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COMMENTARY

Podcast: Influenza-Associated Complications and the Impact of Vaccination on Public Health

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ABSTRACT

Influenza is primarily considered an acute respiratory infection but can lead to a myriad of medium and long-term sequelae across every major organ system in the body. Increasing awareness, gaining broader understanding of its mechanistic pathways, identifying at-risk individuals, and determining how to better protect them could help minimize its impact. The aim of this podcast, featuring Dr Stefania Maggi, Dr Annemarijn de Boer, and Dr Melissa K. Andrew, is to outline the main influenza complications and their impact beyond acute respiratory disease, as well as highlighting vaccination as a tool at our disposal. Both physical and cognitive function can be affected as a result of influenza infection, notably in frailer individuals, which in turn may lead to a loss of independence. Observational studies have identified beneficial effects of vaccination for cardioprotection as well as preventing dementia, but more evidence is required. In conclusion, influenza can cause a wide array of complications, which vaccination may help prevent.

Podcast available for this article.

Podcast: Influenza-associated complications and the impact of vaccination against influenza on public health (MP4 384341 KB)

Keywords: Disease burden; Long-term impact; Vaccination; Complications; Frailty; Mortality; Prevention

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Key Summary Points

Influenza can present with broad complications beyond respiratory illness that can have a long-term impact.

Complications include adverse cardiovascular outcomes, functional decline and disability, dementia and frailty, which all contribute to the disease burden.

Vaccination presents as the key method of prevention against both acute infection and long-term sequelae of influenza, with evidence suggesting beneficial effects on dementia, cardiovascular health, and frailty.

Further real-world evidence on the impact of influenza vaccination is key.

DIGITAL FEATURES

This article is published with digital features, including podcast audio of the podcast transcript to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.24243721.

PODCAST COMMENTARY TRANSCRIPT

Podcast Attendees and Introduction

Stefania Maggi (SM): Hello, and welcome to all our listeners to the podcast on influenza and the burden of disease. My name is Stefania Maggi. I'm a research director at the National Research Council of Italy. And with me today are Dr Annemarijn de Boer and also Professor Melissa Andrew. Would you please introduce yourself?

Annemarijn de Boer (AdeB): My name is Annemarijn de Boer. I'm an assistant professor working at the University Medical Center in Utrecht with a focus area in clinical epidemiology, infectious disease, and cardiovascular disease.

Melissa Andrew (MA): And I'm Melissa Andrew. I'm a geriatrician in Halifax, Canada with an interest on how frailty impacts responses to illnesses, infections, and vaccines in older people.

The Broader Consequences and Complications of Infection

SM: Thank you very much. And so we can start discussing about the burden of influenza. Influenza is usually considered an acute respiratory infection with a full recovery within a week without requiring medical attention. But, unfortunately, influenza may lead to severe illness, hospitalization, and death in the most vulnerable segments of the population, meaning the youngest, the oldest, and the pregnant women, plus all the immunocompromised patients and those with comorbidities [1]. Moreover, the burden of influenza goes well beyond the acute phase. And we have strong evidence that it has an additional burden due to broader consequences of the illness. Some of these consequences have been reported extensively in the literature and are cardiovascular events, neurological complications, including cognitive decline and dementia in older adults, exacerbation of chronic underlying conditions, such as COPD and diabetes, increased susceptibility to secondary bacterial infections, functional decline that might lead to falls and fractures, and poor pregnancy outcomes, all of which may contribute to an increased risk of hospitalization and mortality [1]. The medium- and long-term sequelae of influenza are difficult to be assessed and the cause–effect relation might be biased by several confounders. But these methodological difficulties have been mostly overcome by advancement in design of epidemiological and interventional studies in the recent years [1]. Recognizing the health and social impact of these consequences is essential to determine the full burden of influenza in different subgroups of the population and to determine the value of preventative approaches such as vaccinations.

