EXPERIMENTAL AND THEORETICAL STUDY OF EARLY DETECTION AND ISOLATION OF INFLUENZA

Request for Office of Management and Budget Review and Approval
for Federally Sponsored Data Collection

Part B

Project Officer: William G. Lindsley, PhD
National Institute for Occupational Safety and Health
1095 Willowdale Rd. MS 2015
Morgantown, WV 26505
wlindsley@cdc.gov
304-285-6336
304-285-5938 (fax)

November 14, 2007

B2. Procedures for the Collection of Information

Study Design

Specific aim 1: Measure the quantity and size of aerosol produced by influenza patients during coughing.

This work will be carried out when influenza activity is reported to be increasing in the community. In this part of the study, volunteer subjects with influenza-like illness will be recruited from the local community and from West Virginia University. Volunteers will be verbally screened initially to verify that they have flu-like symptoms and that they meet the health requirements for the study. Subjects who meet these criteria will be invited to come to a study room in the Health Sciences Center at West Virginia University. Upon arrival, a test coordinator will explain the study to the subject and answer any questions. If the subjects decide to participate in the study, they will be asked to fill out the health questionnaire. The questionnaire will be reviewed to determine if the subject is eligible to participate in the study. If so, the subject will be asked to read and sign the informed consent form. A nurse or medical technician will measure the subject's oral temperature, and collect a nasal swab which will be tested for influenza virus. Measurements will then be made of the aerosol produced during three coughs using the system described below in the Apparatus section. Test subjects will be asked to return for a second test after four weeks when their symptoms have been resolved in order to compare aerosol production in the healthy and infected states.

Cough-generated aerosol measurements have not been previously reported for influenza patients. However, based on tests using healthy subjects in an earlier project, we estimate that a sample size of twenty will allow us to characterize the aerosol produced by people with influenza when they cough. To avoid forcing participants to wait for the results of the influenza test and to maintain good will, all eligible subjects with febrile respiratory illness who report to the study room will be allowed to participate in the study. We will continue enrolling subjects until we have recorded results from twenty subjects who test positive for influenza. Using a conservative estimate that 50% of the volunteers will test positive for the flu, we estimate that a maximum of forty subjects will be required to complete this part of the study.

Specific aim 2: Measure the quantity and size range of airborne particles laden with influenza virus that are present in a hospital emergency department during flu season.

This work will be carried out during a one month period when influenza activity is reported to be increasing in the community and the number of visits to the

Emergency Department (ED) of Ruby Memorial Hospital for febrile respiratory infections has increased. Health care workers in the ED who volunteer to participate will be asked to fill out a health questionnaire. The questionnaire will be reviewed to determine if the subject is eligible to participate in the study. If so, the subject will be asked to read and sign the informed consent form. A nurse or medical technician will measure the subject's oral temperature, and collect a nasal swab which will be tested for influenza virus. Workers who do not test positive for influenza and who do not have symptoms of febrile respiratory illness will be equipped with personal aerosol samplers (described in the Apparatus section below) to collect airborne material in their immediate environment during a normal work shift. Six healthcare workers in each of the following five categories will be equipped with a sampler to be worn for an 8 hour shift: Physician, Nurse, Receptionist, Security guard, and Respiratory Therapist. A total of thirty healthcare workers will be monitored. We anticipate performing the study during one work shift in each of three consecutive weeks, with two workers in each category being equipped with samplers during each shift. If necessary, the worker categories and the schedule will be adapted to accommodate the availability and needs of the workers and the hospital.

During each study shift, adult patients who present at the ED with febrile respiratory viral infections will be asked to volunteer to provide nasal swabs for influenza testing to provide an estimate of the number of patients with influenza in the ED during monitoring. Patients who agree to participate in the study will be asked to read and sign the informed consent form. Based on previous influenza seasons, we expect about 4 to 8 adult patients with influenza-like symptoms in the ED during each shift, for a total of about 12 to 24.

This study will not interfere with the normal operation of the ED. During this study, the ED will continue to follow its normal infectious disease precautions (standard and droplet precautions, hand hygiene, respiratory hygiene and cough etiquette).

Apparatus

Specific aim 1: Measure the quantity and size of aerosol produced by influenza patients during coughing.

This project will use the apparatus shown in Figure B2-A to collect and characterize the aerosols produced by human volunteers during a cough. This system consists of a HEPA-filtered air cabinet (Fisher Scientific), a temperature-controlled chamber, an ultrasonic spirometer (EasyOne, ndd Medical Technologies) and an aerosol collection bag. Aerosol aerodynamic diameters and concentrations will be measured using two commercial aerosol analyzers.

