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 A

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)

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Section A. Justification

A1. Circumstances Making the Collection of Information Necessary

The National Institute for Occupational Safety and Health (NIOSH) is authorized to conduct research to advance the health and safety of workers under Section 20(a) (1) of the 1970 Occupational Safety and Health Act (PL 91-256). The relevant section of this law is in Attachment 1.

Influenza is a highly transmissible respiratory virus that causes an average of 114,000 hospitalizations and 36,000 deaths in the United States each year [1]. This virus is of particular concern today because of the potential for newly-emerging strains of influenza to cause a global pandemic. For this reason, the various possible modes of transmission of the influenza virus are of great interest to the public health community.

Influenza is known to spread through direct contact with respiratory secretions and indirect contact with large respiratory droplets that settle onto fomites [2]. Influenza is also thought to spread by dissemination and inhalation of aerosols of small droplet nuclei that are produced by coughing and remain airborne for an extended time [2]. However, the airborne transmission of influenza is not well understood, in part because the potentially infectious aerosols produced by people with influenza have not been well-characterized. If a pandemic occurred, it is unlikely that enough facilities would be available to isolate patients in rooms with negative air pressure and the required number of air exchanges. Thus, a better understanding of the exact role of the various modes of transmission of the influenza virus is extremely important. This information also is needed to aid in planning and allocation of resources during the normal annually recurring influenza outbreaks.

Coughing is a ubiquitous symptom of respiratory illnesses. Several studies have shown that coughing can produce aerosols containing infectious materials [3]. Gerone et al. showed that humans infected with Coxsackie virus produce aerosols when they cough that contained viable viral material [4]; they later showed that the virus could be transmitted from person to person through the air [5]. Riley et al. [6] established that tuberculosis is spread by inhalation of respirable particles generated by infected individuals. British studies of classrooms and offices found aerosols containing viable salivary streptococci and other oral bacteria that were thought to be created during speaking, coughing, and sneezing [7]. Severe acute respiratory syndrome (SARS) and avian influenza are known to spread through infectious aerosols [8; 9], and this may include cough-generated aerosols as well [9; 10].

The studies described above have provided important information on the transmission of disease by cough-generated aerosols. However, large gaps remain in our understanding in the spread of influenza by coughing. Only a few

studies have examined the size distribution of cough-generated aerosols, and none have examined aerosols created by patients with influenza. Studies of virus-laden aerosols in healthcare facilities have also been very limited, and none of these have looked at influenza. As a result, it is unclear how important cough-generated aerosols are in the spread of this disease.

A2. Purpose and Use of the Information Collection

The purpose of this study is to gain a better understanding of the production of potentially-infectious aerosols by coughing among patients with influenza, and to examine the actual quantities and size distribution of airborne particles containing the influenza virus in a health care setting during influenza season. The study has two specific aims:

1) *Measure the size and quantity of aerosol droplets produced by patients with influenza when they cough.* Volunteer subjects with influenza will be asked to sit under a HEPA-filtered air cabinet and cough into a collection bag. Aerosol measurement instruments will then draw the air from the bag and measure the quantity and size of airborne droplets that were produced.

2) *Measure the amount and size of airborne particles containing influenza virus that are present in a hospital emergency department during influenza season.* Healthcare workers in a hospital emergency department (ED) will be asked to wear personal aerosol samplers in order to collect airborne material while they work during flu season. After collection, the two stages of the sampler and the filter will be tested for influenza virus using a polymerase chain reaction (PCR)-based assay. Stationary aerosol samplers will also collect the ambient aerosol at different locations in the ED. Adult patients presenting at the ED with flu-like symptoms will be asked for nasal swabs, which will be tested for the flu virus in order to estimate the number of individuals with the flu in the study area.

The study will be conducted in collaboration with researchers at West Virginia University. This effort is a follow-on project to the study, “Aerosol Generation by Cough”, which will look at aerosol production by healthy individuals.

