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COMMENTARY

Understanding Influenza Vaccine Clinical Performance: A Podcast

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ABSTRACT

Despite well-established vaccination programs, seasonal influenza is still causing substantial clinical, economic and societal burdens. As part of strategies to continually improve influenza vaccine clinical performance, several new approaches are being examined, including high-dose vaccines, adjuvanted vaccines, egg-free vaccines, nasal spray vaccines and mRNA vaccines. Given this range of influenza vaccines, coupled with various vaccine hesitancy concerns, healthcare professionals' understanding and confidence in the clinical performance of influenza vaccines remain key. In this podcast, we discuss the challenges for healthcare professionals in understanding the clinical performance of influenza vaccines and the importance of education in this area, particularly to address perceptions of influenza vaccine failure. We also explore several elements that should be considered in the assessment of influenza vaccine clinical performance: (1) assessing relevant clinical outcomes, such as hospitalization data, (2) utilizing robust methodology in influenza vaccine trials to ensure high quality evidence and (3) approaches used when considering the full body of evidence.

Keywords: Influenza; Vaccines; Influenza vaccination; Influenza burden; Hospitalization; RCTs; Real-world evidence; Methodology; Healthcare professionals; GRADE

DIGITAL FEATURES

This article is published with digital features, including podcast audio, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.27161799.

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Key Summary Points
With the continuous development of influenza vaccines, assessing clinical performance is critical.
There is a lack of understanding of the study data and endpoints in influenza vaccine studies, so education is required to appreciate the full breadth of protection.
The effect of influenza on severe outcomes across major organ systems (e.g., cardiovascular disease) is underappreciated. Assessments to further understand the impact on severe disease include hospitalization, mortality and quality of life data.
When studying such endpoints, in addition to the gold standard randomized controlled trials, there is a need for robust real-world evidence to provide longer-term assessment across seasons and inclusion of diverse populations.
Qualitative approaches of the full body of evidence are needed to determine the quality of evidence and make recommendations.

Podcast Transcript

00:00:00 Nihar Desai

Hello and welcome to this podcast discussion, "Understanding Influenza Vaccine Clinical Performance". I'm Dr Nihar Desai, Associate Professor of Medicine at the Yale School of Medicine and Vice Chief of the Section of Cardiovascular Medicine at the Yale New Haven Health System.

00:00:15 Pier Luigi Lopalco

Hello, I am Pier Luigi Lopalco. I am Professor of Hygiene and Preventive Medicine and I work at the University of Salento, Lecce, Italy.

00:00:26 Nihar Desai

So Luigi, I'm absolutely delighted to do this with you and I'm looking forward to our discussion. I think maybe I'll just set the stage a little bit for the podcast. We know that seasonal influenza causes substantial clinical, economic and societal burdens. Each year, seasonal influenza results in an estimated 290,000–650,000 global respiratory deaths. Due to population growth and shifting age distributions, the direct and indirect economic burden of influenza is set to rise substantially over the next 30 years.

We also know that influenza vaccines have a well-established history. Building upon this history, vaccine developments have been focused on improving influenza vaccine performance over the standard of care.

High-dose vaccines, adjuvanted vaccines, egg-free vaccines, nasal-spray vaccines and other upcoming pipeline mRNA vaccines…; with several influenza vaccine options available, how should the optimal vaccine be chosen and how can we instil confidence in the clinical performance of these vaccines?

So, in this short podcast, we're going to go through and provide some thoughts on several elements that should be considered when we're trying to understand influenza vaccine clinical performance—specifically, assessing the relevant clinical outcomes, utilising robust methodology in influenza vaccine efficacy and effectiveness studies and approaches to examine the full body of evidence, and so again, delighted to be here with Luigi, and maybe I'll turn it over to you for the next section.

