ORIGINAL ARTICLE

Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection

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ABSTRACT

BACKGROUND

Acute myocardial infarction can be triggered by acute respiratory infections. Previous studies have suggested an association between influenza and acute myocardial infarction, but those studies used nonspecific measures of influenza infection or study designs that were susceptible to bias. We evaluated the association between laboratory-confirmed influenza infection and acute myocardial infarction.

METHODS

We used the self-controlled case-series design to evaluate the association between laboratory-confirmed influenza infection and hospitalization for acute myocardial infarction. We used various high-specificity laboratory methods to confirm influenza infection in respiratory specimens, and we ascertained hospitalization for acute myocardial infarction from administrative data. We defined the "risk interval" as the first 7 days after respiratory specimen collection and the "control interval" as 1 year before and 1 year after the risk interval.

RESULTS

We identified 364 hospitalizations for acute myocardial infarction that occurred within 1 year before and 1 year after a positive test result for influenza. Of these, 20 (20.0 admissions per week) occurred during the risk interval and 344 (3.3 admissions per week) occurred during the control interval. The incidence ratio of an admission for acute myocardial infarction during the risk interval as compared with the control interval was 6.05 (95% confidence interval [CI], 3.86 to 9.50). No increased incidence was observed after day 7. Incidence ratios for acute myocardial infarction within 7 days after detection of influenza B, influenza A, respiratory syncytial virus, and other viruses were 10.11 (95% CI, 4.37 to 23.38), 5.17 (95% CI, 3.02 to 8.84), 3.51 (95% CI, 1.11 to 11.12), and 2.77 (95% CI, 1.23 to 6.24), respectively.

CONCLUSIONS

We found a significant association between respiratory infections, especially influenza, and acute myocardial infarction. (Funded by the Canadian Institutes of Health Research and others.)

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Coronary artery disease remains a leading cause of death worldwide.[1] The hypothesis that influenza may trigger acute cardiovascular events and death was advanced as early as the 1930s, when the association between seasonal influenza activity and cardiovascular mortality was first noted.[2,3] Several case–control and self-controlled studies have since shown an association between visits to physicians' offices for acute respiratory infections or influenza-like illnesses and subsequent acute cardiovascular events.[4-14] However, the clinical diagnoses of acute respiratory infections and influenza-like illnesses in these studies were neither sensitive nor specific for influenza, and the few studies that used laboratory-confirmed influenza as the measure of exposure were underpowered, had inconsistent findings, and used the case–control design, which is susceptible to selection bias and residual confounding.[15-18]

It is important to confirm the association between influenza and acute myocardial infarction because cardiovascular events triggered by influenza are potentially preventable by vaccination. Better evidence that influenza triggers cardiovascular events may lead to a change in practice that would improve the currently suboptimal vaccine coverage among persons who are at high risk for acute myocardial infarction.[19-21] Given the limitations of the current data, we sought to evaluate the association between laboratory-confirmed influenza infection and acute myocardial infarction using the self-controlled case-series study design.

Methods

Study Setting, Population, and Support

The health insurance program of Ontario provides universal access to physician services, hospital care, and laboratory testing for virtually all residents. We included in our study all Ontario residents who were registered for provincial publicly funded health insurance; who underwent testing for one or more respiratory viruses between May 1, 2009, and May 31, 2014; who were 35 years of age or older at the time of testing; and who were hospitalized for an acute myocardial infarction between May 1, 2008, and May 31, 2015. We obtained ethics approval from the institutional review board at Sunnybrook Health Sciences Centre in Toronto.

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Data Sources and Definitions

We obtained respiratory virus testing results from the Flu and Other Respiratory Viruses Research (FOREVER) Cohort (see the Supplementary Appendix, available with the full text of this article at NEJM.org). In brief, the cohort features individual-level linkage of respiratory virus testing results from 11 Public Health Ontario laboratories and 8 academic hospital–based laboratories with an extensive array of administrative databases held at the Institute for Clinical Evaluative Sciences. The respiratory specimens that were tested were submitted from physician offices, emergency departments, hospitals, long-term care facilities, and public health departments as part of routine clinical care, outbreak investigations, or research. They were tested for influenza A (with subtype information available for 56% of the positive specimens) and influenza B, and 88% of the specimens were also tested for one or more of the following respiratory viruses: respiratory syncytial virus (RSV), adenovirus, coronavirus, enterovirus (including rhinovirus), parainfluenza virus, and human metapneumovirus. Testing methods included reverse-transcriptase polymerase chain reaction (PCR; monoplex or multiplex assays), viral culture, direct fluorescent antibody staining, and enzyme immunoassays. Limited information regarding clinical symptoms was available for approximately 40% of the cases included in this study (see the Supplementary Appendix). To avoid capturing multiple exposures for the same illness episode, we excluded positive specimens that were obtained within 14 days after a previous positive specimen from the same patient.