A3. Use of Improved Information Technology and Burden Reduction

The health questionnaire data and informed consent will be collected using printed forms which are completed manually. Aerosol data will be collected using computerized data acquisition systems operated by the researchers; this will require no effort by the participant.

A4. Efforts to Identify Duplication and Use of Similar Information

This study does not duplicate previous research. An extensive search of the biomedical literature and discussions with other researchers in this field found

that aerosol generation by subjects with influenza has not been previously examined, nor have any studies directly quantified the number and size distribution of airborne particles containing the influenza virus that are present in a healthcare setting.

A5. Impact on Small Businesses or Other Small Entities

No small entities are involved in this project.

A6. Consequences of Collecting the Information Less Frequently

No alternative methods are available to obtain the needed health information and informed consent from the participants. There are no legal obstacles to reducing the burden.

A7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

There are no special circumstances for this data collection.

A8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

1. Federal Register Notice

In accordance with CFR 1320.8(d), a review of the proposed study was sought through a 60-day publication period in the Federal Register (on April 27, 2007, Vol. 72, No. 81, p. 21021-2; shown in Attachment 2). One comment was received; the comment and response are shown in Attachment 11.

2. Consultation Outside the Agency

This project was subjected to anonymous external peer review outside of NIOSH. Because the reviews were anonymous, the identities of the reviewers are not permitted to be released to the project officer. The review process was supervised by:

W. Allen Robison, Ph. D.
Scientific Program Administrator
Office of Extramural Programs
National Institute of Occupational Safety and Health
Centers for Disease Control and Prevention
1600 Clifton Road NE, MS-E-74
Atlanta, GA 30333
404/498-2509 (t)
404/498-2571 (f)
WRobison@cdc.gov

A9. Explanation of Any Payment or Gift to Respondents

Previous NIOSH studies have experienced difficulties recruiting respondents when the studies involved clinical tests and the respondents were not reimbursed for their time. To enhance recruitment, previous studies at NIOSH and other CDC centers have provided incentives to respondents in clinical studies. For example, in the NIOSH study "Workplace Stress Among Underground Coal Miners" (OMB No. 0920-0657), volunteers were recruited to complete a saliva test and avoid food, drink and exercise before they collected the samples. Volunteers received an incentive of $35 for completing the test. This incentive plan has proven to be a very effective technique for recruiting volunteers.

For Specific Aim 1, subjects will receive $40.00 to reimburse them for the time and inconvenience needed to participate in each session of the study. If the study participant leaves prior to the completion of a session, their reimbursement will be prorated for the amount of time they have spent in that session at a rate of $40/hour. Subjects will be asked to participate in one session while they are ill and another four weeks later after their symptoms have been resolved; subjects will be reimbursed for both sessions at the same rate. Subjects will receive reimbursement for the first session regardless of whether or not they return for a second session.

For Specific Aim 2, healthcare workers will receive $25.00 for each 8 hour work shift (in addition to their normal salary) to reimburse them for their time and inconvenience while participating in the study. If the worker terminates their participation prior to the completion of a shift, their reimbursement will be prorated for the amount of time they participated during that shift. Patients at the ED who are asked for nasal swabs will not be paid. They will not be charged for the cost of the influenza test, and the results will be provided to them.

A10. Assurance of Confidentiality Provided to Respondents

This submission has been reviewed for Privacy Act applicability and it has been determined that the Privacy Act applies under 09-20-0147 Occupational Health Epidemiological Studies. Although data will be kept in a secure manner, NIOSH will hold the link matching respondents with code numbers.

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

Use of code numbers

Names of the participants will not be recorded on the health questionnaire or in computer data files. Instead, participants in Specific Aim 1 will be assigned a code number from a master list maintained by the project officer. This number will be recorded on the health questionnaire, influenza test results and aerosol measurements. The list matching participants with their code numbers will be

filed in a locked cabinet accessible only by NIOSH employees conducting the study.

