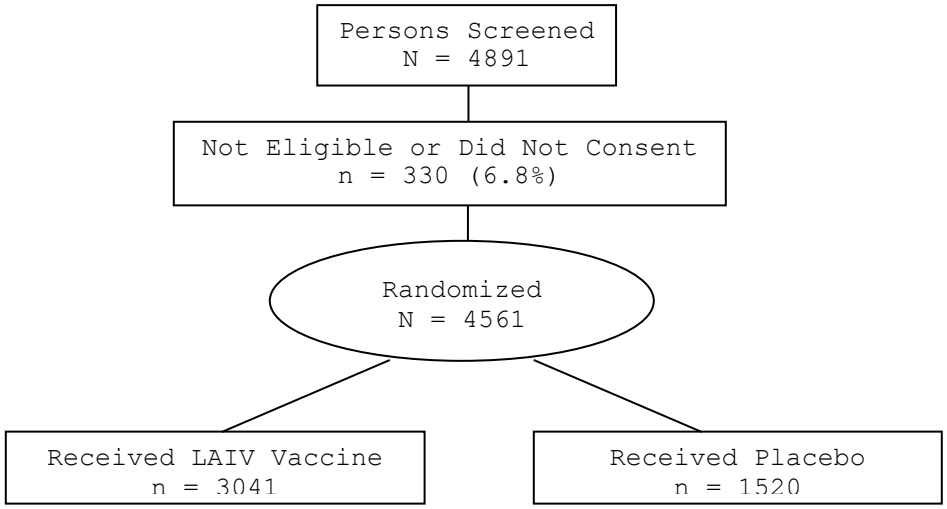
Acute illness	Criteria
Febrile illness	Symptoms for at least 2 consecutive days, with fever on at least 1 day, and if they had two or more symptoms (fever, chills, headache, runny nose, sore throat, cough, muscle aches, tiredness/weakness) on at least one day
Severe febrile illness	Symptoms for at least 3 consecutive days, with fever on at least 1 day and 2 more symptoms on at least 3 days
Febrile upper respiratory illness	Upper respiratory tract illness (runny nose, sore throat, cough) for at least 2 consecutive days, with fever on at least one day and 2 symptoms on at least one day

Table 5: Numbers and Incidence Rates of Acute Illness during the Total Outbreak Period

	Vaccine Group		Placebo Group		P – V	$\frac{(P - V)}{P}$
Acute Illness	Number	Incidence Rate*	Number	Incidence Rate*		
Febrile illness	751	276.5	412	302.5	302.5 – 276.5 = 26.0	(26.0 / 302.5) x100% = 8.6%
Severe febrile illness	543	199.9	326	239.3		
Febrile upper respiratory tract illness	472	173.8	285	209.2		
Total Persons	*2,874*		*1,433*			

* Incidence rate of illness per 1,000 persons per 14-week outbreak period

Figure 1: **Trial Profile**



D. Transmission of Influenza

Reference**:** Hurwitz ES, et al. Effectiveness of Influenza Vaccination of Day Care Children in Reducing Influenza-Related Morbidity among Household Contacts. *JAMA.* 2000; 284:1677-1682.

ABSTRACT

Context

A growing proportion of young children in the United States participate in day care, and these children are considered to be at high risk for influenza infection. Whether vaccinating day care children reduces household transmission of influenza is not known.

Objective

To evaluate the effect of vaccinating day care children on reducing influenza-related morbidity among their household contacts.

Design

Single-blind, randomized controlled trial conducted during the 1996-1997 influenza season.

Setting

Ten day care centers for children of US Navy personnel in San Diego, California.

Participants

A total of 149 day care attendees (aged 24-60 months) and their families were randomized; 127 children received 2 vaccine doses. These 127 children and their 328 household contacts were included in the analysis.

Interventions

Inactivated influenza vaccine was administered to 60 children (with 162 household contacts), and hepatitis A vaccine as a control was administered to 67 age-matched children (with 166 household contacts).

Main Outcome Measures

Information regarding febrile respiratory illnesses and related morbidity for household contacts of influenza-vaccinated vs control children (subgrouped by influenza-vaccinated and unvaccinated contacts), obtained by telephone interviews with parents every 2 weeks from November 1996 through April 1997.

Table 6. Efficacy of Influenza Vaccination of Day Care Children in Reducing Influenza-Related Morbidity among Vaccinated and Unvaccinated Household Contacts

Respiratory Illness	Control Children Contacts, No.	Control Children Contacts Total Incidence*	Vaccine Children Contacts, No.	Vaccine Children Contacts Total Incidence*	Vaccine Efficacy $\frac{(P-V)}{P} x100\%$
Unvaccinated household contacts					
Any	64/115	55.6	53/113	46.9	15.6%
With fever	23/115	20.0	13/113	11.5	42.5%
With temperature of ≥ 38°C (101°F)	21/115	18.3	11/113	9.7	47.0%
Vaccinated household contacts					
Any	32/51		22/49		
With fever	4/51		4/49		
With temperature of ≥ 38°C (101°F)	4/51		3/49		

* Total incidence per 100 household contacts at risk

YOU WILL NEED THE STUDY DESCRIPTIONS, COMPLETED TABLES AND FIGURE TO COMPLETE THE ACTIVITY.

