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Califf's Covid Twitter Communications Reveal Knowledge Gaps Partially Of FDA's Own Making

by Sarah Karlin-Smith

FDA Commissioner's recent Twitter threads highlight the challenges of discussing the unknowns of therapeutic interventions – and raise questions about why FDA isn't doing more to close the information gaps.

Recent Twitter threads from US Food and Drug Administration Commissioner Robert Califf related to the bivalent COVID-19 vaccines and the antiviral Paxlovid focused on potential misimpressions people may be making about the pharmaceuticals.

The threads, which seem to stem from Califf's desire to tackle misinformation, highlight evidence gaps and uncertainties about the products that have helped fuel some of the scientific community and the public's skepticism about their precise value.

Credible scientists aren't questioning that they are very valuable products, but there are questions around exactly who needs to take Paxlovid (nirmatrelvir/ritonavir) or what, if any benefit, the updated boosters offer over the older ones.

In one of the two Twitter exchanges Califf seems to blame other scientists for some of the public's misconceptions about the updated vaccines.

However, many scientists, doctors and members of the public have valid questions about the products due to research holes – holes that exist in part because FDA authorized the products without requiring the sponsors to address the questions and in some cases still isn't requiring additional research on the topics.

More Answers Wanted On Paxlovid In Vaccinated People

Califf's *Twitter thread* on *Pfizer Inc.*'s Paxlovid was posted on 1 November, one day after the Centers for Disease Control and Prevention Director Rochelle Walensky tested positive for COVID, days after completing a course of Paxlovid and initially testing negative for the virus. Less than two weeks later, Califf would also test positive for the virus and begin taking the drug himself.

Califf's tweets expressed concern that a focus on "Paxlovid rebound," as may have occurred in Walenksy's case, is distracting from the evidence for which the drug was granted its emergency use authorization – namely that it provided a substantial reduction in death and hospitalization for high-risk patients.

The thread however didn't mention that the authorization was based on data from a trial in unvaccinated adults and there are unanswered questions around the role of the drug in a vaccinated person like Walensky, a fact other Twitter users were quick to point out. (Also see "*Paxlovid, Molnupiravir, Sotrovimab Appear Cost Effective To ICER; But Data, Price Could Change*" - Pink Sheet, 3 Feb, 2022.)

Such a gap is notable because in the UK a large open-label study of a similar antiviral, *Merck & Co., Inc.*'s Lagevrio (molnupiravir), conducted in a highly vaccinated population has so far found no evidence of a benefit in the reduction of hospitalizations or death from that drug. A Pfizer study of Paxlovid in standard-risk patients, which included vaccinated people, also failed. (Also see "*Pfizer's Paxlovid Likely Relegated To High-Risk COVID-19 Patients*" - Scrip, 15 Jun, 2022.)

The UK in April added Paxlovid to its study, called PANORAMIC. (Also see "*Coronavirus Notebook: UK Adds Paxlovid To PANORAMIC Study, Germany Funds Adrecizumab Phase II Trial*" - Pink Sheet, 12 Apr, 2022.) And it is once again the UK and its health authorities, not the US and not the FDA, that is helping fill key evidence gaps in COVID. (Also see "*How COVID-19 Disrupted The Clinical Trial Status Quo*" - In Vivo, 11 Apr, 2022.)

Califf has noted the advantage of the systems the UK has set in place to answer key research questions during COVID, but it is not clear whether FDA is motivated to help push companies to do this type of work to address questions that Americans also want answers to. (Also see "*COVID-19 Therapeutic Trials: Investigators Should Join Forces Rather Than Conduct Single Site Studies*" - Pink Sheet, 16 Apr, 2021.)

Holes In Rebound Research?

Califf's Paxlovid thread did point out other evidence gaps with the antiviral including the need "to understand how much of rebound is due to Paxlovid itself or a byproduct of Covid infection per se. And whether the recurrence is a recurrent infection or an immunological phenomenon. And how to treat it." He said that randomized controlled trials were underway.

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However, when pressed for more information about the additional studies being conducted to address these lingering questions, FDA pointed to two studies it is requiring Pfizer conduct– *one trial* will explore using Paxlovid to treat a rebound of COVID-19 after finishing a course of the drug.

The *second trial* will look at longer duration of therapy for immunocompromised individuals.

These studies will provide valuable information and potentially lead to additional uses of the drug, but do not appear to be able to address the questions about the cause of rebound discussed in Califf's tweets.

The agency declined to respond to additional questions on what studies are being done to address these lingering knowledge gaps, including which vaccinated people need the drug. FDA has wide latitude to require further study of the drug to understand these issues if it wanted to.

Preliminary Data Communication Criticized

Califf's *thread on the updated COVID vaccines* came on 4 November in response to Pfizer issuing a *press release* on immunogenicity data with its updated bivalent booster compared to the original prototype booster. The study showed the bivalent vaccine elicited approximately four-fold higher neutralizing antibody titers against Omicron BA.4/BA.5 compared to the original COVID-19 vaccine in people 55 years of age and older.

A week earlier two independent immunogenicity studies conducted at Harvard and Columbia concluded that while the updated vaccine led to higher antibody responses against these Omicron variants, the difference was not significant.

Califf's Twitter thread was critical of the attention brought to the two smaller studies, which he said had "inherent limitations."

"While the scientists who did this work are first rate, I do worry that the rush to be first can lead to results that don't stand the test of time. And because of the hyper-reactivity of the press and the rapid transmission in the scientific community, incorrect first impressions can be difficult to dislodge. This can lead to confusion in the public and non-specialist clinicians on the front lines."

