From: "Su, John (CDC/NCEZID/DHQP/ISO)" [redacted]
To: "Nair, Narayan (FDA/CBER)" [redacted], "Shimabukuro, Tom (CDC/NCEZID/DHQP/ISO)" [redacted]
Cc: "Duffy, Jonathan M. (CDC/NCEZID/DHQP/ISO)" [redacted]
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper
Date: Fri, 19 Jan 2024 13:56:03 +0000
Importance: Normal
Attachments: tinnitus_after_COVID_vaccination_17_Jan_2024.docx

---

You're awesome --- thanks! Please see enclosed.

- John

From: Nair, Narayan [redacted]
Sent: Friday, January 19, 2024 8:45 AM
To: Su, John (CDC/NCEZID/DHQP/ISO) [redacted]; Shimabukuro, Tom (CDC/NCEZID/DHQP/ISO) [redacted]
Cc: Duffy, Jonathan M. (CDC/NCEZID/DHQP/ISO) [redacted]
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Sure, I think we can do that. Do you have the latest draft?

Narayan

From: Su, John (CDC/NCEZID/DHQP/ISO) [redacted]
Sent: Thursday, January 18, 2024 3:32 PM
To: Nair, Narayan [redacted]; Shimabukuro, Tom (CDC) [redacted]
Cc: Duffy, Jonathan M (CDC) [redacted]
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Hi Narayan,

Adding Jon Duffy to this thread, for his awareness.

Also, while I'd indicated Jan 31 as a target date, there's interest in moving this paper forward with haste. Would the end of next week (Jan 26) be doable? Any priority you could put on this ask would be greatly appreciated. Thanks!

- John

From: Nair, Narayan [redacted]
Sent: Wednesday, January 17, 2024 11:27 PM
To: Su, John (CDC/NCEZID/DHQP/ISO) [redacted]; Shimabukuro, Tom (CDC/NCEZID/DHQP/ISO) [redacted]
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Thanks John. Good to hear from you. We will try and get back to you by the due date.

Narayan

From: Su, John (CDC/NCEZID/DHQP/ISO) [redacted]
Sent: Wednesday, January 17, 2024 6:09 PM
To: Nair, Narayan [redacted]; Shimabukuro, Tom (CDC) [redacted]
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Hi Narayan,

I hope you're keeping warm! It's frosty out there. ❄

I think this paper fell off a lot of radars. We're trying to move this paper forward. I'm working on updating the most current draft with data from VAERS by dose number; I'll send later tonight under separate cover. Please amend with EB data mining language (methods, results). I don't know of a due date per se – would Jan 31 be reasonable? Of course, sooner would be greatly appreciated.

Thanks!

- John

From: Nair, Narayan [redacted]
Sent: Friday, December 1, 2023 11:03 AM
To: Shimabukuro, Tom (CDC/NCEZID/DHQP/ISO) [redacted]; Su, John (CDC/NCEZID/DHQP/ISO) [redacted]
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Hi Tom and John,
This fell off my radar with competing priorities. Did you have a due date for us to provide comments/edits on this paper?

Narayan

From: Shimabukuro, Tom (CDC/NCEZID/DHQP) [redacted]
Sent: Friday, October 27, 2023 9:25 PM
To: Su, John (CDC) [redacted]; Nair, Narayan [redacted]; Bazel, Samaneh [redacted]
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Agreed. I think we should use the FDA EB data mining and describe the limitations that might be unique to COVID-19 vaccines.

From: Su, John (CDC/NCEZID/DHQP) [redacted]
Sent: Friday, October 27, 2023 3:18 PM
To: Nair, Narayan (FDA/CBER) [redacted]; Bazel, Samaneh (FDA/CBER) [redacted]
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) [redacted]
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Hi Narayan,

Thanks for the feedback! I'll discuss with Katherine and company. My inclination is to either use existing EB data mining data from FDA, or not – novel methodologies make me uncomfortable if they haven't been vetted or otherwise validated.

- John

From: Nair, Narayan [redacted]
Sent: Friday, October 27, 2023 3:04 PM
To: Su, John (CDC/NCEZID/DHQP) [redacted]; Bazel, Samaneh (FDA/CBER) [redacted]
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) [redacted]
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Hi John,
She does bring up a good point. As you know, data mining has all the limitations of passive surveillance as well as others. However, during the COVID vaccine era there is an additional limitation. Since most reports received involve COVID-19 vaccines, disproportionately scores (which are adjusted by year to control for time-dependent, potentially confounding, exposure and outcome variables) can be driven towards the null by COVID-19 vaccine reports contributing substantially to the comparator group. This would could occur in the setting if there was some type of class-effect (e.g., if both mRNA COVID-19 vaccines are associated with the same adverse event).
We were aware of this limitation before and during the pandemic. There are many data mining tools and there was some discussion about utilizing a novel tool to adjust for this. However, we thought it would be problematic to use a brand new, possibly unvalidated tool in the context of an EUA. We ended up using the same EBGM data mining we use for all vaccines and has a long history of use rather than take an experimental approach. As new non-COVID vaccine reports are added we think this limitation will be mitigated to some degree.
As far as the paper goes there are several options to address this:

- We could report our data mining findings and just acknowledge this as a limitation (this is what we have done in other papers)
- We could not include any data mining findings
- You could develop another tool that would compensate for the greater number of COVID vaccine reports. I am not sure how to do this but you would need a statistician with DM experience. This would be beyond our capabilities at FDA.

Narayan

From: Su, John (CDC/NCEZID/DHQP) [redacted]
Sent: Thursday, October 26, 2023 9:32 AM
To: Nair, Narayan [redacted]; Bazel, Samaneh [redacted]
Cc: Shimabukuro, Tom (CDC) [redacted]
Subject: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Hi folks,

Please see below email (it was late, and I got a bit confused). I know EB data mining looks at vaccine-event pairs between the vaccine of interest and an adverse event, and compares against all other vaccines in the VAERS database and the same adverse event, to see if a disproportionality beyond an established threshold is present. However, I don't know the methods well enough to address Judy's comments. How do the methods FDA uses address these points? Thanks!

