

**ARIC Manuscript Proposal # 3141**

**PC Reviewed:** 03/20/2018  
**SC Reviewed:** \_\_\_\_\_

**Status:** \_\_\_\_\_  
**Status:** \_\_\_\_\_

**Priority:** 2  
**Priority:** \_\_\_\_\_

**1.a. Full Title:**

Temporal relation between influenza and hospitalization for heart failure or myocardial infarction in the Atherosclerosis Risk in Communities (ARIC) study

**b. Abbreviated Title (Length 26 characters):**

Flu, HF and MI trends in ARIC

**2. Writing Group:**

Writing group members:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. SKK [please confirm with your initials electronically or in writing]

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**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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**3. Timeline:**  
3 months

**4. Rationale:**

Influenza infection is known to be associated with an increased risk of cardiovascular (CV) events<sup>i</sup>. Several studies have reported an increase in CV mortality and acute myocardial infarction (AMI) during times when influenza was circulating. These results have been consistent across studies using various measures for AMI, such as autopsy-confirmed AMI deaths<sup>ii</sup> and ICD-9 discharge codes<sup>iii-iv</sup>, and influenza activity at both the population level through surveillance data<sup>ii-iv</sup> and at the individual level with lab-confirmed infection<sup>v</sup>. Furthermore, a self-controlled case series study in the United Kingdom compared risk of first MI and stroke with timing of preceding acute respiratory infection (ARI) and found that MI and stroke risks were significantly raised 1-3 days after ARI, with incidence ratios of 4.95 (95%CI: 4.43-5.53) and 3.19 (95%CI: 2.81-3.62), respectively<sup>vi</sup>. This shows a temporal relationship between infections and CV events, and suggests that influenza and influenza-like illness trigger AMI as well as stroke.

While many previous studies examining the relationship between influenza and CV disease have focused on mortality and CV mortality, fewer have explored the extent to which influenza contributes to CV hospitalizations, especially events associated with congestive heart failure (HF)<sup>i</sup>. Among studies that have investigated the relationship between influenza and HF, results have been inconsistent. A Canadian study examined the impact of influenza on HF hospital admissions, and found no significant correlation between influenza and hospital admissions for HF among people over the age of 65. They identified all hospital discharges in Ontario, Canada with discharge diagnosis *International Classification of Disease, Ninth Revision (ICD-9)* codes for HF between 1988-1993<sup>vii</sup>. However, there was no additional adjudication process to confirm the diagnosis. Another Canadian study explored the impact of influenza on the risk of all cause hospitalization among patients with congestive heart failure and found that the overall hospitalization rate was higher during the influenza season compared to non-influenza seasons (RR=1.08, 95%CI=.01-1.16)<sup>viii</sup>. However, this study population consisted of patients from two randomized placebo-controlled trials.

The temporal relationship between influenza-like illness and number of adjudicated hospitalizations for acute heart failure and myocardial infarction has not been previously well described in a community cohort

## **5. Main Hypothesis/Study Questions:**

Is there a temporal relation between influenza and cardiovascular hospitalization for heart failure or myocardial infarction in a community cohort? Specifically, we hypothesize that an increase in influenza-like illness is associated with an increase in the number of hospitalizations for both myocardial infarction and acute heart failure.

## **6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

*Study design:* Retrospective ecological study

*Exposure:* The exposure of interest is influenza activity from October 2010 to December 2014, as indicated by the percent of patient visits to sentinel health care providers for influenza-like illness (ILI) in Mississippi, Minnesota, Maryland and North Carolina. These data are publicly available and collected through the U.S. Outpatient Influenza-Like Illness Surveillance Network (<https://www.cdc.gov/flu/weekly/overview.htm>).

*Outcomes:* Number of adjudicated MI and acute HF hospitalizations among ARIC communities per month from October 2010 to December 2014 from community surveillance.

*Other variables of interest:* To account for the potential protective effects of vaccination, influenza vaccination coverage in each state will also be included in the analysis. The CDC estimates for monthly influenza vaccination coverage are publicly available and based on several representative surveys, including the Behavioral Risk Factor Surveillance System (BRFSS), the National Health Interview Survey (NHIS), and the National Immunization Survey-Flu (NIS-Flu) (<https://www.cdc.gov/flu/fluview/index.htm>).