The Effects on the Cardiovascular System Specifically and Their Contribution to Mortality Burden

SM: And in order to outline the main influenza complications and their impact beyond the acute respiratory disease, I would start with a question to Dr de Boer. What do we know about, specifically, the influenza effect on the cardiovascular system? Is it a major contribution to morbidity and mortality?

AdeB: Yeah, so there is a significant amount of literature and studies that have investigated the link between influenza infection and cardiovascular outcomes [2–6]. One in particular, published in 2018, investigated the influenza infection and acute myocardial infarction connection [2]. So it was the first study using both a laboratory-confirmed definition for influenza infection as well as a self-controlled case series design to investigate the association. So this design controls for so-called time-invariant confounding, which is important when performing observational studies to investigate associations like this. And this study showed an increased risk of myocardial infarction in the first week following influenza infection. And I believe it was six times increased risk in that first week [2]. So since then, the results of this study have been confirmed in replication studies in several countries, including the USA, Scotland, Denmark, and recently, the Netherlands as well [2–5]. And the studies from Scotland and Denmark have also observed a similar connection between influenza infection and stroke [4, 5]. What we do know is that if an influenza infection gets complicated with cardiac events, the risk of short-term mortality increases significantly. The question that you can ask yourself is, why does this happen? So what are the pathways underlying the connection between influenza virus infection and myocardial infarction? So there are several hypotheses about these pathways, first being the inflammatory response of the body following acute infection. So direct effects of it and response can lead to an influx of inflammatory cells into a pre-existing atherosclerotic plaque in the coronary arteries, which leads to growth and destabilization or even rupture of the plaque [3]. As a second mechanism, acute infection has an effect on the body's coagulation pathways. So the formation of thrombi or clots in the coronary artery is promoted through platelet activation, vasoconstriction, and endothelial dysfunction [2, 3]. And, lastly, the balance between the metabolic demand and supply of the heart is disrupted through the infection [2]. So through a systemic inflammation response, the demand rises, while the supply in the blood flow decreases. And these mechanisms, the inflammatory response, activation of the coagulation response, and this balance between demand and supply can all contribute to obstruction of the coronary artery and development of myocardial infarction [2, 3].

SM: Thank you very much, Annemarijn, for these comprehensive statements.

The Longer-Term Impact of Influenza

SM: And let me move to Melissa with a question related to what we know and what we have learned after the pandemic and the emergence of long COVID. We know that there is increasing awareness now in the scientific community about the potential long-term sequelae of viral infections. And what do we know about the long-term effect of influenza? And do we have a long flu as well?

MA: So with the COVID pandemic, we've had increased awareness of the longer-term complications of COVID illness. And, in fact, we can learn a lot from influenza. Over many years, we've built an evidence base about how influenza can have longer-term consequences beyond the usual 2-week acute illness that many people think of [7–11]. For example, there's an important impact on functional decline. So we know from some of our surveillance studies in Canada and elsewhere that when people are admitted to the hospital, they often don't leave the hospital with the same degree of function that they came in with [7, 8, 10, 11]. For example, up to about 20% of people can have a persistent, significant functional decline that persists even after they leave the hospital [12]. And that decline can be catastrophic in that they may become

dependent in activities of daily living that they were once able to do. That means that they may need increased home care, support from family, and of course, long-term care or nursing home admission [11].

Another thing that we have been seeing with influenza is that there's an increased risk of falls and fractures, and that can happen right at the time of the illness and also persisting afterwards [8]. And there is, in fact, a link to a longer-term risk of dementia, particularly Alzheimer's disease [9]. And some of that can be because of the direct impact of having the influenza illness, developing delirium and not recovering cognition. But some of it is felt to be through direct impact on the brain.

So I think there's quite a lot more to be discovered here. And what we do also know is that people who are frail are at increased risk of having all of these persistent complications and even increasing their frailty afterwards.

SM: Well, thank you very much, Melissa.