Hospitalizations for acute myocardial infarction were ascertained from the Discharge Abstract Database of the Canadian Institute for Health Information, which contains detailed administrative, diagnostic, and clinical information for all admissions to acute care hospitals.[22] We included admissions with acute myocardial infarction as the primary diagnosis, defined on the basis of diagnosis code I21 in the Interna-

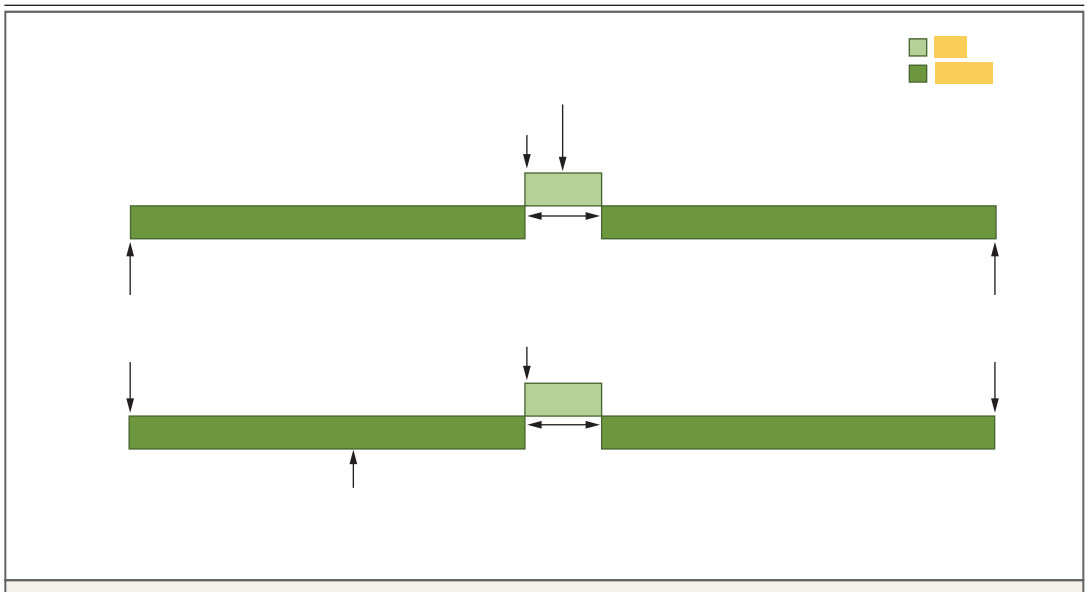

Figure 1. Schematic of the Study Design.

Patient A represents a person who is infected with influenza and is hospitalized for acute myocardial infarction at any time during the 7-day risk interval (light-shaded areas) after exposure. Patient B represents a person infected with influenza who has an acute myocardial infarction during the control interval (dark-shaded areas). The study assessed the relative incidence of acute myocardial infarction during the risk interval as compared with the control interval. Note that the figure is not to scale.

tional Classification of Diseases, 10th Revision (ICD-10). In a validation study, conducted in Ontario, that used a registry of patients who had been admitted to cardiac care units with acute coronary syndromes as the reference standard, the sensitivity of acute myocardial infarction diagnostic codes was 89%, the specificity was 93%, and the positive predictive value was 89%.[32] We restricted the analysis to the first event in an episode of care by excluding transfers between hospitals and admissions within 30 days after a previous hospital discharge for acute myocardial infarction for the same patient. The laboratory and hospitalization data were linked at the individual level with the use of unique encoded identifiers (linkage proportion, 97%) and were analyzed at the Institute for Clinical Evaluative Sciences.

Statistical Analysis

The statistical analysis was based on the self-controlled case-series design, as shown in Figure 1. The date the respiratory specimen was obtained served as the index date for defining the exposure (laboratory-confirmed influenza infection) because the date of symptom onset was generally not available and the date of infection could not be determined. We defined the observation period as the interval from 1 year before to 1 year after the index date, and we included in our analyses patients who had at least one admission for acute myocardial infarction during this period. The observation time was truncated in this manner to minimize time-varying confounding, since the self-controlled case-series design does not control for time-varying confounding.

In the primary analysis, we defined the "risk interval" as the first 7 days after the index date and the "control interval" as all other times during the observation period (i.e., 52 weeks before the index date and 51 weeks after the end of the risk interval) (Fig. 1). There is often a lag between influenza infection, symptom onset, and subsequent laboratory testing for influenza.[33] Therefore, we excluded cases of acute myocardial infarction if the positive influenza specimen was obtained during the admission for acute myocardial infarction because we could not determine the temporal relationship between the influenza exposure and the cardiac outcome.