Consent form

Before participating in Specific Aim 1 of the study, participants will be asked to read and sign a consent form. Participants will be given as much time as needed to read and understand the form, and any questions they have will be answered. The consent form does not contain any personal information aside from the name of the participant. Consent forms will be filed in a locked cabinet accessible only by NIOSH employees conducting the study. Consent forms will be kept for one year after the study results are published, after which they will be destroyed.

Health questionnaire

Each participant in Specific Aim 1 will be asked to fill out a health questionnaire. The health questionnaires will be filed in a locked cabinet in the NIOSH Morgantown facility accessible only by NIOSH employees conducting the study. The health questionnaires will be kept until one year after the study results are published, after which they will be destroyed. Tabulated results from the health questionnaires will be entered into a computer using the code numbers, but the computerized data will not include personal identifiers. Computer files will be secured in compliance with OMB memorandum M-06-16, “Protection of Sensitive Agency Information”.

Influenza test results

Participants in Specific Aim 1 will be asked to submit to an influenza test. The test results will be recorded on the health questionnaire.

Aerosol measurement results

Computer files containing the results from aerosol measurements will be secured in compliance with OMB memorandum M-06-16, “Protection of Sensitive Agency Information”. These files will contain the participant code numbers but will not include personal identifiers.

***Specific Aim 2**: Measure the amount and size of airborne particles containing influenza virus that are present in a hospital emergency department during influenza season.*

Use of code numbers

As with Specific Aim 1, names of the participants will not be recorded on the health questionnaire or in computer data files. Health care workers participating in Specific Aim 2 will be assigned a code number from a master list maintained by the project officer. This number will be recorded on the health questionnaire and used to associate health questionnaires to influenza test results and results from the personal aerosol samplers. The list matching participants with their code numbers will be filed in a locked cabinet accessible only by NIOSH employees conducting the study. Aside from the consent forms, no personally identifiable information will be collected from patients in the Emergency Department and thus code numbers will not be assigned to them.

Consent form

As with Specific Aim 1, participants in Specific Aim 2 will be asked to read and sign a consent form. Participants will be given as much time as needed to read and understand the form, and any questions they have will be answered. The consent form does not contain any personal information aside from the name of the participant. Consent forms will be filed in a locked cabinet accessible only by NIOSH employees conducting the study. Consent forms will be kept for one year after the study results are published, after which they will be destroyed.

Health questionnaire

Health care workers participating in Specific Aim 2 will be asked to fill out a brief health questionnaire. The health questionnaires will be filed in a locked cabinet in the NIOSH Morgantown facility accessible only by NIOSH employees conducting the study. The health questionnaires will be kept until one year after the study results are published, after which they will be destroyed. Tabulated results from the health questionnaires will be entered into a computer using the code numbers, but the computerized data will not include personal identifiers. Computer files will be secured in compliance with OMB memorandum M-06-16, “Protection of Sensitive Agency Information”.

Influenza test results

Health care workers participating in Specific Aim 2 will be asked to submit to an influenza test. These test results will be recorded on the health questionnaire. Adult patients in the Emergency Department with influenza-like illness also will be asked to submit to an influenza test. The results of these tests will be provided to the patient. A count will be kept each day of the number of patients with positive and negative test results, but no personally identifiable information will be retained.

Personal aerosol sampler results

Computer files containing the results from assays of material collected by the personal aerosol samplers will be secured in compliance with OMB memorandum M-06-16, "Protection of Sensitive Agency Information". These files will contain the participant code numbers but will not include personal identifiers.

Respondents will be informed that participation in the study is voluntary and that the data supplied to NIOSH will be kept in a secure manner. NIOSH's internal Human Subject Review Board (HSRB) has reviewed and approved all instruments, informed consent materials and procedures to ensure that the rights of respondents are safeguarded (Attachment 10). Only authorized NIOSH project staff will have access to respondent names and identifiers.

A11. Justification for Sensitive Questions

No sensitive information will be collected during this study.