- John

From: Su, John (CDC/NCEZID/DHQP)
Sent: Thursday, October 26, 2023 9:10 AM
To: Maro, Judy [redacted]; Yih, Katherine [redacted]
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) [redacted]; Moro, Pedro (CDC/NCEZID/DHQP) [redacted]; Nair, Narayan (FDA/CBER) [redacted]
Subject: RE: FDA coauthor for tinnitus paper

Hi Judy,

Sorry, I've been juggling a bit and got my coauthors crossed. FDA performs EB data mining for VAERS, and throughout postauthorization safety monitoring for COVID-19 vaccines, has shared with CDC the results. While I'm familiar conceptually with EB data mining, I'll need to discuss with FDA to better understand how the methods they use address the concerns you've raised. Thanks!

- John

From: Su, John (CDC/NCEZID/DHQP)
Sent: Thursday, October 26, 2023 8:59 AM
To: Maro, Judy [redacted]; Yih, Katherine [redacted]
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) [redacted]; Moro, Pedro (CDC/NCEZID/DHQP) [redacted]; Nair, Narayan (FDA/CBER) [redacted]
Subject: RE: FDA coauthor for tinnitus paper

Hi Judy,

Thanks for the feedback. CCing Narayan for awareness. We'll get back to you.

- John

From: Maro, Judy [redacted]
Sent: Wednesday, October 25, 2023 11:43 PM
To: Su, John (CDC/NCEZID/DHQP) [redacted]; Yih, Katherine [redacted]
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) [redacted]; Moro, Pedro (CDC/NCEZID/DHQP) [redacted]
Subject: RE: FDA coauthor for tinnitus paper

Hi John –

To do a disproportionality analysis of any kind (EBGM is just one version but they are statistically similar), you need 4 quantities or a typical 2 x 2 contingency table.

So, one would need

Exposure Yes, Disease yes – any specific vaccine + tinnitus reports

Exposure Yes, Disease no – any specific vaccine + non-tinnitus reports

Exposure no, Disease yes – all exposures but for the specific vaccine. In the covid era, this means basically COVID + tinnitus

Exposure no, Disease no – all exposures but for the specific vaccine + non-tinnitus reports. Again, in this era, that means COVID + non-tinnitus

So, for the 17,859, it's important to know how these are spread among what vaccines and to choose the vaccines that you want to examine for a signal. It will be mostly useless to try to make statements about the COVID vaccines because the database will have so many COVID reports that you can't create a comparator. You also need to know what the capture is for the period you are examining of the non-tinnitus reports.

Best
Judy

From: Su, John (CDC/NCEZID/DHQP) [redacted]
Sent: Wednesday, October 25, 2023 11:15 PM
To: Maro, Judy [redacted]; Yih, Katherine [redacted]
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) [redacted]; Moro, Pedro (CDC/NCEZID/DHQP) [redacted]
Subject: RE: FDA coauthor for tinnitus paper

Hi Judy,

Glad you're able to help. We're hoping for an analysis of reports to VAERS with the MedDRA Preferred Term (PT) "tinnitus" received during Dec 14, 2020 through May 4, 2023. Specifically, if vaccine-pairs for this PT exceed thresholds for statistical significance.

If having counts or a line list would help, we can put you in touch with our senior data manager. We identified 17,859 reports during the analytic period. I can share the latest draft of the manuscript (confidentially, of course) if that would help.

Please let me know if you have any other questions. Thanks!

- John

From: Maro, Judy [redacted]
Sent: Wednesday, October 25, 2023 10:19 PM
To: Su, John (CDC/NCEZID/DHQP) [redacted]; Yih, Katherine [redacted]
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) [redacted]; Moro, Pedro (CDC/NCEZID/DHQP) [redacted]
Subject: RE: FDA coauthor for tinnitus paper

Folks,
I'm fairly familiar with EBGM – do you have the numbers that were used?

On including the FDA, I have no objections but want to note that it will involve another clearance chain which will add probably a good amount of time into the timeline.

Happy to help in any way I can,

Best
Judy

From: Su, John (CDC/NCEZID/DHQP) [redacted]
Sent: Wednesday, October 25, 2023 11:15 AM
To: Yih, Katherine [redacted]

Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) [redacted]; Moro, Pedro (CDC/NCEZID/DHQP) [redacted]; Maro, Judy [redacted]
Subject: RE: FDA coauthor for tinnitus paper

Sounds great – thanks!

- John

From: Yih, Katherine [redacted]
Sent: Wednesday, October 25, 2023 11:11 AM
To: Su, John (CDC/NCEZID/DHQP) [redacted]
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) [redacted]; Moro, Pedro (CDC/NCEZID/DHQP) [redacted]; Maro, Judy [redacted]
Subject: RE: FDA coauthor for tinnitus paper

Hi John,
If you all think it's important to include this analysis, then it's fine with me to include a couple of co-authors from FDA. (I'm expecting some or all of the VSD sites to propose a co-author, too, so wouldn't want the number of co-authors to get *too* high (for logistical reasons).)
Thanks for checking. Cc-ing Judy Maro, in case she has comments about this plan.
Katherine

From: Su, John (CDC/NCEZID/DHQP) [redacted]
Sent: Wednesday, October 25, 2023 10:30 AM
To: Yih, Katherine [redacted]
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) [redacted]; Moro, Pedro (CDC/NCEZID/DHQP) [redacted]
Subject: FDA coauthor for tinnitus paper

Hi Katherine,

We appreciate your continued patience as we work on this paper! Desire has been expressed to include Empirical Bayesian data mining of the VAERS data, which is performed by our colleagues at FDA. If we include those data, we'll need to include coauthors from FDA. Are you okay with this approach? If so, I'll reach out and get them involved. Thanks!

- John

disclosing it.

