Factors Influencing the Transmission of Influenza

Reinstatement with Change
OMB #0920-0888 expires 6/30/17

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Goals of the study

The goals of this study are to gain information about the amount of potentially infectious airborne particles that are expelled by people with influenza when they breathe and cough, and to relate this to the levels of biological markers in the blood.

Intended use of the resulting data

The data will be used to help determine the protective measures and equipment that will be needed to safeguard healthcare personnel during an influenza pandemic, and to explore possible screening methods for patients who are especially likely to transmit the virus to workers and the general public.

Methods to be used to collect

Volunteers for the study will be asked to read and sign a written informed consent form and to fill out a brief health questionnaire. Blood samples and nasopharyngeal mucus specimens will be collected using normal clinical procedures. Airborne particles produced by subjects during breathing and coughing will be collected using a custom-built aerosol particle collection system.

The subpopulation to be studied

The study will examine adult clinical outpatients recruited in Morgantown, West Virginia. Volunteer participants will be recruited from adult patients presenting with influenza-like illness at outpatient healthcare clinics. A matched number of control volunteers will also be recruited from adult outpatients at the clinic who are not ill (for example, patients at the clinic for physical examinations, medical screenings or routine check-ups or who are being treated for injuries such as minor sprains or cuts). Participants with influenza and control participants will undergo the same testing.

How data will be analyzed

The airborne particles produced by the patients, the blood samples and the nasopharyngeal mucus samples will be analyzed using viral culture and genetic analytical methods. These results will be compared to each other and to the health questionnaire data to look for correlations and markers of higher levels of viral shedding.

Section A. Justification

A1. Circumstances Making the Collection of Information Necessary

This OMB request is for a reinstatement with change data collection for project OMB # 0920-0888, which will expire on 6/30/2017. The proposed project will examine the amount of influenza virus in airborne particles produced by subjects with influenza and its relationship to biomarkers in the blood. OMB approval is requested for three years extension.

Under 29 USC 669 Section 20(a)(1) of the 1970 Occupational Safety and Health Act (Attachment 1), the National Institute for Occupational Safety and Health (NIOSH) is tasked with conducting research involving innovative methods, techniques, and approaches for dealing with occupational safety and health problems. Similarly, the Centers for Disease Control and Prevention's Health Protection Goals include a Healthy Workplace goal to "promote and protect the health and safety of people who work by preventing workplace-related fatalities, illnesses, injuries, and personal health risks." The proposed project will provide needed information for addressing both of these goals in the healthcare worker population by characterizing their exposure to potentially infectious airborne material. The availability of this information will help determine the infection control and personal protective measures needed to protect healthcare workers from this hazard.

The National Occupational Research Agenda (NORA) effort led by NIOSH established national research and activity goals for groups of industry sectors. One of these groups is the Healthcare and Social Assistance (HCSA) Sector. The proposed project will contribute to HCSA Strategic Goal 5, "Stop transmission of infectious diseases in healthcare and social assistance settings among workers, patients and visitors"; HCSA Intermediate Goal 5.1, "Understanding mechanisms and routes – Investigators across a broad range of disciplines will conduct research to understand mechanisms and determinants of routes by which infectious diseases are transmitted in the healthcare and social assistance setting" and HCSA Activity/Output Goal 5.1.3, "Conduct research to better understand characteristics associated with airborne transmission, such as quantity and size distribution of aerosols generated by coughing and sneezing, determinants of survival and infectivity in airborne droplet nuclei, and virulence after airborne transmission."

Influenza is a highly transmissible respiratory virus that is of great concern because of the potential for newly-emerging strains to cause a global pandemic. If a pandemic occurs, tremendous demands will be placed on the healthcare system. However, at the same time, healthcare workers and emergency responders will face a much greater likelihood of exposure to the virus than the general public. In the early stages of the 2009 H1N1 influenza pandemic, CDC estimated that at least half of the healthcare workers who became ill with H1N1 influenza were infected on the job [1]. For this reason, it is important to understand how the virus is transmitted from person to person so that healthcare workers can be protected while they are caring for the sick, and to find ways to screen patients who are especially likely to spread the virus so that extra precautions may be taken.