To perform a cough-generated aerosol measurement, the following procedure is used: The system is turned on and the chamber containing the spirometer and

collection bag is allowed to stabilize at 37°C. When the system is ready, the subject sits with their head inside the HEPA-filtered air cabinet and breathes normally; the purpose of this step is to remove background aerosols from the subject's respiratory tract. After 5 minutes, the subject is asked to exhale completely, inhale as much as possible, seal their lips around the mouthpiece and cough. Subjects are asked to cough forcefully using as much of the air in their lungs as possible. After coughing, the subject resumes breathing HEPA-filtered air while the aerosol is analyzed and the system is flushed. Aerosol counts and size information are recorded using an attached computer system and software from TSI. The entire aerosol from a typical cough can be analyzed in 2 minutes.

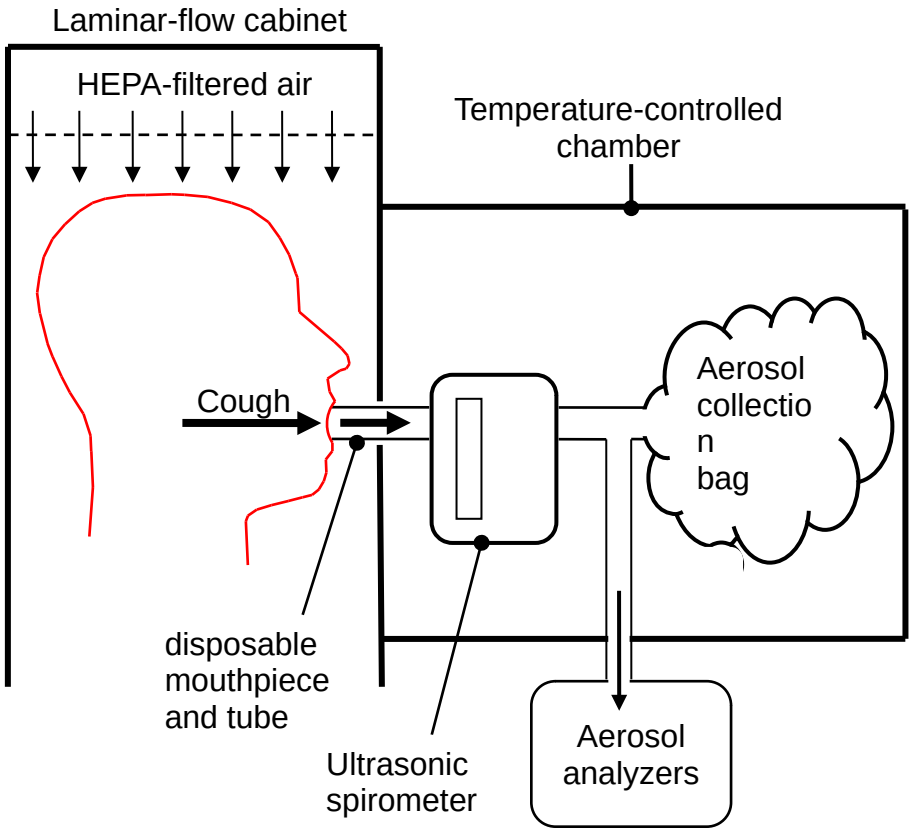

Figure B2-A: System for measuring aerosols produced by human volunteers during coughing. When the subject coughs into the mouthpiece, the cough first flows through the ultrasonic spirometer, which measures the volume of the cough. Next, the cough inflates an aerosol collection bag. The respiratory gases and aerosol from the cough are then drawn into the aerosol analyzers for quantification and sizing. The mouthpiece (which extends through the ultrasonic spirometer) and the aerosol collection bag are removed and discarded after each subject.

Specific aim 2: Measure the quantity and size range of airborne particles laden with influenza virus that are present in a hospital emergency department during flu season.

This part of the study will use a two-stage cyclone personal bioaerosol sampler newly-developed by NIOSH (Figure B2-B). The NIOSH bioaerosol sampler collects aerosol particles in two disposable centrifuge tubes and on a filter. Air is drawn through the sampler using a commercial sampling pump (Model 224-PCXR4, SKC) that is enclosed in a custom pouch to reduce noise.

All samples obtained with the bioaerosol samplers will be analyzed for influenza virus using a PCR-based assay. For these tests, universal PCR primers capable of amplification of all influenza strains will be used. A virucidal extraction buffer will be placed in the bottom of the sample tubes to inactivate any infectious virus prior to performing the PCR reactions.

Nasal swabs will be collected from participating workers and from patients who present at the ED with febrile respiratory illness and volunteer to participate. The swabs will be tested with the QuickVue Influenza A+B test (Quidel Corp.) Quidel reports that, when used with nasal swabs, this test correctly identified 94% and 74% respectively of culture-positive influenza A and B specimens, and 90% and 97% respectively of culture-negative influenza A and B specimens.