SMR1.Point32Health.org made the following annotations

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SMR1.Point32Health.org made the following annotations

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From: "Nair, Narayan" [redacted]
To: "Zinderman, Craig E" [redacted], "Menschik, David" [redacted]
Subject: RE: suggested edits as discussed...
Date: Fri, 07 May 2021 19:40:02 -0000
Importance: Normal
Attachments: Data_Mining_Note_to_CDER_2021_0507_dm_cz_nn_(2).docx

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Hi Craig and David,
Thanks for working on this email. I think it is excellent. I had a couple of suggestions but definitely nothing I feel strong about so feel free to ignore if they don't work for you. I plan to talk to Karen about this issue early next week.

Narayan

From: Zinderman, Craig E [redacted]
Sent: Friday, May 7, 2021 2:59 PM
To: Menschik, David [redacted] Nair, Narayan [redacted]
Subject: RE: suggested edits as discussed...

Narayan:
Sorry to send a second version, but David and I made a tweak to the last paragraph that we think works better.

Thanks,
Craig

From: Zinderman, Craig E
Sent: Friday, May 07, 2021 2:49 PM
To: Menschik, David [redacted]; Narayan Nair ([redacted])
Subject: RE: suggested edits as discussed...

Narayan:
I drafted, and David edited, the attached message to Ana as discussed. Please feel free to edits as you see fit. It's pretty long so feel to shorten if you can see any opportunity for that.

I put it in Word for ease of tracked changes.

Thanks,
Craig

From: Menschik, David [redacted]
Sent: Friday, May 07, 2021 12:33 PM
To: Zinderman, Craig E [redacted]
Subject: suggested edits as discussed...

…attached…

Good AfternoonMorning Ana,

Thank you again for talking with us back in March about your work exploring new data mining approaches and discussing your interest in CBER's COVID-19 vaccine products. We are writing to kindly ask that you to please hold off on stop creating and sending data mining reports and analyses using COVID-19 vaccine AE data.

Commented [NN1]: Agree with not using "stop". But I was worried she may misread the sentence as "please hold on" to doing what she is doing.
Nair, Narayan
2021-05-07 15:35:00

In CBER OBE, we have been reviewing the various COVID-19 vaccine data mining results that you have been forwarding. While we appreciate your interest in sharing your results, they have not contributed to our alreadywe already have a robust process for continuous monitoring ofreviewing incoming and aggregated VAERS (and other vaccine safety) data. I will describe a little bit below:including:

-AESIs: CBER and CDC have established sets of AESIs (sets of PTs representing Adverse Events of Special Interest) for key events. Incoming reports captured by these AESIs are highlighted for FDA reviewer screening, as well as medical record follow-up and chart abstraction by CDC reviewers. Many of the alerts that you have been sending relate to AESIs for which we are already screening and reviewing reports, such as AMI, TTS, Thromboembolic events, and other forms of coagulopathy. Having our staff examine your alerts creates an extra, and somewhat redundant workstream for them, since these AESIs are already under close observation. AESIs for which we are seeing substantial or notable reporting are further evaluated via comparisons to background rates (using known COVID vaccine administration data tracked by CDC and provided weekly to FDA) as well as in population-based data sources both at FDA and CDC (e.g., BEST, CMS, Vaccine Safety Datalink (VSD)).

-Serious report screening: FDA MOs review sSerious reports coming into VAERS daily until meeting pre-specified milestones (i.e., certain time since authorization and doses administered) and then ; for the first couple months with the mRNA vaccines, and still currently for JnJ, FDA MOs review each serious report as it is processed into VAERS. For the older mRNA vaccines, MOs now conduct weekly review of aggregated PT counts weekly, by seriousness, AESI, Lot number, most frequent PTs, weekly changes in PT rankings, and other metrics.

-Pre-screening: for a couple of notable issues, the VAERS program contractor flags reports when they hit the door: these pre-screened events will have expedited gathering of medical records and CDC review and abstraction. TTS and anaphylaxis both have fallen into this category.

Of note, data mining alerts, which are designed to generate hypotheses of possible safety issues, are no longer particularly useful for our pharmacovigilance purposes when a signal has already been identified, such as for TTS, or when an issue (e.g., an AESI such as AMI) is being worked up in a more robust (e.g., active surveillance) system.. Some alerts that you have sent, like for AMI, have already temporarily signaled in population-based surveillance, which has already triggered a more thorough review of VAERS data.

Also as you knowFurther, we have a standard process for data mining screening in place for VAERS data; this screening was in place at the start of, and throughout, the COVID vaccine campaign; the frequency/nature of the calculations, stratifications and other parameters, are known and understood by us and our stakeholders. We understand that exploring new approaches and varying the stratifications or other parameters might improve the methodology and is of interest to you. However, from our perspective, the approach employed during a period of intense, high profile surveillance should be standard, and predictable, and road-tested. Results from Aadjusting parameters thato raise or lower sensitivity of the alerts as the vaccination campaign is underway could lead to some artificial creation of alerts and an apparent, but not real, sudden change in safety results. confusion and have unintended consequences (e.g., regarding vaccine confidence).

We would be happy to engage with you should you wish to explore your new approaches on CDER regulated products.

So, while we appreciate your work and interest at CDER on the COVID vaccine VAERS data, ~~for all of the above reasons,~~ in the above context, we have found ~~that examining the analyses you have been sending has largely reflected events otherwise under evaluation~~no indication for action based on your findings, which have been consuming a lot of resources at a time when resources are stretched across ~~a~~ preexisting robust pharmacovigilance ~~infrastructure~~activities. ~~We haven't seen a proportionate increase in efficiency or yield, given the robust screening and scrutiny of VAERS data already in place as described above. We'd hate for you to be wasting your time and efforts, so we thought we should suggest that it might be a better use of resources for you to refocus your data mining efforts on other product types. Perhaps there are CDER products and drug related data in your Center that could benefit more from your continued data mining explorations and analyses.~~ So, we are asking that you please hold off on creating and sending data mining results for COVID-19 vaccine AE data. Thanks much for your time and ~~attention~~understanding, and~~,~~ sorry for the long email.