Although influenza is known to be transmitted by infectious secretions, these secretions can be transferred from person to person in different ways, and the relative importance of the various pathways is not known [2; 3]. In particular, the role of airborne transmission in the spread of influenza is unclear, with some investigators concluding that airborne transmission is a key route (reviewed in [4-6]), while others maintain that it rarely, if ever, occurs (reviewed in [7]). The question of airborne transmission is especially important in healthcare facilities, where influenza patients tend to congregate during influenza season, because it directly impacts the infection control and personal protective measures that should be taken. During the 2009 H1N1 pandemic, for example, an Institute of Medicine (IOM) panel recommended that healthcare workers in close contact with influenza patients wear respirators to avoid infectious aerosols [8]. This recommendation was subsequently adopted by some health authorities such as the Centers for Disease Control and Prevention (CDC), but not by others, such as the World Health Organization (WHO). The IOM panel also noted that many questions about the airborne transmission of influenza are unresolved, and the issue remains controversial.

In previous studies, we showed that influenza virus RNA could be detected in airborne particles in healthcare facilities [9; 10], and that patients with influenza produced aerosol particles while coughing and exhaling that contain influenza virus [11-13]. Similar results have been reported in other studies. Stelzer-Braid et al. [14] detected influenza viral RNA produced by influenza patients during breathing and talking. Fabian et al. [15] showed that 60% of patients with influenza A and 14% of patients with influenza B had detectable levels of viral RNA in their exhaled breath. Milton et al. [16] collected aerosol particles exhaled by influenza patients and found that patients shed about 33 viral copies/minute in aerosol particles ≥5 µm and 187 viral copies/minute in particles <5 µm. Bischoff et al. [17] and Lednicky and Loeb [18] demonstrated that airborne influenza virus could be detected several feet from patients with influenza.

MicroRNAs are small regulatory molecules that are secreted by cells into the bloodstream. These molecules have been shown to play a key role in the regulation of a diverse array of cellular responses including inflammation and cell death. Since their initial discovery, microRNA molecules have been developed as both diagnostic tools and therapeutic targets. Research over the past several years has demonstrated that identification of specific microRNA molecules in the peripheral circulation is associated with specific disease states. Furthermore, peripherally circulating microRNA molecules are extremely stable, and resistant to extreme changes in temperature and pH, which further enhances their utility as potential biomarkers for disease. More recent studies have demonstrated that multiple changes in the microRNA profile can be detected in human serum in the presence of influenza infection when compared with uninfected patients. The majority of the microRNA molecules identified under this scenario are predicted to target key elements of the immune response and cell survival pathways [19-21].

The purpose of this study is to gain a better understanding of the production of infectious aerosols by patients with influenza, and to compare this to the levels of biomarkers in the blood of these patients. To do this, aerosol particles produced by volunteer subjects with influenza will be collected and tested for influenza virus, and the levels of influenza infection-associated microRNA molecules will be measured in blood samples from these subjects.

A2. Purpose and Use of the Information Collection

Under the previous approval, 61 volunteer subjects were recruited and tested, 53 of whom were founded to be infected with influenza A virus. Of these, 28 (53%) produced aerosol particles containing viable influenza A virus during coughing, and 22 (42%) produced aerosols with viable virus during exhalation. From these results, we concluded that viable airborne influenza virus is produced by patients during both breathing and coughing, but that breathing may generate more airborne infectious material than coughing over time. However, both respiratory activities could be important in airborne influenza transmission. Our results were also consistent with the theory that much of the aerosol containing viable influenza virus originates deep in the lungs. The results of this study were presented at a scientific conference (WG Lindsley, FM Blachere, DH Beezhold, et al. Viable Influenza Virus in Cough and Exhaled Breath Aerosol Particles. *American Association for Aerosol Research 34th Annual Conference*, October 12-16, 2015, Minneapolis, MN) and were published in a peer-reviewed scientific journal (WG Lindsley, FM Blachere, DH Beezhold, et al. (2016). Viable influenza A virus in airborne particles expelled during coughs versus exhalations. *Influenza and Other Respiratory Viruses* 10(5): 404-13).