Questions 1-6 refer to the study by Nichol et al. (Effectiveness of live, attenuated intranasal influenza virus vaccine in health, working adults: a randomized controlled trial)

Question 1
What type of study design was used to address the research question?

a. Cross-sectional study

b. Case-control study

c. Prospective cohort study

d. Randomized trial

Question 2
Where does this study fit in the stages of vaccine development?

a. Preclinical study

b. Phase I: Dose finding and safety

c. Phase III: Comparative efficacy

d. Effectiveness and Monitoring Adverse Events

One goal of the study was to ascertain the level of reactions to the vaccine. Table 3 shows the frequency of reporting of various symptoms according to the time of onset after inoculation. Complete Table 3 by calculating V-P for each reaction. The calculation for runny nose has been done for you.

Question 3
Using the information in Table 3, what symptoms are associated with the vaccine? (Note: The investigators determined that vaccine-associated symptoms had V–P differences that exceeded 10%)

a. Runny nose

b. Sore throat

c. Runny nose and sore throat

d. Runny nose, sore throat and fever

Diagnosis of influenza was not confirmed for the study participants by laboratory testing. Instead, diagnoses of influenza for study participants were made based on clinical evidence from the returned symptom cards. Case definitions used by investigators are summarized in Table 4.

For each acute illness definition in Table 5, calculate the difference in the outcome incidence rate between the placebo and vaccine groups (P – V) per 1,000 persons per 14-week outbreak period. Febrile illness has been calculated for you as an example.

Question 4

Based on Table 5, which acute illnesses would you include in your case definition for influenza if you would like to *maximize specificity* of your case definition?

a. Febrile illness
b. Febrile illness and Severe febrile illness
c. Febrile illness and Febrile upper respiratory tract illness
d. Severe febrile illness and Febrile upper respiratory tract illness

The investigators are interested in determining the proportion of influenza cases that are prevented by the vaccine (called "vaccine efficacy").

Vaccine efficacy is expressed as:

$$\frac{P - V}{P} \times 100\%$$

Using the information in the Table 5, calculate the efficacy of the LAIV vaccine (V) relative to placebo (P) in preventing influenza in the study participants for severe febrile illness and febrile upper respiratory tract illness. The efficacy for febrile illness has been calculated for you as an example.

Question 5

What is the efficacy of Severe febrile illness and of Febrile upper respiratory tract illness?

a. Severe febrile illness: 8.6% and Febrile upper respiratory tract illness: 10.6%
b. Severe febrile illness: 16.5% and Febrile upper respiratory tract illness: 16.9%
c. Severe febrile illness: 10.6% and Febrile upper respiratory tract illness: 16.9%
d. Severe febrile illness: 16.5% and Febrile upper respiratory tract illness: 10.6%

At one extreme, one could assume that all febrile upper respiratory tract illness during the epidemic period is due to influenza. Alternatively, one could assume that some "background" level of non-influenza febrile upper respiratory tract illness continues during the epidemic and this background level of illness can be taken this into account in the calculation of vaccine efficacy:

$$\frac{(P_{epidemic} - P_{background}) - (V_{epidemic} - P_{background})}{(P_{epidemic} - P_{background})} \text{ X } 100\%$$

Acute Illness	**Vaccine Incidence Rate***	**Placebo Incidence Rate***	**$(P - P_b) - (V - P_b)$ Incidence Rate***	$\frac{(P - P_b) - (V - P_b)}{P - P_b}$
Febrile upper respiratory tract illness	173.8	209.2	159.2 – 123.8 = 35.4	

* Incidence rate of illness per 1,000 persons per 14-week outbreak period

Question 6

Using the information in the table above, calculate the efficacy of the LAIV vaccine relative to placebo for febrile upper respiratory tract illness, assuming that the background level of non-influenza febrile upper respiratory tract illness is 50.0 cases per 1000 persons per 14-week outbreak period.

a. 17%
b. 20%
c. 22%
d. 29%

Questions 7-10 refer to study by Hurwitz et al. (Effectiveness of Influenza Vaccination of Day Care Children in Reducing Influenza-Related Morbidity among Household Contacts)

Question 7

Which of the following statements best describes the *study* population?

a. Children (aged 24-60 months) who attended 10 day care centers for children of US Navy personnel in San Diego, California in 1996-97 and their household contacts

b. 127 children (aged 24-60 months) who attended day care centers for children of US Navy personnel in San Diego, California in 1996-97 and their 328 household contacts

c. 60 children (aged 24-60 months) and 67 age-matched children who attended day care centers for children of US Navy personnel in San Diego, California in 1996-97

d. 455 young children in the United States who participate in day care and are considered to be at high risk for influenza infection

Question 8

If you assume that none of the household contacts have previously received the inactivated influenza vaccine, how many people in this study are susceptible to influenza infection?

a. 67

b. 162

c. 328

d. 395

Since these families were part of the US Navy, many adult household contacts received the influenza vaccine due to military requirement. The authors, therefore, stratified their results by vaccinated and unvaccinated household contacts.

Complete Table 6 by calculating the total incidence of respiratory illness and the vaccine efficacy for each subgroup of the Vaccinated household contacts. Answers have been provided for you for the unvaccinated household contacts as an example.

Question 9

Using the data in Table 6, what is the total incidence of *any respiratory illness* per 100 household contacts at risk for *vaccinated household contacts* of children who received the *placebo* and of children who received the *vaccine*?

a. Control Children Contacts: 7.8; Vaccine Children Contacts: 6.1
b. Control Children Contacts: 7.8; Vaccine Children Contacts: 8.2
c. Control Children Contacts: 55.6; Vaccine Children Contacts: 62.7
d. Control Children Contacts: 62.7; Vaccine Children Contacts: 44.9

Question 10

Using the data in Table 6, what is the vaccine efficacy of any respiratory illness for the vaccinated household contacts?

a. 7.8%
b. 21.8%
c. 28.4%
d. 44.9%