Kind regards,~~Thanks~~,

Craig Zinderman, MD, MPH
Associate Director for Medical Policy
Office of Biostatistics and Epidemiology
FDA/Center for Biologics Evaluation and Research
[redacted]

Commented [NN2]: This is my clumsy attempt to redirect her. Feel free to delete this sentence if not desirable or feasible
Nair, Narayan
2021-05-07 15:33:00

From: "Nair, Narayan" [redacted]
To: "Menschik, David" [redacted], "Zinderman, Craig" [redacted], "Baer, Bethany" [redacted]
Subject: RE: Data mining question
Date: Fri, 15 Mar 2024 19:21:26 -0000
Importance: Normal
Inline-Images: image001.png; image002.jpg; image003.jpg; image004.jpg; image005.jpg; image006.jpg

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Ok, thank you for checking.

Narayan

From: Menschik, David [redacted]
Sent: Friday, March 15, 2024 1:30 PM
To: Nair, Narayan [redacted]; Zinderman, Craig [redacted]; Baer, Bethany [redacted]
Subject: RE: Data mining question

I understood we provided CDC language for this limitation for the 6 month safety review of mRNA vaccines (and I could share that language if helpful) but in looking at the published article, it now appears that they took it out before publication. I'm not aware of such language included in another publication.

From: Nair, Narayan [redacted]
Sent: Friday, March 15, 2024 1:04 PM
To: Menschik, David [redacted]; Zinderman, Craig [redacted]; Baer, Bethany [redacted]
Subject: Data mining question

Good afternoon,
I know in the past we have discussed one of the possible limitations of data mining currently is the vast number of VAERS reports from the COVID vaccines may limit our ability to detect statistical alerts because disproportionality scores may be driven towards the null. Do you know if there is a public reference that discusses this limitation? I have found some references that discuss general limitations for data mining but not sure if there is one that talks about how a large volume of reports from a single class of products could masks results.

Narayan Nair, MD (he/him/his)
Division Director

Division of Pharmacovigilance
Office of Biostatistics and Pharmacovigilance
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

[redacted]

FDA U.S. FOOD & DRUG ADMINISTRATION

From: "Nair, Narayan" [redacted]
To: "Sly, Elizabeth" [redacted], "Zinderman, Craig E" [redacted], "Alimchandani, Meghna" [redacted]
Cc: "Burk, Suzann" [redacted]
Subject: RE: [EXTERNAL] Empirical Bayesian (EB) Data Mining
Date: Fri, 30 Sep 2022 14:21:04 -0000
Importance: Normal

Thanks – I hope you have a nice weekend also (I think it will be a rainy one!)

Narayan

From: Sly, Elizabeth [redacted]
Sent: Friday, September 30, 2022 10:16 AM
To: Zinderman, Craig E [redacted]; Alimchandani, Meghna [redacted]; Nair, Narayan [redacted]
Cc: Burk, Suzann [redacted]
Subject: RE: [EXTERNAL] Empirical Bayesian (EB) Data Mining

Hi All,

Thank you all so much. I'll simply let them know that this information is inaccurate and FDA continues to regularly conduct data mining for all approved/authorized vaccines (and I'll direct them to the link you provided).

I'll also encourage them to have their CDC SME's speak with you directly if they need any further information as I know you communicate regularly.

Thanks again for the prompt reply and have a wonderful weekend.

-Liz

From: Zinderman, Craig E [redacted]
Sent: Friday, September 30, 2022 10:10 AM
To: Alimchandani, Meghna [redacted]; Nair, Narayan [redacted]; Sly, Elizabeth [redacted]
Cc: Burk, Suzann [redacted]
Subject: RE: [EXTERNAL] Empirical Bayesian (EB) Data Mining

Nothing for me either.

Thanks,
Craig

From: Alimchandani, Meghna [redacted]
Sent: Friday, September 30, 2022 9:53 AM
To: Nair, Narayan [redacted]; Sly, Elizabeth [redacted]; Zinderman, Craig E [redacted]
Cc: Burk, Suzann [redacted]
Subject: RE: [EXTERNAL] Empirical Bayesian (EB) Data Mining

I did not have anything to add; thank you.

Best regards,
Meghna

From: Nair, Narayan [redacted]
Sent: Friday, September 30, 2022 9:44 AM
To: Sly, Elizabeth [redacted]; Zinderman, Craig E [redacted]; Alimchandani, Meghna [redacted]
Cc: Burk, Suzann [redacted]
Subject: RE: [EXTERNAL] Empirical Bayesian (EB) Data Mining

Hi Liz,
Seem my responses below in red. Craig/Meghna, please let me know if you have anything to add. Happy to discuss further if needed.

1) Please let me know if information they have summarized is accurate and/or if there is any further clarification you can provide.
The statement is not accurate. FDA is still regularly conducting data mining for all approved/authorized vaccines.
2) Is there any cleared language/statement available on this topic that we could share with CDC that's publicly releasable?
I am not quite sure what they are looking for but here is a link that describes FDA datamining efforts.
https://www.fda.gov/science-research/data-mining

Some additional background with regard to Question #1 – we would regularly send CDC the results of our datamining for the COVID vaccines by email. Earlier, this summer I suggested to CDC ISO that we discontinue the routine regular emails. I told them that DPV would continue to conduct data mining and would notify CDC if we found any datamining alerts that were clinical relevant and required further action. This was intended as a time saving measure and to reduce email traffic. Since it had been some time that we had a datamining alert that required further evaluation, CDC agreed with this approach. It appears someone at CDC mistook the discontinuation of the weekly emails to mean that we had stopped conducting data mining

Narayan

From: Sly, Elizabeth [redacted]
Sent: Thursday, September 29, 2022 4:55 PM
To: Nair, Narayan [redacted]; Zinderman, Craig E [redacted]; Alimchandani, Meghna [redacted]
Cc: Burk, Suzann [redacted]
Subject: FW: [EXTERNAL] Empirical Bayesian (EB) Data Mining

Good Afternoon,

Please see below for an e-mail from CDC seeking clarification related to data mining. They've let me know that right now they are just seeking clarification for background purposes but they also mentioned that they would appreciate a statement/quote (if available) which could be used to respond to a FOIA request, if necessary.

1. Please let me know if information they have summarized is accurate and/or if there is any further clarification you can provide.