Although the results of this study were useful in advancing our understanding of influenza transmission, our work was hampered because the amounts of influenza virus in almost all of the aerosol samples were below our limit of quantification. Thus, although we could confirm that the samples contained viable influenza virus, we could not quantify the amount of virus that was present. In addition, we think it is likely that at least some of the subjects with negative results probably were expelling viable virus, but not enough for us to detect with the methods used. As a consequence, we propose to modify our aerosol collection system so that it collects particles continuously for 40 minutes rather than collecting discrete coughs and exhalations. We believe this will greatly increase the amount of influenza virus that is collected from each subject.

In addition, in our previous study, we did not collect blood specimens from our test subjects. However, recent work has shown that influenza infection leads to changes in microRNA expression in cultured cells and in mice [22-24]. If influenza infection has a similar effect in people, and if the levels of blood microRNA have a consistent relationship with the amount of infectious aerosol particles expelled by influenza patients, then this could both provide insight into influenza transmission and suggest a simple screening method to find the patients most likely to transmit influenza to others.

The purpose of the revised study is to measure the amount of influenza virus in airborne particles that are produced by infected participants when they breathe and cough, and compare this to the levels of influenza-associated biomarkers in the blood. The results of the tests of influenza-infected participants also will be compared to those from a matched number of control non-infected participants. An understanding of the relationship between the amount of potentially infectious material released by infected people and the levels of microRNA biomarkers in the blood will assist in determining the possible role of airborne transmission in

the spread of influenza and in devising methods to screen for patients who are most likely to spread influenza by airborne particles.

Adult clinical outpatients presenting with influenza at participating medical clinics will be referred by the clinic staff to a recruiter if they are interested. The recruiter will use the initial verbal screening (Attachment 3) to recruit volunteers for the study and to screen them for eligibility to participate. The informed consent form (Attachment 4) ensures and documents that volunteers understand the study and are willing to participate in it. The health questionnaire (Attachment 5) allows us to verify that the volunteers are eligible for the study and determine if they have any medical conditions that would preclude their participation. The health questionnaire also allows us to relate the results of the tests on the nasopharyngeal mucus, blood samples, and aerosol production to participant characteristics such as duration and type of symptoms, body size, and oral temperature.

The positive needs for the data to be collected in this study include:

- The Institute of Medicine (part of the US National Academy of Sciences) has identified information on the modes of influenza transmission, and in particular on airborne transmission by infectious aerosols, as being a critical gap that urgently needs to be filled in order to plan for infection control procedures during an influenza pandemic. The IOM urged CDC and NIOSH to undertake research in this area [8]. The proposed study will help to better understand influenza transmission and address this need.

- The NIOSH National Occupational Research Agenda includes a goal to "Conduct research to better understand characteristics associated with airborne transmission, such as quantity and size distribution of aerosols generated by coughing and sneezing, determinants of survival and infectivity in airborne droplet nuclei, and virulence after airborne transmission." (HCSA Activity/Output Goal 5.1.3, National Occupational Research Agenda, http://www.cdc.gov/NIOSH/NORA/). The proposed research directly addresses this need for information.

The negative consequences of not collecting this data include:

- The modes of transmission of influenza will continue to be poorly understood, which will hamper the ability to determine which infection controls procedures are vital and which are unnecessary.

- The public health community, healthcare-providing organizations and healthcare workers will lack the information they need to confidently determine which procedures and personal protective measures and equipment should be implemented during periods of seasonal influenza or in an influenza pandemic.

The data collected in this project will be used to produce publications (both peer reviewed and non-peer reviewed), presentations, guidelines and recommended practices for dissemination among healthcare workers, their employers, and persons tasked with protecting the health and safety of healthcare workers. Dissemination of this information is expected to enable people

concerned with infection control and pandemic planning to develop informed and targeted prevention and screening methods. The CDC maintains an extensive catalog of guidelines, recommended practices and information resources for healthcare professionals, including information on infection control in general and influenza in particular. The information learned in this project will be used to help formulate and revise these resources in order to better serve the healthcare community.

