

More than just the flu: Influenza-associated myocardial infarction and its recent revelations.

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Approximately 12,200 Canadians are hospitalized with seasonal influenza virus annually, posing a mounting public health issue that has become the epicentre of community-based vaccination campaigns. However, this public health issue has become exacerbated by the recent emergence of literature investigating the association between influenza infection and myocardial infarction, commonly known as heart attack. In other words, does contracting the flu make one more likely to experience a heart attack? This is the question at the heart of previous epidemiological and correlational studies due to the far-reaching clinical implications with respect to vaccination programs. However, previous research on this subject presented a common limitation regarding the lack of standardized assessment of influenza infection. With methodologies and selection criteria differing between studies, the presence and extent of any association between influenza infection and myocardial infarction has been tentative at best. In recognizing these limitations and appreciating the clinical importance of this issue, Dr. Jeffrey C. Kwong and colleagues set out to characterize the precise nature of this association by employing a methodologically robust design. Their findings were included in the article “Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection”, published in *The New England Journal of Medicine* in January 2018.

The authors utilized a self-controlled case-series design to investigate the association between influenza infection and myocardial infarction. The patients’ respiratory specimens were tested for influenza and other viruses, while the data for acute myocardial infarction were included based on the diagnosis outlined in the International Classification of Disease (ICD-10). The observation period ranged from one year before to one year after the respiratory samples were obtained (termed the index date), and patients who had at least one instance of acute myocardial infarction during this period were included in the data. A risk interval and control interval were established, with the former extending to the first week following the index date and the latter extending to the remaining fifty-one weeks.

Dr. Kwong and colleagues found that the incidence of hospital admissions for acute myocardial infarction was six times higher during the week that followed a laboratory-confirmed diagnosis of influenza than it was during the control interval. This result demonstrated a significant

association between influenza infection and subsequent myocardial infarction.

In deciding to delve deeper into the topics discussed, we spoke directly with the authors of the paper. We wanted to understand the article with regards to its potential impact on clinical practice as well as parse out the ideas of the researchers in their own words. Here we interview a few notable experts in the field. First, we spoke with Dr. Jeffrey C. Kwong, a senior scientist at the Institute for Clinical Evaluative Sciences (ICES), family physician, and first author of the article in question.

Q: What was the motivation for studying and researching the subject?



JK: For some time, it has been known that influenza is linked with cardiovascular outcomes, for example, during the influenza season, more people die from heart attacks. So, we just wanted to confirm this association in order to show that influenza truly is associated with myocardial infarction—the idea being that if influenza infections truly are associated with heart attacks, [we would be able to prevent these] heart attacks with flu shots. [Specifically],

we used serology to [identify] influenza infection and also used a self-controlled case series design, which greatly reduces bias.

Q: We were wondering whether you thought that influenza will display similar associations with diseases other than cardiovascular disease (CVD). Or do you think this association is specific to CVD due to underlying mechanisms?

JK: That’s a very good question! Outcomes we were planning to look at include stroke, renal disease, and others. We’re planning to conduct studies on these in the future; we just haven’t gotten to that yet.

Q: So, why do you think that influenza may be associated with these other diseases, is there a particular mechanism you’re interested in investigating?

JK: You know, I think influenza can cause a lot of different problems in the body such as making people sick, causing inflammation and can even lead to death for people who have [pre-existing] chronic diseases. We know people with chronic conditions are at higher risk for complications if they do become infected with influenza, and so it might be a good idea just to show how strong this association is with other diseases.

Q: Do you think further research would be warranted in terms of examining specific CVD risk factors (e.g. diabetes) so that we could tease apart the individual associations between influenza and these risk factors?

JK: Yeah! I think it's a good idea because people would be able to understand who is at higher risk for complications if they are infected with influenza. Hopefully this would give patients more motivation to get vaccinated against influenza.

Q: It was also noted that there was increased incidence of myocardial infarction after influenza infection despite vaccination and it was stated that this was probably because the vaccinations were only 40-60% effective for adults in preventing laboratory-confirmed influenza. On this note, we found another article suggesting high-dose vaccinations [as a remedy to this problem]. Do you think high-dose vaccines would be effective for the CVD patient population that may be older and may exhibit decreased immune responsiveness to regular-dose vaccines?

JK: Yeah, so there's this big randomized controlled trial going on right now asking this very question! So what they are doing is they are recruiting patients who are at risk for myocardial infarction and who have already had a cardiovascular event, and then they've been randomizing [these patients] to high-dose versus standard-dose vaccines. We do have good evidence that the high-dose vaccine is more effective than the standard-dose vaccines in preventing influenza infection, with the idea being that if we can prevent infection, we can prevent myocardial infarctions from occurring.