*Data analysis:* Since the data are collected over time, events may be predicted by using counts from prior months, thus violating the assumption of independent observations. To determine if there is autocorrelation, influenza, MI and HF values will be correlated with values from previous and subsequent months. The number of MI and HF events will then be cross correlated with the percent of patient visits for ILI, as well as ILI values from previous months to determine the appropriate lag. A Poisson regression will be used to further assess the relation between both MI and HF with influenza with adjustments for monthly vaccination coverage, site, and autocorrelation.

In addition, a sensitivity analysis will be performed using regional/county-level data from the 2017-2018 influenza season to estimate how significantly influenza activity differs between regional and state levels.

*Limitations:* The individual influenza illness or vaccination status of those hospitalized for HF or MI is not known. Therefore, we cannot make inferences about the association of influenza and HF or MI at the individual level. Additionally, the data on influenza-like illness is available at the state level, while the HF and MI hospitalization data is representative of the counties with surveillance sites. This could bias the results, as influenza activity at the state level may not be representative of the surveilled counties. To address this limitation, we plan to use regional/county-level data from the 2017-2018 influenza season to estimate how significantly influenza activity differs between regional and state levels to perform a sensitivity analysis as described above.

**7.a. Will the data be used for non-CVD analysis in this manuscript?** \_\_\_ Yes \_\_\_X\_\_\_ No

**b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES\_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES\_DNA = "CVD Research" would be used?** \_\_\_ Yes \_\_\_ No

(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

**8.a. Will the DNA data be used in this manuscript?** \_\_\_ Yes \_\_\_X\_\_\_ No

**8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES\_DNA = "No use/storage DNA"?** \_\_\_ Yes \_\_\_ No

**9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://www.csc.unc.edu/ARIC/search.php>**

Yes     No

**10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?**

Hospitalized infection as a trigger for acute ischemic stroke in the ARIC study (Proposal #2391)

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  Yes     No**

**11.b. If yes, is the proposal**

**A. primarily the result of an ancillary study (list number\* \_\_\_\_\_)**

**B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)\* \_\_\_\_\_)**

\*ancillary studies are listed by number at <http://www.csc.unc.edu/aric/forms/>

**12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.**

**12b. The NIH instituted a Public Access Policy in April, 2008** which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.

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<sup>i</sup> Kwok, C., Aslam, S., Kontopantelis E., Myint, P., Zaman, M., Buchan, I., Loke, Y., Mamas, M. Influenza, influenza-like symptoms and their association with cardiovascular risk: a systemic review and meta-analysis of observational studies. *International Journal of Clinical Practice*, 2015.

<sup>ii</sup> Madjid, M., Miller, C., Zarubaev, V., Marinich, I., Kiselev, O., Lobzin, Y., Filippov, A., Casscells, S. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34892 subjects. *European Heart Journal*, 2007.

<sup>iii</sup> Warren-Gash, C., Bhaskaran, K., Hayward, A., Leung, G., Lo, S., Wong, C., Ellis, J., Pebody, R., Smeeth, L., Cowling, B. Circulating influenza virus, climate factors and acute myocardial infarction: a time series study in England and Wales and Hong Kong. *Journal of Infectious Disease*, 2011.

<sup>iv</sup> Nguyen, J., Yang, W., Ito, K., Matte, T., Shaman, J., Kinney, P. Seasonal influenza infections and cardiovascular disease mortality. *JAMA Cardiology*, 2016.

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<sup>v</sup> Kwong, J., Schwartz, K., Campitelli, M., Chung, H., Crowcroft, N., Karnauchow, T., Katz, K., Ko, D., McGeer, A., McNally, D., Richardson, D., Rosella, L., Simor, A., Smieja, M., Zahariadis, G., Gubbay, J. Acute myocardial infarction after laboratory-confirmed influenza infection. *New England Journal of Medicine*, 2018.

<sup>vi</sup> Smeeth, L., Thomas, S., Hall, A., Hubbard, R., Farrington, P., Vallance, P. Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination. *New England Journal of Medicine*, 2004.

<sup>vii</sup> Upshur, R., Knight, K., Goel, V. Time-series analysis of the relation between influenza virus and hospital admissions of the elderly in Ontario, Canada, for Pneumonia, Chronic Lung Disease, and Congestive Heart Failure.

<sup>viii</sup> Sandoval, C., Walter, S., Krueger, P., Smieja, M., Smith, A., Yusuf, S., Loeb, M. Risk of hospitalization during influenza season among a cohort of patients with congestive heart failure. *Journal of Epidemiology and Infection*, 2007.