2. Is there any cleared language/statement available on this topic that we could share with CDC that's publicly releasable?

Thank you,

Liz

From: Mitchell, Elnetta (CDC/DDID/NCEZID/DHQP) (CTR) [redacted]
Sent: Monday, September 26, 2022 3:58 PM
To: Sly, Elizabeth [redacted]
Cc: Thompson, Perstephanie (CDC) [redacted]
Subject: [EXTERNAL] Empirical Bayesian (EB) Data Mining

Good Afternoon Elizabeth,

One of our SMEs stated that it is their understanding that FDA discontinued Empirical Bayesian (EB) data mining for COVID-19 vaccines after July 5, 2022, on the basis that after over 600 million doses administered, and the stability of observations of the weekly data, the data were mature and no additional potential safety signals would be found. Is this accurate? Please advise. Thanks.

Elnetta Mitchell, MBA
Goldbelt C6, LLC
DHQP/NCEZID/CDC
Centers for Disease Control and Prevention
[redacted]

From: "Nair, Narayan" [redacted]
To: "Sly, Elizabeth" [redacted], "Zinderman, Craig E" [redacted] "Alimchandani, Meghna" [redacted]
Cc: "Burk, Suzann" [redacted]
Subject: RE: [EXTERNAL] Empirical Bayesian (EB) Data Mining
Date: Fri, 30 Sep 2022 13:43:32 -0000
Importance: Normal

Hi Liz,
Seem my responses below in red. Craig/Meghna, please let me know if you have anything to add. Happy to discuss further if needed.

1) Please let me know if information they have summarized is accurate and/or if there is any further clarification you can provide.
The statement is not accurate. FDA is still regularly conducting data mining for all approved/authorized vaccines.
2) Is there any cleared language/statement available on this topic that we could share with CDC that's publicly releasable?
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Narayan

From: Sly, Elizabeth [redacted]
Sent: Thursday, September 29, 2022 4:55 PM
To: Nair, Narayan [redacted]; Zinderman, Craig E [redacted]; Alimchandani, Meghna [redacted]
Cc: Burk, Suzann [redacted]
Subject: FW: [EXTERNAL] Empirical Bayesian (EB) Data Mining

Good Afternoon,

Please see below for an e-mail from CDC seeking clarification related to data mining. They've let me know that right now they are just seeking clarification for background purposes but they also mentioned that they would appreciate a statement/quote (if available) which could be used to respond to a FOIA request, if necessary.

1. Please let me know if information they have summarized is accurate and/or if there is any further clarification you can provide.

2. Is there any cleared language/statement available on this topic that we could share with CDC that's publicly releasable?

Thank you,

Liz

From: Mitchell, Elnetta (CDC/DDID/NCEZID/DHQP) (CTR) [redacted]
Sent: Monday, September 26, 2022 3:58 PM
To: Sly, Elizabeth [redacted]
Cc: Thompson, Perstephanie (CDC) [redacted]
Subject: [EXTERNAL] Empirical Bayesian (EB) Data Mining

Good Afternoon Elizabeth,

One of our SMEs stated that it is their understanding that FDA discontinued Empirical Bayesian (EB) data mining for COVID-19 vaccines after July 5, 2022, on the basis that after over 600 million doses administered, and the stability of observations of the weekly data, the data were mature and no additional potential safety signals would be found. Is this accurate? Please advise. Thanks.

Elnetta Mitchell, MBA
Goldbelt C6, LLC
DHQP/NCEZID/CDC
Centers for Disease Control and Prevention
[redacted]

From: "Zinderman, Craig E" [redacted]
To: "Menschik, David" [redacted], "Nair, Narayan" [redacted]
Subject: RE: suggested edits as discussed...
Date: Fri, 7 May 2021 18:58:58 +0000
Importance: Normal
Attachments: Data_Mining_Note_to_CDER_2021_0507_dm_cz_(2).docx

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Narayan:
Sorry to send a second version, but David and I made a tweak to the last paragraph that we think works better.

Thanks,
Craig

From: Zinderman, Craig E
Sent: Friday, May 07, 2021 2:49 PM
To: Menschik, David [redacted]; Narayan Nair (Narayan.Nair@fda.hhs.gov) [redacted]
Subject: RE: suggested edits as discussed...

Narayan:
I drafted, and David edited, the attached message to Ana as discussed. Please feel free to edits as you see fit. It's pretty long so feel to shorten if you can see any opportunity for that.

I put it in Word for ease of tracked changes.

Thanks,
Craig

From: Menschik, David [redacted]
Sent: Friday, May 07, 2021 12:33 PM
To: Zinderman, Craig E [redacted]
Subject: suggested edits as discussed...

...attached...

Good AfternoonMorning Ana,

:

Thank you again for talking with us back in March about your work exploring new data mining approaches and discussing your interest in CBER's COVID-19 vaccine products. We are writing to kindly ask that you to please hold on stop creating and sending data mining reports and analyses using COVID-19 vaccine AE data.

In CBER OBE, we have been reviewing the various COVID-19 vaccine data mining results that you have been forwarding. While we appreciate your interest in sharing your results, they have not contributed to our alreadywe already have a robust process for continuous monitoring ofreviewing incoming and aggregated VAERS (and other vaccine safety) data. I will describe a little bit below:including:

-AESIs: CBER and CDC have established sets of AESIs (sets of PTs representing Adverse Events of Special Interest) for key events. Incoming reports captured by these AESIs are highlighted for FDA reviewer screening, as well as medical record follow-up and chart abstraction by CDC reviewers. Many of the alerts that you have been sending relate to AESIs for which we are already screening and reviewing reports, such as AMI, TTS, Thromboembolic events, and other forms of coagulopathy. Having our staff examine your alerts creates an extra, and somewhat redundant workstream for them, since these AESIs are already under close observation. AESIs for which we are seeing substantial or notable reporting are further evaluated via comparisons to background rates (using known COVID vaccine administration data tracked by CDC and provided weekly to FDA) as well as in population-based data sources both at FDA and CDC (e.g., BEST, CMS, Vaccine Safety Datalink (VSD)).