A12. Estimates of Annualized Burden Hours and Costs

1. Estimated Annual Burden Hours

For Specific Aim 1, a health questionnaire (Attachment 4) will be used for initial screening of participants. Assuming 5% of volunteers do not qualify for the study, we estimate that forty-two participants will be needed to obtain forty volunteers for the study. After completing the health questionnaire, these forty subjects will respond once to the consent form (Attachment 5). All eligible subjects with febrile respiratory illness who report to the study room will be allowed to participate in the study. Using a conservative estimate that 50% of the volunteers will test positive for the flu, this will provide results from twenty patients with influenza.

For Specific Aim 2, a health questionnaire (Attachment 7) will be used for initial screening of health care worker participants. Assuming 5% of volunteers do not qualify for the study, we estimate that thirty-two participants will be needed to obtain thirty volunteer health care workers for the study over three shifts (ten people per shift). These thirty workers will respond to the consent form (Attachment 8), provide a nasal swab and be outfitted with aerosol samplers once.

Patients presenting in the Emergency Department are screened for influenza-like illness by the medical staff as part of the normal intake procedure. As an additional part of Specific Aim 2, patients with influenza-like illness will be asked to participate in the study. Patients who agree to participate will complete the consent form (Attachment 9) and provide a nasal swab. Based on previous influenza seasons, we estimate a maximum of about eight adult patients per shift (24 total) will present with influenza-like illness. Assuming 63% of these patients will agree to participate in the study, five patients per shift (15 total) will need to complete the consent form once.

Table A12-A. Estimated Annual Burden Hours

Type of respondent	*Form*	*No. of respondents*	*No. of responses per respondent*	*Average burden per response (in hours)*	*Total burden hours*
Specific Aim 1: Volunteers with influenza					
Initial participants	Health questionnaire	42	1	5/60	4
Qualified participants	Consent form	40	1	20/60	13
Specific Aim 2: Health care workers					
Initial participants	Health questionnaire	32	1	5/60	3
Qualified participants	Consent form	30	1	20/60	10
Specific Aim 2: Emergency Department patients					
Participants	Consent form	15	1	20/60	5
TOTAL					**35**

2. Estimated Annual Burden Cost

Estimated annual burden costs for those surveyed are shown in Table A12-B. Costs are based on the mean hourly rate for the US civilian labor force, which is $19.29 based on data from the US Bureau of Labor Statistics for June of 2006.

Table A12-B: Estimated Annual Burden Cost

Type of respondent	*Form*	*No. of respondents*	*Total burden hours*	*Mean hourly wage*	*Estimated Annual Burden Cost*
Specific Aim 1: Volunteers with influenza					
Initial participants	Health questionnaire	42	4	$19.29	$77.16
Qualified participants	Consent form	40	13	$19.29	$250.77
Specific Aim 2: Health care workers					
Initial participants	Health questionnaire	32	3	$19.29	$57.87
Qualified participants	Consent form	30	10	$19.29	$192.90
Specific Aim 2: Emergency Department patients					
Participants	Consent form	15	5	$19.29	$96.45
TOTAL					**$675.15**

A13. Estimates of Other Total Annual Cost Burden to Respondents and Record Keepers

There will be no additional cost burden.

A14. Annualized Cost to the Federal Government

Costs for conducting the survey are summarized in Table A14. The total cost for this project is annualized over one year. There will be no new overhead, support staff, or construction required for the survey administration and data analysis. The study will last two years and will not require any travel.

Table A14. Annualized cost to the Federal Government

Personnel--1 GS-12, 20% time	$15,600
Personnel--1 GS-9, 20% time	$10,800
Supplies for aerosol measurement systems	$2,500
Gloves, masks, wipes, copies of questionnaires, etc.	$1,000
Total of Annualized estimate of federal cost	**$29,900**

A15. Explanation for Program Changes or Adjustments

Not applicable. These data collection efforts are new activities.

A16. Plans for Tabulation and Publication and Project Time Schedule

Table A16. Proposed time schedule.