A3. Use of Improved Information Technology and Burden Reduction

The informed consent and health questionnaire data will be collected using printed forms which are completed manually. Nasopharyngeal mucus samples, oral temperatures, blood samples and aerosol samples will be collected 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. No published studies have related infectious aerosol production by subjects with influenza to blood biomarkers, including microRNAs. A report by the Institute of Medicine stated that insufficient information was available to assess the potential risk from infectious aerosols produced by influenza patients, and that such research was urgently needed [8].

A5. Impact on Small Businesses or Other Small Entities

No small businesses or other small entities will be involved in this data collection.

A6. Consequences of Collecting the Information Less Frequently

Respondents will be asked to provide information one time only. No alternative methods are available to obtain the needed health information and informed consent from the participants. There are no legal obstacles to reduce the burden.

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

“ This request fully complies with the regulations 5 CFR 1320.5”

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

Federal Register Notice

The 60-day Federal Register Notice (Federal Register Vol. 82, No. 40, p. 12360) was published on Thursday, March 2, 2017 and is shown in Attachment 2. No public comments were received in response to the 60-day Federal Register Notice.

Consultation outside the Agency

This project was reviewed and approved by the CDC Influenza Research Agenda Working Group in 2010. The project and preliminary results from previous related work were presented at a public workshop at the US Institute of Medicine titled “Workshop on Personal Protective Equipment for Healthcare Workers in the Workplace Against Novel H1N1 Influenza A” on August 12, 2010; at a public meeting titled “Personal Protective Technology Program Healthcare

Stakeholder Meeting", conducted by the CDC on June 18, 2013; at a workshop titled "Influenza Transmission and the Built Environment–understanding modes of transmission in a sustainable future", conducted by the National Socio-Environmental Synthesis Center on March 6-7, 2014; and at the 34th annual conference of the American Association for Aerosol Research on October 12-16, 2015. Oral public comments on the presentations were taken during the workshops and the meetings. Some suggestions for improvements to this work were received and incorporated, but no significant problems or concerns were identified by these consultations.

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 did not receive a token of appreciation for their participation. This is especially true when subjects are not feeling well and thus are less inclined to participate. In addition, studies that require blood collection often have difficulty recruiting test subjects because of strong aversions to hypodermic needles and blood draws.

In the previous approval, potential volunteers were offered $25 as a token of appreciation for their participation in the study. The previous study required less time (63 minutes vs. 95 minutes for the present study) and no blood collection was performed, but only about 50% of eligible subjects agreed to participate. A recent study at West Virginia University (in the same clinic where our study will be conducted) collected blood from outpatients. Those researchers offered $25 as an incentive and only required 15 minutes to participate. The researchers only had about a 33% participation rate, apparently due in large part to an unwillingness of subjects to undergo a blood draw. Because the proposed study will require a longer time commitment than our previous study and because the study includes blood collection, which acts as a strong disincentive to many potential participants, we propose to increase the token of appreciation offered to the test subjects to $40 in the form of a gift card.

A10. Protection of the Privacy and Confidentiality of Information Provided by Respondents

This submission has been reviewed by NIOSH ISSO, who determined that the Privacy Act does not apply.

Participants will be informed at the time of recruitment that their participation is completely voluntary, and that participating or not participating in the study will not have any effect on them. The study will be explained to all respondents at the beginning of their participation, and they will be asked to review and sign a written informed consent form which explains the purpose of the study and how their information will be used and shared (Attachment 4). Participants are offered a copy of the informed consent form to take with them. In the informed consent form, respondents are informed that the data supplied to NIOSH will be kept in a secure manner**,** unless compelled by law. The NIOSH IRB has reviewed and approved all instruments, informed consent materials and procedures to ensure that the rights of respondents are safeguarded (Attachment 7).