Influenza and Frailty

SM: I think you both clearly expressed that in frail individuals influenza may affect both physical and cognitive function through multiple mechanisms. We know that may be inflammatory response in various organs and systems, prolonged immobilization, decreased nutritional caloric intake, hypoxia. And, in fact, an often underappreciated consequence of influenza in older adults is the accelerated functional decline often leading to loss of independence. And... we know that aging per se is associated with functional changes, such as decline in muscle strength, aerobic capacity, bone density, and pulmonary ventilation, all of which may impact the functional status of older adults and increase their vulnerability. But these people, although frail, they are still autonomous until even a mild flu event—or a few days of [being] bedridden—would be sufficient to start a cascade of functional decline and dependence, leading to negative outcomes such as hospitalization, institutionalization, and death. So my question, again to Professor Andrew would be, does influenza directly cause complications such as frailty, or is it always mediated through other intermediate factors?

MA: This is such an interesting question. So it's probably that it's both, in fact. So the influenza infection itself could contribute to some of the inflammation that happens in people's brains and nervous systems that then can unleash this cascade that becomes worsening cognition and function and the changes that we see in neuropathology or brain changes that are associated with dementia. For example, there is an interesting hypothesis called the antimicrobial hypothesis of dementia, in which the brain changes seen in Alzheimer's disease might in fact be the result of fighting infections [9]. So amyloid beta, which is a typical brain change that happens in Alzheimer's disease, in fact has some antimicrobial properties. So what we're seeing in dementia, these brain changes with amyloid plaques and tangles may in fact be a by-product of the inflammation from having encountered infections in the past, such as influenza [9]. But, of course, there is also the important general and systemic effects that can happen, impacting people's function. So we know that older, frail people are at higher risk of having a hospital stay and all the complications that can come along with that, including being deconditioned and losing function [13]. And so it may be that an important piece of the persistent changes that we see in people's health and functioning come because of these other effects that happen just with a prolonged illness and hospitalization.

SM: Thank you, Melissa.

Tools to Prevent the Broad and Persistent Complications of Influenza

SM: And let's see now what tools we have at our disposal to prevent these broad and persistent complications of influenza. We know that vaccination is the best and most effective tool for prevention and control of influenza. Evaluation of an influenza vaccine's benefits for regulatory purposes includes the assessment of immunogenicity and efficacy, meaning the degree to which a vaccine prevents diseases in an ideal and controlled circumstance, such as in

randomized controlled trials, assessing the reduction in rates of laboratory-confirmed influenza. The carefully conducted studies with prospective, double-blind, randomized controlled designs are considered the gold standard for assessment of efficacy. And it is important to analyze all available evidence with standardized and validated methodologies, such as the grade system. But, of course, we are interested also in the effectiveness of vaccines, how well the vaccine performs in the real world, preventing not only the infection per se but also hospitalization, mortality, and long-term sequelae. Older, vulnerable, and high-risk individuals might show, indeed, the greatest benefit from vaccinations. But often, they are not included in the pivotal randomized controlled trials. So we need well-conducted, methodologically-sound both intervention and observational studies to assess the impact in the real world of vaccines on the complications and sequelae that we have discussed up to now.

Beneficial Effects of Vaccination on Influenza-Associated Complications

SM: So my question to both of you would be, is there any evidence showing the beneficial effects of vaccines on influenza-associated complications? And I would ask Annemarijn to start addressing this question.