Q: In terms of tailoring this information to patient population in clinical practice, what are your thoughts on using SQL (Structured Query Language) computerized queries to create a database of patients with CVD risk factors and follow up with these high-risk patients for vaccinations?

JK: Yeah, I think that's a great idea and I think that's definitely possible. Nowadays, many physicians use electronic medical records, and I think it would be smart to use this in order to notify and contact patients.

Q: What are your thoughts on community-based outreach programs that are organized to raise awareness and encourage patients with CVD and CVD risk factors to get their influenza vaccinations? Would these programs be effective?

JK: It's really hard to say. It is incredibly difficult to convince people to get their flu shots in the first place let alone every year. There's this huge misperception out there that influenza vaccines don't work, that it's not a big deal, and concerns about the safety of the vaccine. There are many misperceptions to overcome. We only vaccinate about one-third of our

population and even in high-risk groups we're not doing as well as we'd ideally want to be.

Q: Based on your research findings, do you think we should take more care in treating patients with CVD or CVD risk factors when they are in a hospital setting due to an elevated risk of catching the flu while in the hospital environment?

JK: That's a huge problem. We haven't been able to get high coverage of healthcare workers [with respect to their vaccination]. We have patients who are in the hospital for one reason, and then they get influenza and end up with something else on top of whatever else they came in with, so this is definitely an issue that we have not been entirely successful in addressing. [But] that's a whole other can of worms!

Q: Aside from seasonal influenza, we know that pandemic influenza can be a potentially devastating public health crisis. Do you think a similar relationship would hold between pandemic influenza and myocardial infarction?

JK: It wouldn't surprise me at all if we saw the same association. Pandemic influenza is usually seen more in younger adults, and as we saw in the 2009 pandemic, the virus did not seem to infect as many older people. This would be something known as a 'Signature Pandemic' where we see more disease in younger adults when normally for influenza we'd expect the majority of the burden to be with very young children and older adults.

Q: We understand that there is likely to be numerous confounding factors (e.g. comorbidities) when conducting research with patients, which can make it hard to isolate any effect and can limit the generalizability of such studies. How have you mitigated this issue?

JK: The nice thing about the self-controlled case series design is that it eliminates confounders. In this design we use each person as their own control; everyone in the study has had laboratory-confirmed influenza and myocardial infarction and so what we did was look at the timing between the myocardial infarction event relative to the laboratory confirmation of their influenza infection.

Q: Do you have any final comments regarding future research endeavours on this subject?

JK: The question I have is whether milder infections are worth looking into. [I'm interested in looking at] the association between milder influenza infections and myocardial infarction with the hopes of determining whether [someone with the average symptom profile] would also have an increased [risk] of myocardial infarction after infection.

We also got in touch with Dr. Kevin L. Schwartz, a paediatric infectious diseases physician, ICES adjunct scientist, and second author of the article, and he provided his thoughts on the implications of this research.

Q: What are the implications of your research findings?

KS: They demonstrated a strong association between confirmed

influenza infection and acute myocardial infarction. This association has important implications for the benefits of

preventing influenza infection in vulnerable individuals which should include annual immunization, hand washing, and other important infection control measures that can reduce transmission.



Q: In your experience, has the management of this issue changed since your research has been published? Do you believe it is being addressed

appropriately?

KS: I am not aware of data on immunization coverage this year, but this will be important to look at going forward. There are multiple factors that motivate the public to get vaccinated (or not) for influenza, and [it] would be hard to attribute any change directly to our study. However, I think it has answered an important research question using a more robust design.

Q: How might your research be used to inform physicians and their training? What changes would you like to see in clinical practice?

KS: It is important for physicians-in-training to consider the pathophysiology of diseases and this is a good example of how understanding the effects of influenza infection on a patient can manifest in a variety of ways including acute myocardial infarction. Physicians should be aware of the risks associated with influenza infection, beyond a respiratory illness. All physicians should be recommending influenza immunization yearly to their patients, particularly those at risk of cardiovascular events.

Q: In your opinion, is further research on this issue warranted? What direction would you like to see this research take in the future?

KS: I think there is need for future research evaluating the effects of both influenza infection and influenza immunization on downstream health outcomes in patients. Innovative ways for knowledge translation are needed to optimize vaccination rates. The self-controlled design is a potentially powerful design for answering questions related to rare events and those susceptible to time-invariant confounding. In this study we observed a relationship with other non-influenza respiratory infections and acute myocardial infarction as well, which deserves further attention and consideration for vaccine development for other respiratory viruses.



With the knowledge of there being an association between influenza infection and myocardial infarction, it becomes clinically relevant to investigate the role of influenza vaccination in preventing major cardiovascular events like myocardial infarction. Furthermore, for patients that are particularly vulnerable in terms of

a decreased immune response to vaccines, it would be important to examine the potential advantages concerning the efficacy of high-dose vaccines. For more information on this related topic, we spoke with Dr. Jacob A. Udell who is a cardiologist, a scientist at Women's College Research Institute, and an author of a recent article on the efficacy of high-dose influenza vaccines for high-risk CVD patients.