00:02:08 Pier Luigi Lopalco

Thank you, Nihar—and thank you for this introduction. We will discuss the challenges facing healthcare professionals in understanding the clinical performance of influenza vaccines and will address the perceptions of vaccine failure and how these can be overcome.

Actually, healthcare professionals in many countries may have limited control over the specific influenza vaccines they administer, but they still often have substantial influence over vaccine uptake among their patients and retention to early vaccination.

So Nihar, considering the range of different influenza vaccine options, what are the challenges for healthcare professionals in understanding the clinical performance of the vaccines they choose to administer?

00:02:59 Nihar Desai

Yeah Luigi, I think that's a great question. It's the ultimate practical, pragmatic question with

all of these different options available, with all of the evidence coming out.

How is the busy frontline clinical practitioner supposed to make sense of these things and then know what to do in the office setting? So, we all know that updates to national/international guidelines and studies are happening all the time—and are being reported in different scientific sessions and different literature. But most of our frontline practitioners—especially internists, family practitioners, paediatricians, geriatricians—are really overwhelmed in their own practices and might not be fully up to date on all of the evidence, all of the guidelines. So, I think there's a real challenge there in terms of trying to distil and synthesise what is the best available evidence and the best available vaccine for a given patient and making that available in a timely way to very busy clinical practitioners.

00:04:06 Pier Luigi Lopalco

Indeed, I think that there is a general lack of medical education on influenza vaccines—as well as a lack of widespread understanding of the study data and endpoints in the influenza vaccine studies. So, consider how complicated the topic is when you talk about efficacy versus effectiveness or when you make a difference between the relative versus the absolute vaccine efficacy or effectiveness.

00:04:39 Nihar Desai

Yeah, and I think—you know—you raised a number of important points there about very nuanced understanding of the literature and appraising different studies and different endpoints—how do we look at and differentiate across different vaccines?

Yeah—I might just take a step back and ask you…if you were to think about (just in a broad sense) influenza vaccines…what are some of the public (and even among the medical community)…just the perceptions on vaccines, clinical performance; what do you think about some of the negative perceptions? You know, what do you think some of those negative perceptions are that are out there about vaccine performance in general?

00:05:18 Pier Luigi Lopalco

I believe that there are several negative perceptions. They are across different topics. First of all, safety concerns. I think that every healthcare professional is very much worried about the safety of the vaccines that they are recommending. And then it's also false perceptions of vaccine failure. Many doctors do not actually understand the effectiveness of the vaccines that they are recommending, and therefore there is a sort of reporting bias. Finally, there are also perceptions of influenza not being serious enough to necessitate the vaccination.

So, in your opinion, how might these negative perceptions on influenza vaccine clinical performance be addressed?

00:06:09 Nihar Desai

Yeah, it's a great question. And again, I think—though it sounds a bit trite—that education is really the first step. I think we need to educate our colleagues, the clinical workforce, on how safety is established. You know how these vaccines are assessed in very rigorous clinical evaluations.

I think we also need education on how we should perceive vaccine success. What are the right metrics that we should look at? What are the right definitions for the success of vaccines? And I think of a particular importance—and I think the COVID experience was helpful in this regard—I think people started to understand that one of the benefits of vaccination is the prevention of severe disease, and especially hospitalisation (and maybe very severe hospitalisation and critical illness), even if it doesn't prevent a mild infection.

I think those are some of the key elements, at least, as we start to think about engaging the public. But just as much, I think engaging our colleagues and clinicians—that education has a very important role to play.

That was a great discussion, Luigi. I think we might shift gears a little bit and get your thoughts on what are the right clinical outcomes? I mean, you've just extended the discussion that we were just having about education—and what are the right, you know, endpoints? How do we think about outcomes in studies? I think there are a couple of elements that we should think through here. I'd love to get your thoughts…so one is the importance of vaccination given the wider effects of influenza on severe disease. And that's a very important discussion about the constellation of clinical

comorbidities a patient might have that presents a particular risk for influenza vaccination, and then severe illness in that setting, and then we'll probably shift gears a little bit and discuss the importance of hospitalisation data in influenza vaccine studies and other assessments to understand the full impact of influenza vaccination. So, I really want to kind of dive into: "what are the relevant clinical outcomes that we should be thinking about?"