We estimated the incidence ratio for hospitalizations for acute myocardial infarction during

the risk interval as compared with the control interval with the use of a fixed-effects conditional Poisson regression model. The model accounted for multiple influenza exposures and hospitalization episodes for acute myocardial infarction per patient during the observation period.[24] In addition to the primary analysis that defined the risk interval as days 1 through 7 after the index date, we also considered narrower risk intervals (days 1 through 3 and days 4 through 7) and alternative risk intervals (days 8 through 14 and days 15 through 28).

To test the robustness of our findings, we conducted a number of sensitivity analyses. These included analyses that controlled for calendar month; that limited the control interval to the postexposure observation time, to the preexposure observation time, or to the 2 months before and after influenza diagnosis; that included patients for whom the specimen was obtained during the admission for acute myocardial infarction; and that applied induction intervals of varying lengths. An induction interval is a portion of the observation time immediately preceding the index date that is excluded from the control interval.[25] To examine the specificity of our findings, we repeated the analyses with data on exposures other than influenza. These included a positive test result for RSV, a positive test result for respiratory viruses other than influenza or RSV, and an illness for which no respiratory virus was identified. The last group included cases of infection with nonviral agents, viral infections that had already cleared in the patient, infection with viruses that were not tested for, and false negative samples. We also examined the association between influenza infection and hospitalizations for diabetes and associated complications (ICD-10 codes E10, E11, E13, and E14), an outcome for which no significant association was anticipated.

We performed analyses in subgroups defined according to age (≤65 years vs. >65 years), sex, influenza type (A [all subtypes] vs. B), influenza A subtype (H1N1 vs. H3N2), influenza vaccination status, history of hospitalization for acute myocardial infarction before the study period (yes vs. no), and laboratory testing method (PCR vs. only non-PCR methods). We evaluated the presence of interactions in these subgroups.

All statistical tests were two-tailed, and P values of less than 0.05 were considered to indicate statistical significance. Analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

TESTING EPISODES AND PARTICIPANT DEMOGRAPHICS

Among 148,307 influenza testing episodes (with a single testing episode including tests of all specimens from the same person on the same day) in adults 35 years of age or older during the study period, 19,729 testing episodes (13%) were positive for influenza (Fig. 2). The final data for the primary analysis consisted of 364 hospitalizations for acute myocardial infarction among 332 patients who had a laboratory-confirmed diagnosis of influenza.

The median age of the study population was 77 years (interquartile range, 65 to 86), 48% of the patients were female, 24% had had a previous hospitalization for acute myocardial infarction, many had established cardiovascular risk factors (49% had diabetes, 38% had dyslipidemia, and 85% had hypertension), and 31% had been vaccinated against influenza for that influenza season (Table 1). Most infections (82%) were due to influenza A.

RISK OF ACUTE MYOCARDIAL INFARCTION AFTER INFLUENZA INFECTION

There were 20 admissions for acute myocardial infarction (20.0 admissions per week) during the risk interval and 344 (3.3 admissions per week) during the control interval (incidence ratio, 6.05; 95% confidence interval [CI], 3.86 to 9.50). The incidence ratios for days 1 through 3 and for days 4 through 7 were 6.30 (95% CI, 3.25 to 12.22) and 5.78 (95% CI, 3.17 to 10.53), respectively. We observed no significant increase in the incidence on days 8 through 14 (incidence ratio, 0.60; 95% CI, 0.15 to 2.41) or on days 15 through 28 (incidence ratio, 0.75; 95% CI, 0.31 to 1.81) (Table 2).

SENSITIVITY AND SUBGROUP ANALYSES

The results were robust in sensitivity analyses in which adjustment was made for calendar month, the control interval was limited in various ways, cases with respiratory specimens obtained during admission were included, and different induction periods before exposure were used (Table 2). The

alternative exposures that we studied (i.e., RSV, other respiratory viruses, and illness with no respiratory virus identified) were also associated with a significantly higher incidence of acute myocardial infarction, but the incidence ratio point estimates were lower than the incidence ratio point estimate for influenza. No significant association was observed between influenza infection and hospitalizations for diabetes and associated complications.

In the subgroup analyses, an elevated incidence of acute myocardial infarction after influenza infection was observed among adults older than 65 years of age but not for younger adults. However, the difference in incidence ratios between the two age groups was not significant (P=0.14 for interaction). The incidence ratios were higher for influenza B than for influenza A, but this difference was also not significant (P=0.19). With the relatively small number of cases of the H1N1 subtype of influenza A, the incidence ratio for the H1N1 subtype was not significantly greater than 1. The incidence of acute myocardial infarction was elevated regardless of influenza vaccination status or history of admission for acute myocardial infarction before the study period (Table 3).

