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.[2-11] 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.[12-14] 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.

This study was supported by an operating grant from the Canadian Institutes of Health Research, by Public Health Ontario, and by the Institute for Clinical Evaluative Sciences. The authors vouch for the completeness and accuracy of the data and all analyses.

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-*

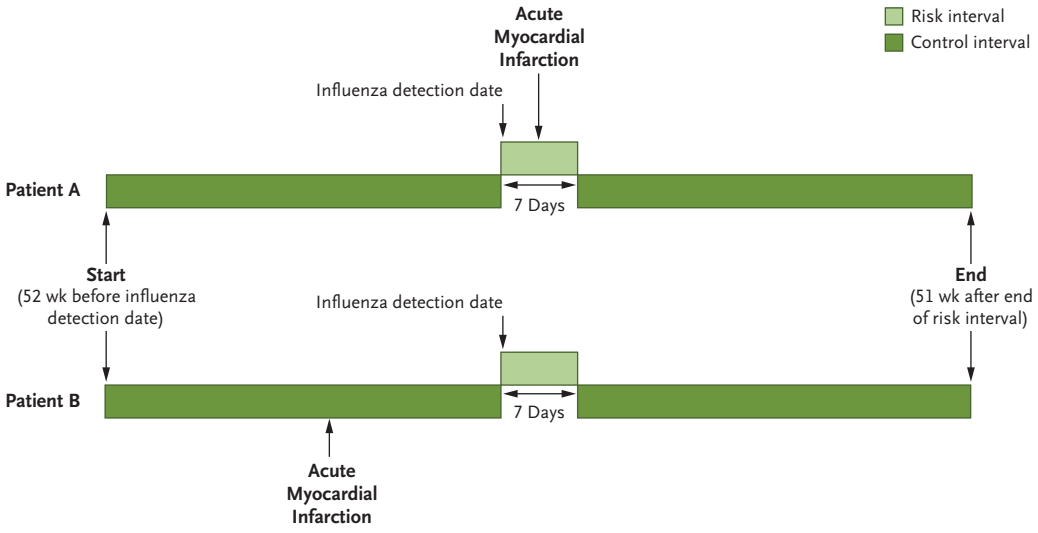

Figure 1. Schematic of the Study Design.

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%.[22] 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.[23] 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).

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

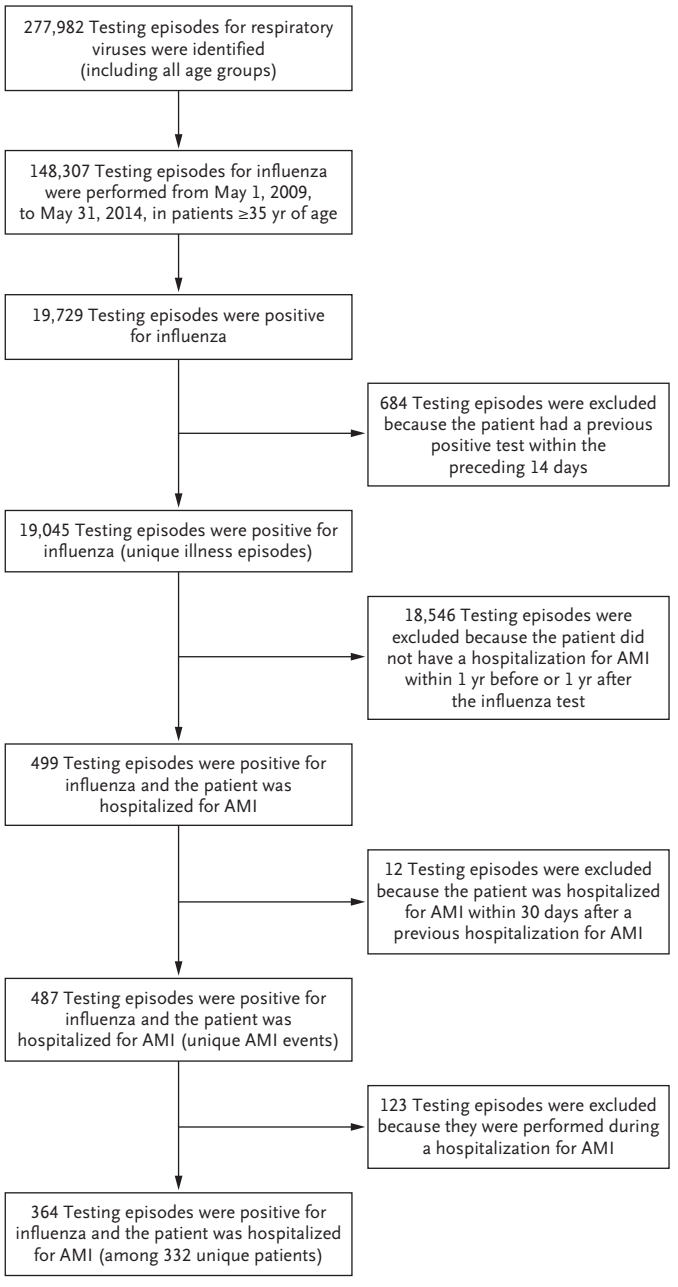

Figure 2. Influenza Testing Episodes Included in the Study.
AMI denotes acute myocardial infarction. A single testing episode included tests of all specimens from the same person on the same day.