Q: From your perspective, what was the motivation for studying this subject regarding your most recent article on the use of high-dose influenza vaccines to improve clinical outcomes in high-risk CVD patients?

JU: I thought it would be interesting to interject into any clinical study, the opportunity to study any public health intervention, in this case vaccination, to reduce the impact of heart disease in Canadians and internationally. We were looking for the right fit, and it ended up at the time when I was training in cardiology and looking at opportunities, a lot of the research was focusing on small studies that were starting to report on the role of flu shots as a cardioprotective mechanism in patients with coronary artery disease. So that was the motivation for it, trying to do something big and important that could have a lot of impact at a very low cost.

Q: After reviewing other articles on the subject, we found that vaccination isn't a complete safeguard with statistics indicating only 40-60% efficacy for adults in preventing laboratory-confirmed influenza infection. Was this the rationale behind studying the potential benefits of high-dose vaccines?

JU: Yes, so that's correct, the flu shot in any one year may not be effective for vulnerable patient populations including those who are older, those afflicted with chronic conditions such as heart disease or exhibit risk factors for heart disease, kidney disease and/or diabetes. However, there is this one vaccine on the market [called the Fluzone High-Dose vaccine] that is four times more concentrated than the flu shot, covering three strains of flu. [This vaccine] has been tested in healthy community adults (some of which have a history of heart disease but not active heart disease), and it was shown that the higher dose flu shot boosted the antiviral response. Now in our study, we're targeting [CVD] patients who [are at greatest risk of decreased response to a flu shot], maybe because they're 65 and older or have a number of comorbidities for heart and lung outcomes, [and as such, these patients] might be better off with a higher dosage flu shot.

With research indicating a link between acute influenza infection and increased incidence of cardiovascular events for people with CVD risk factors, it is imperative that the implications of such findings are discussed in both clinical and community-based contexts. Specifically, it may be wise for primary care physicians to implement computerized queries that efficiently generate lists of patients with CVD risk factors who have yet to receive a flu vaccination. Following up with these patients to set an appointment for vaccination would then serve as a preventative measure for both influenza infection and myocardial infarction. Furthermore, the use of high-dose vaccines for these high-risk patients, as explored in Dr. Udell's research, has proved to be effective since their

immune response to regular-dose vaccines is often compromised. Another concern is that patients with cardiovascular conditions, while receiving care in hospitals, would have to be carefully monitored to prevent contraction of hospital-sourced influenza. This scenario could otherwise spiral out of control by increasing the risk of myocardial infarction and potentially exacerbating these patients' conditions.

Despite the insights gleaned from Dr. Kwong, Dr. Schwartz, and Dr. Udell, further research is still warranted in the realm of investigating the association between milder influenza infection and myocardial infarction as well as the interaction between influenza infection and different CVD risk factors. Presently, the current literature provides an impetus for promoting awareness of the intimate link between influenza and myocardial infarction for patients at elevated risk of CVD through community-based programs. These programs would ideally advocate for patients by promoting accessible, preventative strategies to combat contraction of influenza and by advancing efforts directed towards increasing vaccination rates more broadly.

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References

1. Canada, P. (2019). Flu (influenza): For health professionals - Canada.ca. Retrieved from <https://www.canada.ca/en/public-health/services/diseases/flu-influenza/healthprofessionals.html>
2. Kwong, J., Schwartz, K., Campitelli, M., Chung, H., Crowcroft, N., & Karnauchow, T. et al. (2018). Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. *New England Journal Of Medicine*, 378(4), 345-353. doi: 10.1056/nejmoa1702090
3. Musher, D., Abers, M., & Corrales-Medina, V. (2019). Acute Infection and Myocardial Infarction. *New England Journal Of Medicine*, 380(2), 171-176. doi: 10.1056/nejmra1808137
4. Udell, J. A., Zawi, R., Bhatt, D. L., Keshtkar-Jahromi, M., Gaughran, F., Phrommintikul, A., . . . Cannon, C. P. (2013). Association Between Influenza Vaccination and Cardiovascular Outcomes in High-Risk Patients. *Jama*, 310(16), 1711. doi:10.1001/jama.2013.279206
5. Vardeny, O., Udell, J. A., Joseph, J., Farkouh, M. E., Hernandez, A. F., McGeer, A. J., . . . Solomon, S. D. (2018). High-dose influenza vaccine to reduce clinical outcomes in high-risk cardiovascular patients: Rationale and design of the INVESTED trial. *American Heart Journal*, 202, 97-103. doi:10.1016/j.ahj.2018.05.007

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