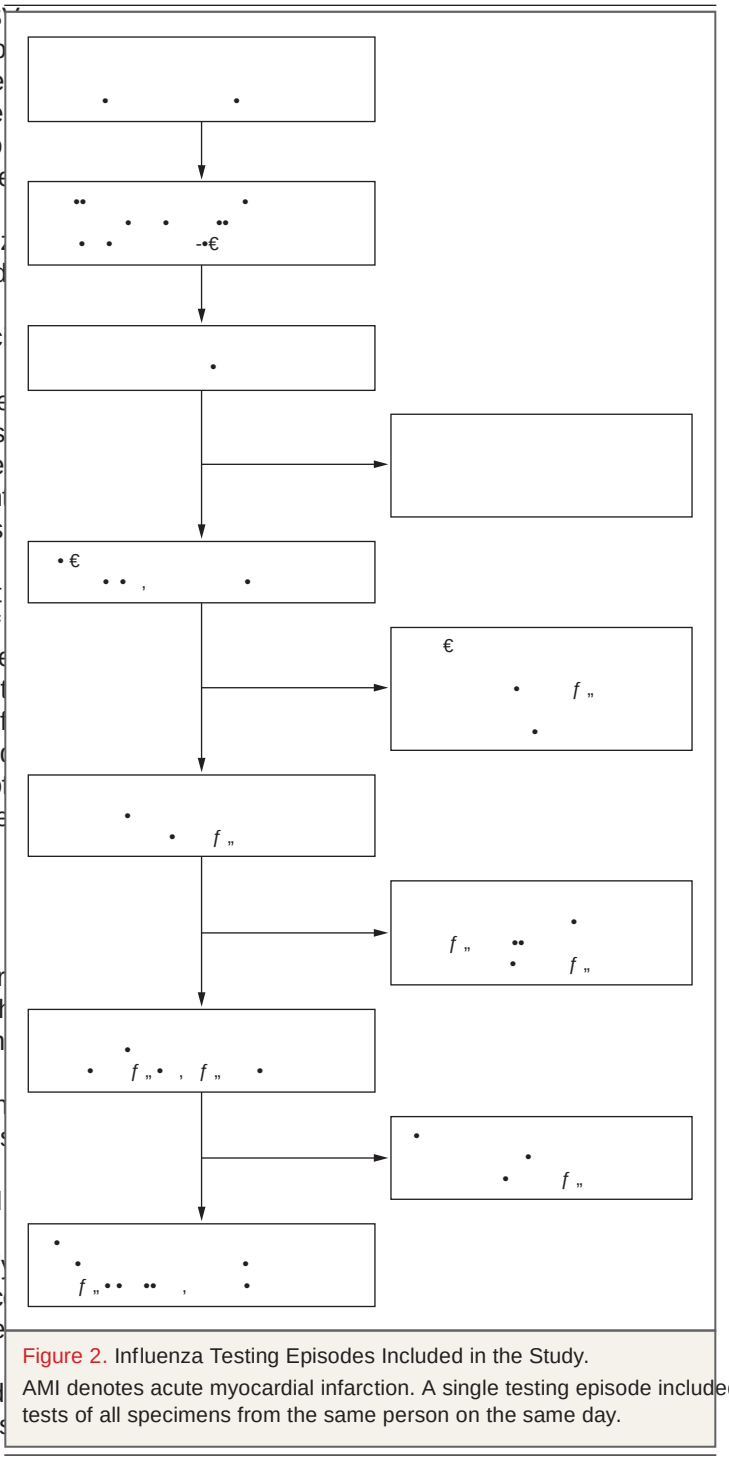

Figure 2. Influenza Testing Episodes Included in the Study.
AMI denotes acute myocardial infarction. A single testing episode included tests of all specimens from the same person on the same day.

Discussion

We found that the incidence of admissions for acute myocardial infarction was six times as high during the 7 days after laboratory confirmation of influenza infection as during the control interval (20.0 admissions per week vs. 3.3 admissions per week). The incidence ratio point estimates were highest for older adults, for patients with influenza B infection, and for patients who had their first acute myocardial infarction, but the analyses were insufficiently powered to identify differences within these subgroups. The incidence of acute myocardial infarction was also elevated (to a lesser extent than for influenza) after infection with noninfluenza respiratory viruses and illnesses that led to testing for respiratory viruses but in which no respiratory virus was identified. These results suggest that influenza is illustrative of the role that acute respiratory infections have in precipitating acute myocardial infarction.

Our findings are consistent with those in previous studies. Similar increases in the incidence of acute myocardial infarction 1 to 3 days after a visit to a physician that was coded as an acute respiratory infection have been shown by both Smeeth et al. (incidence ratio, 4.95; 95% CI, 4.43

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CLINICAL TRIAL REGISTRATION

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