-Serious report screening: FDA MOs review sSerious reports coming into VAERS daily until meeting specified milestones (i.e., certain time since authorization and doses administered) and then ; for the first couple months with the mRNA vaccines, and still currently for JnJ, FDA MOs review each serious report as it is processed into VAERS. For the older mRNA vaccines, MOs now conduct weekly review of aggregated PT counts weekly, by seriousness, AESI, Lot number, most frequent PTs, weekly changes in PT rankings, and other metrics.

-Pre-screening: for a couple of notable issues, the VAERS program contractor flags reports when they hit the door: these pre-screened events will have expedited gathering of medical records and CDC review and abstraction. TTS and anaphylaxis both have fallen into this category.

Of note, data mining alerts, which are designed to generate hypotheses of possible safety issues, are no longer particularly useful for our pharmacovigilance purposes when a signal has already been identified, such as for TTS, or when an issue (e.g., an AESI such as AMI) is being worked up in a more robust (e.g., active surveillance) system.. Some alerts that you have sent, like for AMI, have already temporarily signaled in population-based surveillance, which has already triggered a more thorough review of VAERS data.

Also as you knowFurther, we have a standard process for data mining screening in place for VAERS data; this screening was in place at the start of, and throughout, the COVID vaccine campaign; the frequency/nature of the calculations, stratifications and other parameters, are known and understood by us and our stakeholders. We understand that exploring new approaches and varying the stratifications or other parameters might improve the methodology and is of interest to you. However, from our perspective, the approach employed during a period of intense, high profile surveillance should be standard, and predictable, and road-tested. Results from Aadjusting parameters thato raise or lower sensitivity of the alerts as the vaccination campaign is underway could lead to some artificial creation of alerts and an apparent, but not real, sudden change in safety results. confusion and have unintended consequences (e.g., regarding vaccine confidence).

So, while we appreciate your work and interest at CDER on the COVID vaccine VAERS data, ~~for all of the above reasons,~~ in the above context, we have found ~~that examining the analyses you have been sending has largely reflected events otherwise under evaluation~~no indication for action based on your findings, which have been consuming a lot of resources at a time when resources are stretched across ~~a~~ preexisting robust pharmacovigilance ~~infrastructure~~activities. ~~We haven't seen a proportionate increase in efficiency or yield, given the robust screening and scrutiny of VAERS data already in place as described above. We'd hate for you to be wasting your time and efforts, so we thought we should suggest that it might be a better use of resources for you to refocus your data mining efforts on other product types. Perhaps there are CDER products and drug related data in your Center that could benefit more from your continued data mining explorations and analyses.~~ So, we are asking that you please hold on creating and sending data mining results for COVID-19 vaccine AE data. Thanks much for your time and ~~attention~~understanding, and~~;~~ sorry for the long email.

Kind regards,~~Thanks~~,

Craig Zinderman, MD, MPH
Associate Director for Medical Policy
Office of Biostatistics and Epidemiology
FDA/Center for Biologics Evaluation and Research
[redacted]

From: "Menschik, David" [redacted]
To: "Su, John (CDC)" [redacted], "Shimabukuro, Tom (CDC)" [redacted]
Cc: "Zinderman, Craig E" [redacted], "Nair, Narayan" [redacted], "Alimchandani, Meghna" [redacted], "Marquez, Paige L (CDC)" [redacted], "Broder, Karen R (CDC)" [redacted], "Harrington, Theresa (CDC)" [redacted]
Subject: RE: Weekly data mining
Date: Tue, 30 Mar 2021 11:02:25 +0000
Importance: Normal
Attachments: DE_VAERS_data_mining_methods_and_limitations_2021_03_DRAFT.pptx; USST_20210326.xls

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Hi John and Tom,

Attached please find a list of all (i.e., unvetted and regardless of notability) PTs with data mining alerts (i.e., EB05 ≥2) for all EUA SARS-CoV-2 vaccine VAERS reports from our 'US Signals Summary Table' ('as of date' 3/26/21) along with 3 slides providing contextual information including caveats and limitations. Please feel free to share this hypothesis generating output with your team/command chain, though this is not intended to be shared more broadly.

Thanks,
David

Data Mining Introduction*

- Statistical method for identifying disproportionality (excess of reported AE for product relative to other products) in large database
- Can be useful for screening and hypothesis generating only
  - Evaluate findings in clinical and epidemiological context (e.g., unexpected?)
  - Compelling hypotheses should be explored (e.g., via case series analyses)
  - Statistical signal of disproportionality ≠ safety signal
- Absence of disproportionality does not confirm absence of safety signal nor negate a signal otherwise detected

*Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff (November 2019; Draft). Available at https://www.fda.gov/media/130216/download

DE VAERS Data Mining Methods

- Empirica™ Signal software (Oracle)
- Calculates Empiric Bayes Geometric Mean (EBGM) using observed to expected (O/E) vaccine-PT pair ratios
  - EBGM derived from statistical model (Multi-item Gamma Poisson Shrinker; MGPS) that accounts for instability from small numbers*
    - adjusted by age, gender and year received
- Vaccine-PT pairs ranked by lower 5% bound of EBGM CI (EB05)
- Standard alert threshold: EB05 >2
- Weekly US summary table includes subset alerts for age (0-1, 2-8, 9-18, 19-44, 45-64, and ≥65 years), gender, and serious/fatal

*Szarfman A, Tonning JM, Doraiswamy PM. Pharmacovigilance in the 21st century: new systematic tools for an old problem. Pharmacotherapy. 2004 Sep;24(9):1099-104. doi: 10.1592/phco.24.13.1099.38090. PMID: 15460169.