So maybe I'll start Luigi with just a broad question—what do we need to do to ensure that healthcare professionals and patients know the true value of influenza vaccines?

00:08:28 Pier Luigi Lopalco

This is crucial. Indeed, we need a better recognition of the full burden of influenza, because influenza is not just an infection, is not just a viral infection, and it is not just an infectious disease. The impact of influenza on severe outcomes goes across major organ systems—and don't forget, for instance, that the impact on cardiovascular disease is really underappreciated.

At the same time, there is also very low awareness of the increased risk of hospitalisation, hospitalisation for all causes, not just hospitalisation for influenza. So, this is underappreciated, and even mortality. This is also a bit weird, because we have robust evidence; a lot of evidence is available on the beneficial impact of influenza vaccination on preventing severe disease. All these things that we are talking about, cardiovascular disease, the risk of major adverse events like heart infarction, health failure…so, we really need to consider this evidence.

So, in your opinion, Nihar, what kind of clinical outcomes should be used to assess how well influenza vaccines prevent severe disease?

00:09:59 Nihar Desai

Yeah, it's a great question. I think very much in line with the discussion that you were just having. I think we have to look holistically and broadly. You know, when we think about vaccine and vaccine performance, I think traditionally immunogenicity laboratory confirmed infections have been considered the accepted standard for assessing the impact of influenza vaccines. But just like you were saying, we know that these vaccines have broader impact on a series of other conditions and comorbidities. So, I think we do have to go beyond these traditional (maybe slightly narrower) endpoints to much more broad clinical endpoints and clinical events. So, hospitalisation data, as you were just saying, remains a very important outcome for demonstrating disease severity and vaccination impact. I know that we have some challenges there—how do we do that globally, with different coding practices, different medical records? So, there are some challenges that we have to work through there. Nonetheless, I think hospitalisation data are something very important for us to ascertain. And then other important assessments that are available (or need to be available) to further and more fully understand the impact on severe disease—including mortality data, quality of life data, other symptom and functional outcomes (you know, from patients). Again, there are some challenges and limitations in terms of data collection there. But I think as we look more holistically, I think we will better capture the benefits of influenza vaccine and I think that becomes a very important part of the narrative for our colleagues as well as the public. So, as we're thinking about sort of these broader endpoints and what the right endpoints are—how else do you think, Luigi…how else can influenza vaccines be assessed in relation to clinical performance?

00:11:50 Pier Luigi Lopalco

There are a lot of different aspects that we should consider to understand the benefits of influenza vaccination. Some of these are commonly examined and, again, there is a lot of robust evidence on that. One of these is a cost-effectiveness analysis evaluation. I mean, vaccination is absolutely cost-effective. It can even save a lot of money, also from a societal perspective.

Another aspect that it is important to include (in a broader assessment) is the tolerability of the vaccines. This is very important—especially from the patient perspective. There are also other less commonly used assessments that, in my opinion, are not fully understood and eventually are worth investigating more thoroughly; for instance, influenza vaccination should be considered as part of a healthy lifestyle—the same as having good food, being active, stopping smoking. At the same time, we should

consider influenza vaccination as part of this healthy lifestyle. And don't forget that also we should vaccinate people to prevent the transmission of the disease—so think about the caregivers of very fragile populations.

So, I think that we have discussed the important clinical outcomes, but now I think we should go more in depth in talking about methodology. So, in this section of the podcast, we will discuss how to utilise robust methodology in influenza vaccine studies; in particular, we will provide an overview of randomised and observational influenza vaccine studies, exploring the benefits and limitations of these studies. In addition, we will discuss some of the measures that can be taken to ensure high quality of evidence in these vaccine study designs.