Table 1. Baseline Characteristics of Patients Who Tested Positive for Influenza and Who Had an AMI within the Observation Period.*

Characteristic	Value
No. of patients	332
Age	
Median (IQR) — yr	77 (65–86)
Age group — no. (%)	
≤65 yr	85 (26)
>65 yr	247 (74)
Sex — no. (%)	
Male	174 (52)
Female	158 (48)
AMI hospitalization before observation period — no. (%)	
Yes	79 (24)
No	253 (76)
Cardiovascular risk factor — no. (%)	
Diabetes	163 (49)
Dyslipidemia	126 (38)
Hypertension	281 (85)
Influenza vaccination status — no. (%)	
Vaccinated	102 (31)
Not vaccinated	230 (69)
Influenza type and subtype — no. (%)	
Influenza A	272 (82)
H1N1	33 (10)
H3N2	112 (34)
Not subtyped	127 (38)
Influenza B	60 (18)
Laboratory testing method identifying influenza — no. (%)†	
Polymerase chain reaction‡	285 (86)
Viral culture	72 (22)
Direct fluorescent antibody staining	16 (5)
Enzyme immunoassay	8 (2)

* AMI denotes acute myocardial infarction, and IQR interquartile range.
† The sum of the values exceeds the total because some patients tested positive by more than one test.
‡ Either a monoplex or multiplex polymerase-chain-reaction assay was used.

to 5.53)[12] and Warren-Gash et al. (incidence ratio, 4.19; 95% CI, 3.18 to 5.53).[14] The magnitude of the incidence increase in our study may have been greater (incidence ratio, 6.30; 95% CI, 3.25 to 12.22) because the risk with influenza is greater than that with other respiratory viral infections. Warren-Gash et al. also found higher incidence ratio estimates with more specific measures of influenza exposure (e.g., onset of acute respiratory infection during peak periods of influenza circulation and diagnostic code of influenza-like illness assigned by the physician), though these methods are not as specific as laboratory detection. In this study, we found that there may be an increased risk among older patients and among patients having their first hospitalization for acute myocardial infarction, as well as an increased risk within 3 days after the index date — findings that are consistent with those in the previous studies. Results from previous studies that used laboratory-confirmed influenza infection were inconsistent,[15-18] but a case–control study from China showed that as compared with controls, patients with acute myocardial infarction had an odds ratio for detection of antibodies to influenza A and B of 5.5 (95% CI, 1.3 to 23.0) and 20.3 (95% CI, 5.6 to 40.8), respectively.[16] However, results from serologic testing are less robust than those from virus-detection tests. These previous studies were also limited by selection bias, sample size, or both.

Our finding of an increased incidence of acute myocardial infarction after laboratory-confirmed influenza infection despite vaccination should not be interpreted as evidence of a lack of vaccine effectiveness, because this study was not designed to evaluate the effectiveness of influenza vaccines. Rather, since vaccination of adults is only approximately 40 to 60% effective in preventing laboratory-confirmed influenza infection,[26,27] this study shows that if vaccinated patients have influenza of sufficient severity to warrant testing, their risk of acute myocardial infarction is increased to a level that is similar to that among unvaccinated patients.

Our findings, combined with previous evidence that influenza vaccination reduces cardiovascular events and mortality,[28] support international guidelines that advocate for influenza immunization in persons older than 65 years of age to protect against ischemic coronary events.[21] Other strategies to mitigate the cardiovascular risk associated with respiratory infections include maximizing the uptake of existing vaccines against other respiratory pathogens, developing more effective influenza vaccines and vaccines against other burdensome respiratory pathogens

(e.g., RSV), and promoting established infection prevention practices such as hand hygiene, respiratory etiquette, and social distancing.

In the context of chronic atherosclerotic vascular disease, an infectious illness may cause an acute coronary syndrome through acute inflammation, biomechanical stress, and vasoconstriction.[13] Infections create a thrombogenic environment through platelet activation and endothelial dysfunction. Furthermore, infections increase metabolic demand and may induce hypoxemia, hypotension, or other stress on the vascular system that can lead to the development of an occlusive thrombus and subsequently an acute coronary syndrome.[13] Our data suggest that a variety of acute respiratory infections may be associated with an increased risk of acute myocardial infarction; this observation is compatible with previous data that show that pneumonia is a risk factor for cardiovascular events.[29]

One limitation of this study is the uncertainty regarding the onset of influenza infection and of acute myocardial infarction. We used the date the specimen was obtained as the index date because the dates of infection and symptom onset were unavailable. The date the specimen was obtained is a reasonable approximation for the index date because the median incubation periods are only 1.4 days for influenza A and 0.6 days for influenza B,[30] because systemic and respiratory symptom scores peak on the day of symptom onset or the day after symptom onset,[31] and because the median interval from symptom onset to a visit to a physician is 2 days.[32] Our sensitivity analysis incorporating induction intervals of 2, 4, and 7 days confirmed that the date the specimen was obtained is a reasonable approximation for the index date. For the onset of acute myocardial infarction, we used the admission date for hospitalizations for which the primary diagnostic code was acute myocardial infarction, and we excluded transfers between hospitals to limit the analysis to distinct episodes of care. In the primary analysis, to eliminate reverse causality bias, we included only patients who underwent testing for influenza before hospital admission.