Limitations of Data Mining Include:

- Impacted by stimulated reporting (e.g., V-safe, media reports)
- False alerts from statistical interaction (e.g., If vaccines X and Y often given concomitantly, statistical signal for vaccine X and AE Z may be driven by vaccine Y)
- MedDRA constraints (e.g., Signal X can be reflected in multiple PTs that individually do not reach alert threshold)
- Confounding (e.g., by indication)
- Other VAERS limitations (e.g., underreporting, variable reporting by source, incomplete reporting, duplicate reporting)

From: "Zinderman, Craig E" [redacted]
To: "Menschik, David" [redacted], "Nair, Narayan" [redacted]
Subject: RE: suggested edits as discussed...
Date: Fri, 7 May 2021 18:49:06 +0000
Importance: Normal
Attachments: Data_Mining_Note_to_CDER_2021_0507_dm_cz.docx

Narayan:
I drafted, and David edited, the attached message to Ana as discussed. Please feel free to edits as you see fit. It's pretty long so feel to shorten if you can see any opportunity for that.

I put it in Word for ease of tracked changes.

Thanks,
Craig

From: Menschik, David [redacted]
Sent: Friday, May 07, 2021 12:33 PM
To: Zinderman, Craig E [redacted]
Subject: suggested edits as discussed...

…attached…

Good AfternoonMorning Ana,

:

Thank you again for talking with us back in March about your work exploring new data mining approaches and discussing your interest in CBER's COVID-19 vaccine products. We are writing to kindly ask that you to please hold on stop creating and sending data mining reports and analyses using COVID-19 vaccine AE data.

In CBER OBE, we have been reviewing the various COVID-19 vaccine data mining results that you have been forwarding. While we appreciate your interest in sharing your results, they have not contributed to our alreadywe already have a robust process for continuous monitoring ofreviewing incoming and aggregated VAERS (and other vaccine safety) data. I will describe a little bit below:including:

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-Serious report screening: FDA MOs review sSerious reports coming into VAERS daily until meeting specified milestones (i.e., certain time since authorization and doses administered) and then ; for the first couple months with the mRNA vaccines, and still currently for JnJ, FDA MOs review each serious report as it is processed into VAERS. For the older mRNA vaccines, MOs now conduct weekly review of aggregated PT counts weekly, by seriousness, AESI, Lot number, most frequent PTs, weekly changes in PT rankings, and other metrics.

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Of note, data mining alerts, which are designed to generate hypotheses of possible safety issues, are no longer particularly useful for our pharmacovigilance purposes when a signal has already been identified, such as for TTS, or when an issue (e.g., an AESI such as AMI) is being worked up in a more robust (e.g., active surveillance) system.. Some alerts that you have sent, like for AMI, have already temporarily signaled in population-based surveillance, which has already triggered a more thorough review of VAERS data.

Also as you knowFurther, we have a standard process for data mining screening in place for VAERS data; this screening was in place at the start of, and throughout, the COVID vaccine campaign; the frequency/nature of the calculations, stratifications and other parameters, are known and understood by us and our stakeholders. We understand that exploring new approaches and varying the stratifications or other parameters might improve the methodology and is of interest to you. However, from our perspective, the approach employed during a period of intense, high profile surveillance should be standard, and predictable, and road-tested. Results from Aadjusting parameters thato raise or lower sensitivity of the alerts as the vaccination campaign is underway could lead to some artificial creation of alerts and an apparent, but not real, sudden change in safety results. confusion and have unintended consequences (e.g., regarding vaccine confidence).

So, while we appreciate your work and interest at CDER on the COVID vaccine VAERS data, ~~for all of the above reasons,~~ in the above context, we have found ~~that examining the analyses you have been sending has largely reflected events otherwise under evaluation~~no indication for action based on your findings, which have been consuming a lot of resources at a time when resources are stretched across ~~a~~ preexisting robust pharmacovigilance ~~infrastructure~~activities. ~~We haven't seen a proportionate increase in efficiency or yield, given the robust screening and scrutiny of VAERS data already in place as described above. We'd hate for you to be wasting your time and efforts, so we thought we should suggest that it might be a better use of resources for you to refocus your data mining efforts on other product types. Perhaps there are CDER products and drug related data in your Center that could benefit more from your continued data mining explorations and analyses.~~
Thanks much for your time and ~~attention~~understanding, and~~;~~ sorry for the long email.

Kind regards,~~Thanks~~,

Craig Zinderman, MD, MPH
Associate Director for Medical Policy
Office of Biostatistics and Epidemiology
FDA/Center for Biologics Evaluation and Research
[redacted]

Commented [ZCE1]: I would lean towards keeping this language, but happy to go with Narayan's thoughts.
Zinderman, Craig E
2021-05-07 14:42:00

From: "Zinderman, Craig E" [redacted]
To: "Menschik, David" [redacted], "Shimabukuro, Tom (CDC)" [redacted], "Su, John (CDC)" [redacted], "Moro, Pedro L (CDC)" [redacted]
Cc: "Nair, Narayan" [redacted], "Alimchandani, Meghna" [redacted], "Broder, Karen R (CDC)" [redacted], "Mcneil, Michael M (CDC)" [redacted], "Lale, Allison (CDC)" [redacted]
Subject: RE: Weekly data mining
Date: Tue, 12 Jul 2022 18:26:05 +0000
Importance: Normal
Attachments: USST_20220708.xls

Good Afternoon :

Attached please find a list of all (i.e., unvetted and regardless of notability) PTs with data mining alerts (i.e., EB05 ≥2) for all SARS-CoV-2 vaccine VAERS reports from our weekly 'US Signals Summary Table' ('as of date' 7/8/22). Please feel free to share this hypothesis generating output with your team/command chain, though this is not intended to be shared more broadly.