So, Nihar, given these discussions on the critically important outcomes, what kind of study design should be used to assess these endpoints? Because these are quite complicated. Are we limited to traditional randomised controlled trials only?

00:14:26 Nihar Desai

Yeah, it's a great question, Luigi. I think you know the evidence generation in this space is such an interesting area to consider. And I think to start, you know, we always need RCTs. RCTs remain the gold standard and are needed to assess, you know, novel influenza vaccines, establish a baseline level of protection compared with standard of care. So, we will always need randomised trials. We always have and we certainly will, going into the future.

That being said, I think we have to acknowledge there are some real challenges and limitations with traditional randomised controlled trials in this setting. Specifically, there's often lack of long-term data across multiple seasons, right? These are short trials or short duration to establish efficacy, but then we don't get the long-term data that we often need to look at performance across multiple seasons. We often exclude patients that are the most interesting and important high-risk patients, cancer patients, other similar patients with multicomorbidities—and there are always challenges then due to sample size, lack of ethical vaccine comparators, difficulties in recruitment. And, you know, how do we then assess (maybe the more incremental) benefits of novel vaccines compared with standard-of-care vaccines? There, the sample size becomes almost prohibitive in a traditional randomised setting.

So, Luigi, I guess maybe I'll ask you to help us think about this a little bit. You know, given some of these challenges, yes, everyone acknowledges that we want some randomised trials. They become, you know, important. They are and remain the gold standard. But given some of these limitations of randomised trials, what role do you think real-world studies play in evaluating and assessing influenza vaccine performance?

00:16:20 Pier Luigi Lopalco

I mean, you already mentioned the limitations of RCTs in this setting. I believe that real-world evidence is a very important complement. So, these studies—the real-world studies—should complement the RCT in building up the whole evidence body.

For instance, if we can study the effectiveness or safety of influenza vaccines in a large population across several seasons, then we can overcome that limitation that is typical of the RCT. So, these real-world studies allow for longer term assessment of influenza vaccines, without a doubt.

Also—as you said—in RCTs it is very difficult to include, for instance, very fragile populations. If we have large populations that are studied in a real-world setting, we can collect a lot of very interesting data on the effects of influenza vaccination in these diverse populations. So, real-world evidence can (and should) be a complement to RCTs.

00:17:37 Nihar Desai

Yeah, and I think—you know—in addition to the role of retrospective studies for hypothesis generation (that can lead to RCTs to verify)… you know, what do you think about using data from observational studies, maybe as the overall body of evidence, despite their limitations? I think we always have this discussion about randomised trials versus observational, you know, real-world studies, and so, you know, yes; I think we all acknowledge that there are risks of biases and confounders. Those are challenges to real-world data. So, give us your sense of that—how do you see real-world evidence? And some of

those issues between randomization and more real-world observational data?

00:18:21 Pier Luigi Lopalco

Again, I think that we should consider real-world evidence as a complement to RCTs. We are aware of the risk that we are talking about. Risk of bias, risk of confounders…but all these risks can eventually be limited with robust methodology. Actually, I think that we can take some measures to ensure also greater confidence. Because at the end of the story, what is important is that we collect these data, we run these real-world studies, and we provide evidence to our colleagues that—at the end of the day—they should recommend vaccination, but they should also be very confident about the fact that the data and the results that we are collecting with the real-world studies are of good quality and the risk of bias is limited. So, I asked this question back to you…in your opinion, what measures can be taken to ensure this greater confidence in these studies?

00:19:31 Nihar Desai

Yeah, I think there are a couple of things. I think you touched on many of them in the lead up here. I think there are some real concerns about publication bias. So, measures that can be taken to address that: prospective declaration of all studies; pre-specification of endpoints; publication of analysis plans…and then implementing systems of protocols to periodically review and adjust study designs, if necessary.