The name and signature of each study participant will be recorded on the informed consent form. For all other information, each study participant will be assigned a unique identification code. The identification code will not be recorded on the informed consent form. The identification code, but not the participant's name, will be recorded on the health questionnaire, aerosol particle samples, the blood specimens, and the nasopharyngeal swabs. Thus, it will not be possible to link the name of a participant with the information that is collected. The name of the test subjects or any other facts that might point to their identity will not appear anywhere in the published results. The information entered into the health questionnaire may be released as part of the publication and dissemination of the information gained in the study; however, the information is not sufficient to allow individuals to be identified. Electronic data files will use the subject ID codes only and will not include the subjects' names or other information that would allow them to be identified.

Information will be maintained by including safeguards such as physical controls for hardcopies (controlled building access, security guard service, locked rooms) and technical controls for electronic copies (password-protected LAN, time-limited log-ins, file access limited to authorized users). All completed forms will be kept in a locked file cabinet in the Morgantown NIOSH facility (1095 Willowdale Road, Morgantown, West Virginia). Access to the facility is controlled by guards and badge-operated locks on all doors. Only the investigators of the study will have access to records that include test subject names or other data that might allow identification.

The following categories of Information in Identifiable Form (IIF) will be collected: The informed consent form will collect the participant's name. The health questionnaire will not include or be linked to the participant's name, but will collect age, gender, height, weight, information about respiratory illnesses, pregnancy status, current illness, influenza vaccination status, flu medications taken, smoking history, and oral temperature. In addition, biological specimens will be collected; these specimens will be linked to the health questionnaire by an identifier code but will not be linked to the participant's name. We will not have access to information from the healthcare provider.

The collection of IIF and other data for this project will have little to no effect on the respondent's privacy. NIOSH takes extensive safeguards to protect against any release of individual level data. The project staff will notify their supervisors immediately upon: (1) discovering any breach or suspected breach of security, (2) discovering any unauthorized disclosure of the confidential information or (3) receipt of any legal, investigatory, or other demand for access to the confidential information in any form. Should any of these issues occur, project progress will be halted until approval is received from NIOSH supervisors to resume project activities. In addition, the NIOSH Institutional Review Board (IRB) will be informally notified of any potential breach of confidentiality within two working days of an incident and formally notified within two weeks of an incident. Proven violation of confidential information related to or obtained from the data is cause for immediate termination of access to any data and additional sanctions.

The informed consent forms and health questionnaires will be retained for 20 years after completion of the study as required by the applicable CDC Records Control Schedule. After 20 years, the forms will be destroyed. The health questionnaire is the only source of information linking subject's names to their identification numbers.

A11. Institutional Review Board (IRB) and Justification for Sensitive Questions

Institutional Review Board (IRB)

The NIOSH IRB has reviewed and approved all instruments, informed consent materials and procedures to ensure that the rights of respondents are safeguarded (Attachment 7).

Justification for Sensitive Questions

No sensitive information will be collected. Social Security numbers will not be collected.

A12. Estimates of Annualized Burden Hours and Costs

A. Estimated Annualized Burden Hours

The estimated annual response burden is shown is Table A12-A. Ninety participants (45 infected with influenza and 45 controls) will be needed each year for a total of 270 participants over 3 years. During previous similar studies, we found that about 50% of the potential participants declined to participate or weren't eligible for the study. Thus, we estimate that we will need to verbally screen about 540 potential participants to reach our goal of 270. In the previous studies, no participants dropped out of the study once they had decided to participate.

The verbal screening (Attachment 3) will take 1-3 minutes, the informed consent form (Attachment 4) will require about 15 minutes to read and sign, and the health questionnaire (Attachment 5) will require about 5 minutes. These times for burden per response are based on our previous studies. The oral temperature collection, nasopharyngeal mucus collection, blood collection, and aerosol collection will take about 72 minutes. A detailed breakdown of the time required for the medical testing is shown in Attachment 6. The total time from initial verbal screening to completion will be about 95 minutes.

Table A12-A. Estimated Annual Response Burden

Type of Respondent	Form Name	No. of Respondents	No. of Responses per Respondent	Avg. Burden per Response (in hrs.)	Total Burden (in hrs.)
Potential participant	Initial verbal screening	180	1	3/60	9
Qualified participant	Informed consent form	90	1	15/60	23
Qualified participant	Health questionnaire	90	1	5/60	8
Qualified participant	Medical testing	90	1	72/60	108
	TOTAL				**148**

B. Estimated Annualized Burden Costs

Estimated annual burden costs for those surveyed are shown in Table A12-B. Wage estimates are based on the *May 2015 State Occupational Employment and Wage Estimates for West Virginia (all occupations)* from the US Bureau of Labor Statistics, which is the most recent data available.