AdeB: Certainly, yeah. So for cardiovascular disease, there have been several observational studies that investigated and also observed a beneficial effect of influenza vaccination on all-cause mortality and acute ischemic events [14–17]. In 2021, these results were confirmed in a randomized double-blind trial [14]. So this study aimed to investigate the effects of influenza vaccination in individuals with myocardial infarction. So what they did is, they administered the vaccine shortly after a person had their first myocardial infarction. And that study found a lower risk of a composite endpoint of all-cause death, myocardial infarction, or stent thrombosis, as well as a lower risk of all-cause death and cardiovascular death at the 12-month period after vaccination [14]. So an interesting question, at least to me, is that why would an influenza vaccination prevent an influenza infection [from] actually causing damage to the heart? Because you could think that both [vaccination and infection] induce an inflammatory response. So, actually, a hypothesis that tries to give an answer to this question suggests that the answer might lie in the difference between a degree of induction of the inflammatory response. So influenza vaccination induces a transient and mild inflammatory response in contrast to acute infection [18]. So instead of triggering pathways that lead to cardiac damage, it is thought that through only a mild activation, the adaptive system is activated, which leads to protection against the new exposure of disease. However, I should say that further research is really necessary to underpin the specific mechanism or mechanisms underlying cardiovascular protection from influenza vaccines. In addition to preventive measures that focus on immunization through vaccination, one could also think of preventive measures that aim to prevent cardiac complications when an individual is already infected, so, for example, antiplatelet therapy administered shortly after a patient is admitted to the hospital with a severe infection. So whether this actually prevents cardiac complications still needs to be investigated. And there has been a study initiated to investigate the effects of aspirin in preventing myocardial infarction in patients admitted to the hospital with community-acquired pneumonia. And, well, personally, I'm looking forward to the results of that study.

MA: And when it comes to preventing frailty, that's such an interesting and open question. And I think we're going to have to wait for more studies to be done that focus on that question of frailty itself. However, the dementia prevention question is a really interesting one. And there are a number of studies that have begun to amass an evidence base to suggest that we can use a vaccine to prevent dementia, which is just quite amazing [9, 19–22]. But here in the setting of influenza vaccines, a few examples: so there's some administrative data, or based on healthcare claims in the USA, where they've included even up to a couple of million people—so a huge sample size—and matched them for

having been vaccinated against influenza or not and followed up to see if they developed dementia. And, in fact, what they found was that there was a 40% reduction in dementia among the people who had been vaccinated. And that's a relative. So when we translate that into absolute terms, they said that the number needed to vaccinate with an influenza vaccine to prevent a case of dementia was only 29 people, which is just astonishing when it comes to these sorts of interventions [21]. There was another study that looked at a systematic review of several studies in different countries, including Taiwan, Canada, and the USA. And they found a similar reduction of about 29% of dementia in these subsequent years [19]. So this is really adding to some of the very meaningful evidence that will translate the need to be vaccinated and the importance of that to things that people really care about, such as preventing dementia. And, again, there are different hypotheses as to why this is. There may be some pathways that are specific to influenza. So influenza infection may damage some of the neural pathways that are similar to what we see in dementia [9]. But then there also may be some training of the immune system that can turn itself to protecting against these other changes that happen in the neurodegenerative conditions [18]. So I'm really looking forward to more evidence amassing in this area. But I think for now, it's very important to talk about all the different ways that influenza vaccination can prevent people's declines in health, including in preventing dementia.

SM: Yes, indeed. Thank you very much, both Annemarijn and Melissa.

Concluding Remarks

SM: I believe we can summarize the main messages in few statements. Influenza leads to complications beyond the respiratory illness, and time horizons need to be expanded to capture the full, longer-term impact of infection. Broader consequences of influenza might include cardiovascular events, cognitive impairment and dementia, increased frailty, and functional decline, all of which may lead to an increased risk of hospitalization and death, as well as long-term functional impairments and disability. Vaccination against influenza provides public health benefits and is the most effective tool to prevent both influenza disease and associated complications, but data providing more evidence on these links should be generated in the future, based also on innovative study designs, such as real-world trials. Despite evidence of the benefits of influenza vaccination and global health authorities' recommendations, vaccination rates unfortunately remain below target among high-risk individuals in most countries, and we all should make an effort to improve vaccination coverage. And with this, I thank very much my colleagues, Dr de Boer and Andrew, and all our listeners for being with us. Thank you very much.

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