Activity	*Time required*
Begin data collection	Start of flu season
Complete data collection	6 months
Complete data analysis	12 months
Publication	6 months
TOTAL	24 months

Data Analysis Plan

Specific Aim 1: Measure the size and quantity of aerosol droplets produced by patients with influenza when they cough.

Specific Aim 1 uses the quantity of aerosol produced, the aerosol size distribution and whether the subject has the flu or has recovered as outcome measures. In addition, the volume of air produced during each cough and the humidity inside

the spirometer will be recorded as possible confounding variables. The quantity of aerosol produced will be determined by grouping the particle concentration data from the aerosol analyzers into three size ranges: 0.01 to 0.1 μm; 0.1 to 1 μm; and 1 to 20 μm. The aerosol size distribution will be determined by fitting a lognormal distribution to the combined particle count data to determine the count median aerodynamic diameter (CMAD) and geometric standard deviation (GSD). The design structure of this experiment is a repeated measure consisting of two measurements, the first made when the subject has influenza and the second made after the subject is healthy again. Analysis will be performed using the Mixed Procedure on the SAS platform to perform an analysis of variance with repeated measures. Results will be considered significant if $p \leq 0.05$.

Specific Aim 2: Measure the amount and size of airborne particles containing influenza virus that are present in a hospital emergency department during influenza season.

The outcome measures for Specific Aim 2 are the quantity of influenza virus detected in each stage of the sampler, the type of healthcare worker wearing the sampler, and the number of patients presenting with influenza in the Emergency Department during the healthcare worker's shift. Analysis will be performed using the Mixed Procedure on the SAS platform to perform an analysis of variance. Results will be considered significant if $p \leq 0.05$.

A17. Reason(s) Display of OMB Expiration Date is Inappropriate

No expiration date display exemption is sought.

A18. Exceptions to Certification for Paperwork Reduction Act Submissions

No exceptions to certification are sought.

Section B. Data Collection Procedures

B1. Respondent Population and Selection of Respondents

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

The study participants for Specific Aim 1 must meet the following eligibility criteria:

- Male or female adult ages 18 to 35
- Lifetime non-smokers
- Influenza-like illness with a fever of 38.5°C (101.3°F) or greater
- Symptoms present for 72 hours or less
- Not vaccinated against the flu during the current season
- No other respiratory illness such as asthma, COPD or tuberculosis
- Otherwise good health with no underlying illnesses
- Not pregnant
- No medical condition or illness that would make it difficult or uncomfortable for them to perform the test procedure

Volunteer subjects will be recruited from the local community and from West Virginia University for these experiments. Participants will be recruited by flyers posted on bulletin boards and distributed at local healthcare offices including the WVU Student Health Service. The recruiting advertisements will explain the eligibility criteria for the study and instruct the potential participants to contact the test coordinator by telephone or email or go to the study room if they are interested.

Subjects will be excluded from the study if they do not meet the eligibility criteria described above. These criteria will be described prominently on the recruitment flyer and during the initial discussion with potential participants. In addition, these criteria will be described to anyone who indicates interest in participating in the study. Potential participants who are children or who are pregnant will be excluded because of the slight risks posed by strenuous coughing. Female subjects will be asked if they are pregnant and the date of their last menstrual period. If the subject's last menstrual period was more than 8 weeks prior to the study date, they will be asked to submit to a free pregnancy test before participating in 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.

The study participants for Specific Aim 2 will be adult healthcare workers and adult patients presenting in the emergency department with influenza-like illness. Healthcare workers will be recruited by flyers distributed by email or in workers' mailboxes and posted on bulletin boards. The recruiting advertisements will explain the eligibility criteria for the study and instruct the potential participants to contact the test coordinator by telephone or email if they are interested. At the time of the study, the participating healthcare workers will need to test negative for the influenza virus and not have symptoms of a febrile respiratory illness. Adult patients in the ED who present with febrile respiratory illness will be asked to volunteer to provide a nasal swab. Patients in the ED who do not present with febrile respiratory illness will not be eligible to participate. Minors in the ED will not be asked to participate.