Califf went on to say that "we should exercise caution before we draw conclusions from preliminary data."

Absent from Califf's discussion, however, was the admission that the reason so much attention was placed on the initial immunogenicity data is because FDA, in an unexpected move, authorized the bivalent vaccines without such data, and federal officials – including White House

leaders on the COVID response team – have made bold claims about the shots in the absence of definitive information. (Also see "*US FDA Appears To Quickly Renege On Next-Gen COVID Vaccine Guidance With Updated Booster Announcement*" - Pink Sheet, 30 Jun, 2022.) and (Also see "*Overhyped? White House COVID Coordinator's Claims About New Boosters Go Beyond Data*" - Pink Sheet, 18 Aug, 2022.)

Pfizer's immunogenicity data still leaves gaps in comparing adults under 55 who took the older booster compared to the new booster. Additionally, there is a lack of understanding of the clinical significance of the increase in antibodies seen in the study.

FDA declined to respond to *Pink Sheet* follow-up questions about this thread, including whether it is fair for FDA to draw conclusions and authorize a product on lesser data but then urge caution from others in interpreting preliminary information. It also wouldn't answer whether it it fair to expect people not to discuss new information on an FDA authorized product whose adoption is being so widely encouraged.

The Big Picture

Health communication experts said one of the crucial things related to Califf's threads is to make sure the main takeaways for the public about these pharmaceuticals don't get lost in the more complicated scientific debate.

"The larger picture here is that often science is really messy and so as all the details are getting sorted out the messiness can sometimes distract from the main message of how to protect the most people from bad outcomes," said Tara Kirk Sell, a senior scholar at the Johns Hopkins Center for Health Security and an Associate Professor in the Department of Environmental Health and Engineering at the Johns Hopkins School of Public Health.

"Sometimes it's hard in these situations to stay on target. It's helpful for FDA to have clear messages about what is known about treatments and what is being done to fill those gaps. Halfway, mealy-mouthed answers help no one and just leave a lot of room for people to get mixed up," she said.

Sell works on research to improve understanding of better risk communication, and she met with Califf this summer on the topic of misinformation and disinformation communication, per FDA's public calendar.

"I think that people should take new studies, including preliminary data, as part of a body of work that together than tell us more what is going on," she said. "While it's a good idea to be able to take in new information and revise our thoughts accordingly, it's not a good idea to be constantly switching directions without some good evidence – the CDC got criticized endlessly for this. I think the concern is that people who should go out and get protected with a vaccine

will get caught in a swirl of uncertainty and skip it all together, when in the end getting vaccinated is the most important thing."

Both of Califf's threads do highlight key topline takeaways. For the vaccine he says, "The most important point is that staying up to date on COVID vaccination has been shown to substantially reduce the risk of death and hospitalization." In the Paxlovid thread he ends by reminding people to talk with their clinician about antiviral treatment if they are high risk and get infected.

Sell said that communication science research has shown that "the first message that people receive often is the one that sticks with people the most."

In his vaccine thread, Califf raised concern about the public not appreciating Pfizer's immunogenicity data given the first impression they might have had from the other studies' data.

But that doesn't necessarily mean the best thing to do is to avoid engaging with information like the preliminary immunogenicity studies, which seems to be a main takeaway of Califf's thread.

Nuance vs. Blaring Headlines

"Research on how to deal with situations where there are a lot of unknowns show that it is important to say what is known and unknown, acknowledge gaps, and then say what is being done to fill gaps," Sell said, along with a disclaimer that much of this research came before the current "deluge" of misinformation and disinformation.

She argues that new results should be communicated and reviewed with the appropriate nuance "rather than via blaring headlines."

Overall, though she again cautions against getting too focused on small disagreements rather than the big picture agreement.

In this case that would be the importance of people getting vaccinated.

"Public health commentators sometimes go at each other based on small disagreements in ways that reduce trust overall. And that's why I'm not going to get nit-picky on this Twitter thread, since that would be exactly the kind of distraction that isn't helpful to the overall message," Sell said.

Is Twitter Part Of The Problem?

Kasisomayajula Viswanath, a professor of health communication at Harvard, said that he believes Twitter is not a good platform to engage in the sort of nuance Califf was striving for in his threads on Paxlovid and the bivalent vaccines. He worries the content Califf shared may just

lead to more confusion among the general public.

“I’m tempted to say this is an insider conversation,” Viswanath said.

The threads “require a certain amount of insider knowledge about how science works,” and it is “an unreasonable burden to be placed on people to make sense of those threads,” he said.

At the same time, FDA has to expect that all the data available on the products will be discussed whether the agency’s commissioner wants it to be or not, particularly given the focus the government is putting on these products, Viswanath said, regarding the preliminary studies Califf criticized in his vaccine thread.

“It’s the public realm. Of course people will discuss given the heightened interest and the continuous advocacy from the government saying go get your booster, we have improved boosters go get it.”

If the press didn’t discuss the data, it “would be accused of hiding something,” he added.

Viswanath argues one of the root causes for the frustration in Califf’s tweets goes back to the government not doing a good job itself communicating the uncertainty that comes with authorizing pharmaceuticals swiftly during a pandemic.

“What we are not doing very well is communicating that uncertainty. Saying if you get the booster, you might still get a breakthrough COVID case. If you get Paxlovid it might ease your symptoms immediately, but you might get it back. But that requires some patience and nuance and transparency in communicating. And it’s not that the government is trying to hide or people are trying to hide it. It is that it requires essentially being very clear, categorical, this is what we know, this what we don’t know and not overpromising.”