Table A12-B: Estimated Annual Burden Cost

Type of Respondents	*Form Name*	*No. of Respondents*	*No. of Responses per Respondent*	*Avg. Burden per Response (in hrs.)*	*Total Burden (in hrs.)*	*Median hourly wage*	*Total respondent costs*
Potential participant	Initial verbal screening	180	1	3/60	9	$14.54	$30.86
Qualified participant	Informed consent form	90	1	15/60	23	$14.54	$334.42
Qualified participant	Health questionnaire	90	1	5/60	8	$14.54	$116.32
Qualified participant	Medical testing	90	1	72/60	108	$14.54	$1,570.32
						TOTAL	$2,051.92

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

There will be no additional cost burden to respondents and record keepers.

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 three years. There will be no new overhead, support staff, or construction required for the survey administration and data analysis. The study will last three years and will not require any funds for travel.

Table A14. Annualized cost to the Federal Government

Personnel--2 GS-13, 25% time per year	$48,629.00
Personnel--2 GS-9, 25% time per year	$28,200.50
Tokens of appreciation given to respondents for study participation (per year)	$3,600.00
Total annualized estimate of federal cost	**$80,429.50**

A15. Explanation for Program Changes or Adjustments

This is a Reinstatement with change. The following changes to the project are proposed:

1) The cough and exhalation aerosol collection system will be modified to collect aerosol particles continuously for 40 minutes, rather than collecting particles from discrete coughs and exhalations as in the previous study. This will increase the amount of influenza virus that is collected.
2) A blood sample will be collected from each participant to allow testing for blood markers of influenza infection and a comparison of the levels of these markers to the amount of influenza that is expelled in aerosol particles.
3) The time required for participation has been increased from 63 minutes to 95 minutes to allow for a longer aerosol collection period and for the blood collection.
4) In addition to subjects with influenza-like illness, an equal number of control subjects without symptoms of respiratory illness will be recruited and tested. This will allow the determination of the differences in blood biomarker levels between healthy and infected subjects.
5) Because of the longer participation time and because blood collection has been found to be a strong disincentive for participation, the token of appreciation for participating in the study has been increased from $25 to $40.

A16. Plans for Tabulation and Publication and Project Time Schedule

Volunteers can only be recruited and tested during influenza season, which typically lasts 1 to 3 months each year but is unpredictable and can vary significantly in time and intensity. Because of time, space and personnel constraints, a maximum of about 90 subjects can be tested each year. Thus, we anticipate that three years will be required to complete the study.

Table A16. Proposed time schedule.

Activity	*Time schedule after OMB approval*	
	Start month	*End month*
Recruit and test 90 volunteers with influenza during first influenza season	0	3
Culture and analyze samples, evaluate results, and refine experimental methodologies	3	12
Recruit and test 90 volunteers with influenza during second influenza season	12	15
Culture and analyze samples, evaluate results, and refine experimental methodologies	15	24
Recruit and test 90 volunteers with influenza during third influenza	24	27
Culture and analyze samples, evaluate results.	27	33
Publication	33	36
TOTAL	**36 months**	

This project is intended to be primarily a descriptive study of the amount of viable influenza virus expelled by participants during coughing and of any correlations between the amount of virus expelled and the levels of influenza-associated microRNA molecules in the blood. Data will be analyzed by comparing the amount of influenza virus detected in the swabs and in the airborne particles to the levels of various microRNA molecules in the blood. Results from infected test subjects will also be compared to those of a matched number of uninfected controls. The different experiment parameters and health questionnaire information (symptoms, length of illness and vaccine status) will be tested for correlations between variables.

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

“The display of the OMB expiration date is not inappropriate.”

A18. Exceptions to Certification for Paperwork Reduction Act Submissions

"There are no exceptions to the certification."

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