A second limitation of the study is the possibility of confounding due to time-varying factors (e.g., since both acute myocardial infarction and influenza exhibit seasonal patterns, another seasonally varying factor could be a confounder). However, the tightly circumscribed period of risk used in our analysis reduces the likelihood that the strong association we observed between influenza and acute myocardial infarction could be accounted for entirely by such seasonal variables. In addition, our results were robust in analyses that controlled for calendar month and that included a substantially shortened control interval. Nevertheless, we cannot completely exclude the possibility of confounding due to time-varying factors.

A third limitation is that these results might

Table 2. Incidence Ratios for Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection.*

Variable	Incidence Ratio (95% CI)
Primary analysis: risk interval, days 1–7	6.05 (3.86–9.50)
Days 1–3	6.30 (3.25–12.22)
Days 4–7	5.78 (3.17–10.53)
Days 8–14	0.60 (0.15–2.41)
Days 15–28	0.75 (0.31–1.81)
Sensitivity analyses	
Controlled for calendar month	6.19 (3.88–9.88)
Control interval limited to postexposure observation time	8.08 (5.04–12.95)
Control interval limited to preexposure observation time	4.84 (3.06–7.65)
Control interval limited to 2 months before and after influenza detection	5.01 (3.04–8.27)
Includes AMI cases with specimen obtained during admission	4.45 (2.85–6.97)
Induction interval†	
2 days before exposure	5.72 (3.65–8.98)
4 days before exposure	5.92 (3.77–9.29)
7 days before exposure	6.02 (3.83–9.45)
Alternative exposure	
RSV	3.51 (1.11–11.12)
Respiratory virus other than influenza or RSV	2.77 (1.23–6.24)
Illness with no respiratory virus identified‡	3.30 (1.90–5.73)
Hospitalization for diabetes and associated complications§	1.35 (0.50–3.62)

* RSV denotes respiratory syncytial virus.
† An induction interval is a portion of the observation time immediately preceding the index date that is excluded from the control interval.
‡ Included is illness not attributable to influenza A, influenza B, RSV, parainfluenza virus, adenovirus, human metapneumovirus, coronavirus, or enterovirus (including rhinovirus).
§ No association was expected.

Table 3. Subgroup Analyses Comparing Incidence Ratios for Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection.

Subgroup	Incidence Ratio (95% CI)	P Value for Interaction
Age		0.14
≤65 yr	2.38 (0.59–9.66)	
>65 yr	7.31 (4.53–11.79)	
Sex		0.92
Male	5.91 (3.13–11.18)	
Female	6.21 (3.28–11.75)	
Influenza type		0.19
Influenza B	10.11 (4.37–23.38)	
Influenza A	5.17 (3.02–8.84)	
Influenza A subtype		0.74
H1N1	3.04 (0.42–22.22)	
H3N2	4.42 (1.81–10.82)	
Influenza vaccination status		0.85
Vaccinated	5.66 (2.49–12.87)	
Not vaccinated	6.24 (3.64–10.70)	
History of AMI hospitalization		0.29
Yes	3.53 (1.12–11.14)	
No	6.93 (4.24–11.33)	
Laboratory testing method to identify influenza		0.23
PCR	6.81 (4.28–10.84)	
Non-PCR methods*	1.94 (0.27–14.05)	

* Testing methods included viral culture, direct fluorescent antibody staining, and enzyme immunoassay.

apply only to respiratory infections that are of sufficient severity to result in laboratory testing. Since most patients with milder symptoms do not undergo testing for respiratory viruses, these findings may not be generalizable to milder infections. Similarly, because many other factors (e.g., age, care setting, and coexisting conditions) may affect the risk of acute myocardial infarction and the likelihood that testing is performed, the absolute risk and consequent clinical effect may be highly variable in different populations.

In conclusion, in this study in which we used specific definitions of the exposure and outcome in a self-controlled design, we found a significant association between acute respiratory infections, particularly influenza, and acute myocardial infarction.

The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information (CIHI) and by Cancer Care Ontario (CCO). However, the analyses, conclusions, opinions, and statements expressed herein are those of the authors and not necessarily those of the CIHI or CCO. No endorsement by the Institute for Clinical Evaluative Sciences, Public Health Ontario, Ontario Ministry of Health and Long-Term Care, the CIHI, or CCO is intended or should be inferred.

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