I think, in a related way, a corollary maybe is that the use of innovative study designs can be implemented to minimise some of the biases of traditional real-world observational analyses while still kind of leveraging the power of real-world data in terms of sample size and generalizability.

So, there's been a lot of work and a lot of interest in conducting more real-world pragmatic trials, where you integrate aspects of randomization. But you also have a broad population—with a result that's generalizable—and longitudinal data capture across multiple seasons and assessment of a range of endpoints that wouldn't be possible in a traditional randomised trial.

00:20:45 Pier Luigi Lopalco

This is very true. Actually, if we are able to ensure these consistent findings, we also have evidence—results—that are coming from multiple real-world evidence studies that can eventually vary in design and were conducted in different seasons.

But, in any case, they reflect the same findings from pivotal RCTs. So, this is also going in the direction that this kind of observation can support—and make the evidence stronger (eventually more limited evidence)—that we have collected with the pivotal RCTs, and shows the importance of viewing evidence on influenza vaccines, as you said at the beginning, as a holistic portfolio of evidence…without cherry-picking it.

This is something that we should avoid, the cherry-picking of certain studies, as both RCTs and the real-world evidence studies can be of high and low quality. So, this is also another problem. It is not always that an RCT is good, real-world bad. But there are good- and bad-quality studies both in real-world evidence and sometimes also in RCTs.

00:22:09 Nihar Desai

Yeah, Luigi, that's such a great point. And I want to maybe pick up and extend on this discussion a little bit with you as we kind of move into the final part of the discussion here.

I think we've both talked about this and I think, you know, we all recognise the importance of looking at the full body of evidence. We've talked a lot about studies and study designs, randomised and real world, and what kind of endpoints we should be looking at, you know, what are the right kinds of outcomes that we should be looking at. And we also talked at the beginning about the very busy clinician in their practice trying to make sense of all of this. So, I guess I'd love to get your thoughts on how do we do all of this? How do we kind of look at the totality, the full body of evidence—and is there a way that we can do that in a more structured or systematic kind of fashion to get us to maybe a best answer or a conclusion for the clinical community as well as the public and the public health?

00:23:09 Pier Luigi Lopalco

Of course, there are structured methodologies to synthesise this large body of evidence

and bring the evidence to the real world as a recommendation. For instance, there are qualitative approaches, such as GRADE, that are used to develop and present summaries of available evidence, determine the quality of evidence and make recommendations to be used as a bridge between science and policy.

GRADE, maybe, I think is the best format currently available in many countries. Of course, it has also some limitations. For instance, the timeliness of data availability, the subjectivity of the bias assessment tools and—this is not trivial—the reliance on sufficient content expertise of GRADE reviewers, because the GRADE reviewers should be experts in influenza vaccination.

It is critical, I believe, that in countries where GRADE is the accepted format, we have to learn how to make it beneficial and effective—for instance, by ensuring high content and disease expertise of GRADE reviewers.

00:24:25 Nihar Desai

Yeah, it's such a critical point and I think, you know, I would just emphasise again the point that you made very, very well, that we want more structured and systematic approaches to really holistically look at the full body of evidence and having that kind of approach is probably preferable over, you know, maybe a checklist kind of a rating system or other similar approaches there that we really need that kind of holistic, qualitative but structured systematic approach. And that leverages true disease expertise on the side of the reviewers.

So, Luigi, I really want to thank you again for kind of joining me on this podcast. I think we've had a terrific discussion about influenza vaccine performance. I think, you know, we started talking about what some of the right endpoints are. How do we get to those endpoints? What's the right methodology? The evidence to really generate about vaccine performance, and how do we do a holistic examination of that kind of body of evidence?

So, you know, I just want to thank you again and I want to thank our listeners. I hope that they have really enjoyed the discussion. I know Luigi and I certainly have. So, with that, we will thank you again for listening and we'll sign off.

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