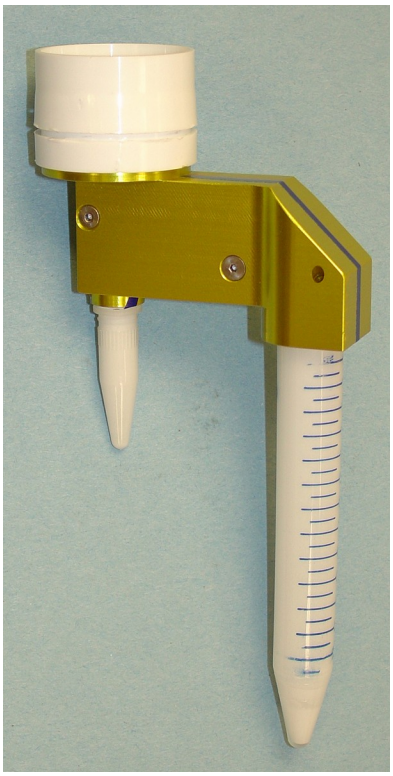

Figure B2-B: NIOSH two-stage cyclone personal bioaerosol sampler. For this study, the sampler will operate at a flow rate of 3.5 liters/minute. Particles with an aerodynamic diameter ≥ 4 μm will collect in the first tube, while particles with aerodynamic diameters between 1 and 4 μm will collect in the second smaller tube. Particles less than 1 μm will collect on the filter. The fractionation of the particles by size will allow us to distinguish between virus-laden particles that settle relatively quickly and virus-laden particles that remain airborne for an extended period of time.

B3. Methods to Maximize Response Rates and Deal with Nonresponse

We will continue to recruit until all sections of the study have been completed. Respondents will be encouraged to participate in the study by incentive payments as described in Section A9. Previous experience with recruiting paid volunteers has indicated that this should not be a problem.

B4. Tests of Procedures or Methods to be Undertaken

The health questionnaire used in this study was adapted from a previous NIOSH pilot study, “Characteristics of Aerosols Generated during a Cough”, conducted within the Health Effects Laboratory Division in 2000 and 2001. The measurement system used in this study was also adapted from the earlier pilot study, which did not require OMB approval.

B5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

The statistical aspects of this study were reviewed by a Mathematical Statistician in the Biostatistics and Epidemiology Branch, Health Effects Laboratory Division, NIOSH. His contact information is:

James Slaven, MS
National Institute for Occupational Safety and Health
1095 Willowdale Rd. M/S 4050
Morgantown, WV 26505
JSlaven@cdc.gov
304-285-6299

The data collection procedures were designed by the project officer, who will also perform the data collection and analysis:

William G. Lindsley, PhD
National Institute for Occupational Safety and Health
1095 Willowdale Rd. M/S 2015
Morgantown, WV 26505
WLindsley@cdc.gov
304-285-6336

References

1. Bridges CB, Harper SA, Fukuda K, Uyeki TM, Cox NJ and Singleton JA. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 52: 1-34, 2003.
2. Bridges CB, Kuehnert MJ and Hall CB. Transmission of influenza: implications for control in health care settings. *Clin Infect Dis* 37: 1094-101, 2003.
3. Gerberding JL. Infectious organisms. In: *Occupational and Environmental Respiratory Disease*, edited by Harber P, Schenker MB and Balmes JR. St. Louis: Mosby, 1996, p. 561-70.
4. Gerone PJ, Couch RB, Keefer GV, Douglas RG, Derrenbacher EB and Knight V. Assessment of experimental and natural viral aerosols. *Bacteriol Rev* 30: 576-88, 1966.
5. Couch RB, Douglas RG, Jr., Lindgren KM, Gerone PJ and Knight V. Airborne transmission of respiratory infection with coxsackievirus A type 21. *Am J Epidemiol* 91: 78-86, 1970.
6. Riley RL, Mills CC, O'Grady F, Sultan LU, Wittstadt F and Shivpuri DN. Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: Comparative infectiousness of different patients. *American Review of Respiratory Disease* 85: 511-25, 1962.
7. Lidwell OM. Aerial dispersal of micro-organisms from the human respiratory tract. *Society for Applied Bacteriology Symposium Series* 3: 135-54, 1974.
8. Yu IT, Li Y, Wong TW, Tam W, Chan AT, Lee JH, Leung DY and Ho T. Evidence of airborne transmission of the severe acute respiratory syndrome virus. *New England Journal of Medicine* 350: 1731-9, 2004.
9. WHO. *Influenza A (H5N1): WHO Interim Infection Control Guidelines for Health Care Facilities.* World Health Organization, 2004, 31 p.
10. Wong TW, Lee CK, Tam W, Lau JT, Yu TS, Lui SF, Chan PK, Li Y, Bresee JS, Sung JJ, Parashar UD and Outbreak Study G. Cluster of SARS among medical students exposed to single patient, Hong Kong. *Emerging Infectious Diseases* 10: 269-76, 2004.