Thanks,
Craig

From: "Niu, Manette" [redacted]
To: "Nair, Narayan" [redacted], "Ahima, Ohenewaa" [redacted]
Subject: FW: Important analysis by DuMouchel -> Peculiarities of disproportionality statistics when the product of interest is in almost all of the reports
Date: Thu, 15 Apr 2021 13:36:47 +0000
Importance: Normal
Inline-Images: image001.png

---

fyi

From: Niu, Manette
Sent: Thursday, April 15, 2021 9:27 AM
To: Baer, Bethany [redacted]; Zinderman, Craig E [redacted] Menschik, David [redacted]
Subject: RE: Important analysis by DuMouchel -> Peculiarities of disproportionality statistics when the product of interest is in almost all of the reports

I'll forward you Ana's email with the attachment. The best person to ask would be Ana as she has close ties with Bill Dumouchel.
Thank you!
Manette

From: Baer, Bethany [redacted]
Sent: Thursday, April 15, 2021 9:00 AM
To: Zinderman, Craig E [redacted]; Menschik, David [redacted]
Cc: Niu, Manette [redacted]
Subject: RE: Important analysis by DuMouchel -> Peculiarities of disproportionality statistics when the product of interest is in almost all of the reports

Thanks for forwarding this on. I agree that we should consider different approaches as the underlying database is changing significantly due to the high volume of COVID vaccine reports. I think we should welcome any expert input. The spreadsheet that Bill mentioned in the first email is not attached so I can't look at it, but David and I have been discussing and are concerned about the effect of so many COVID reports on the standard system we use. Is there a way that Bill can be more involved in our data mining process and interpretation during this unprecedented reporting time?

Thanks,
Bethany

From: Zinderman, Craig E [redacted]
Sent: Wednesday, April 14, 2021 2:02 PM
To: Menschik, David [redacted] Baer, Bethany [redacted]
Cc: Niu, Manette [redacted]
Subject: FW: Important analysis by DuMouchel -> Peculiarities of disproportionality statistics when the product of interest is in almost all of the reports

David, Bethany:
Might be worth considering the below? I don't pretend to understand it, but sounds like they are suggesting an analysis not stratified by year. Thoughts?

Thanks,
Craig

From: Niu, Manette [redacted]
Sent: Wednesday, April 14, 2021 6:24 AM
To: Zinderman, Craig E [redacted]
Subject: FW: Important analysis by DuMouchel -> Peculiarities of disproportionality statistics when the product of interest is in almost all of the reports

fyi

From: Szarfman, Ana [redacted]
Sent: Tuesday, April 13, 2021 9:17 PM
To: Niu, Manette [redacted]
Cc: Stockbridge, Norman L [redacted]
Subject: RE: Important analysis by DuMouchel -> Peculiarities of disproportionality statistics when the product of interest is in almost all of the reports

Thanks Manette.

Exactly. As DuMouchel pinpointed, there is a need to extend the stratification brackets by the fact that 99% of the results for FY2021 are for COVID-19 vaccines this indeed affects the results.

From: Niu, Manette [redacted]
Sent: Monday, April 12, 2021 7:01 AM
To: Szarfman, Ana [redacted]
Subject: FW: Important analysis by DuMouchel -> Peculiarities of disproportionality statistics when the product of interest is in almost all of the reports

Ana,
Does this effect the data mining results we are receiving in 2021? As you know, there is a backlog in VAERS reports with the contractor due to the high volume of reports we are receiving for the COVID-19 vaccines and the prioritization of those vaccine reports.
Thank you!
Manette

From: Szarfman, Ana [redacted]
Sent: Saturday, April 10, 2021 1:22 PM
To: Niu, Manette [redacted]
Cc: Vega, Amarilys [redacted]; Stockbridge, Norman L [redacted]; Quinn, John [redacted]; bill.dumouchel [redacted] Rave Harpaz [redacted]; Pease-Fye, Meg [redacted] Weichold, Frank [redacted]; Callahan, Lawrence [redacted]; Paredes, Antonio [redacted]; Temple, Robert [redacted]; Blum, Michael [redacted]; Dal Pan, Gerald [redacted]; Zander, Judith [redacted]; Munoz, Monica [redacted] Diak, Ida-Lina [redacted]
Subject: Important analysis by DuMouchel -> Peculiarities of disproportionality statistics when the product of interest is in almost all of the reports

Hello all,

Please refer to the message from Bill DuMouchel that I am forwarding and to his attached spreadsheet.

Notice how Bill discovered the need to eliminate the stratification by year when the reports for the COVID-19 vaccine in VAERS are 99% of all reports for a year (2021).

I think that we need to invite him to talk with us about the effect of adjustment factors, given the data, so we can all learn from his knowledge.

Warmest regards to all,

--Ana

Ana Szarfman, MD, PhD, FAMIA,
Diplomate by the American Board of Pathology in both, Clinical Pathology (1984) and Clinical Informatics (2017), and Fellow of the American Medical Informatics Association (2020)
Medical Officer, Safety Data Mining Developer and Medical Informatics Analyst,
Celebrating nearly a quarter of a century of successful implementation of safety data mining, interactive patient profiles, and other automated analytical tools.
Division of Cardiology and Nephrology, OCHEN, Center for Drug Evaluation and Research, Food and Drug Administration
[redacted]

U.S. FOOD & DRUG ADMINISTRATION

From: Bill DuMouchel [redacted]
Sent: Saturday, April 10, 2021 2:25 AM
To: Rave Harpaz [redacted]; Steve Bright [redacted]; Rob Van Manen [redacted]
Cc: Szarfman, Ana [redacted]; Mohammad Al-Ansari [redacted]; Robert Weber [redacted] Bruce Palsulich [redacted]
Subject: [EXTERNAL] Peculiarities of disproportionality statistics when the product of interest is in almost all of the reports

The attached spreadsheet shows some COVID19 results for the three-year period 2019-2021
2019 has no COVID19 reports
2020 has a few
2021 consists of almost all (33929/34256 > 99%) COVID99 reports

Look at the values of A, B, C, D ... A+C is much greater than B+D in 2021.

The years 2020 and 2021 are shown as separate analyses. Note that RR as well as the Bayesian estimates are almost equal to 1.
They stay almost equal to one if the run is stratified by year, because the 2021 results dominate.
The next two sets of results show the full 3-year estimates with and without including year as one of the stratification covariates.
Only if you mix in more non-covid reports within each stratum can you get enough diversity to allow larger disproportionalities.

-Bill

From: "Lale, Allison (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Moro, Pedro (CDC/DDID/NCEZID/DHQP)" [redacted]
Cc: "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: RE: Weekly data mining
Date: Mon, 28 Nov 2022 23:09:10 +0000
Importance: Normal

Oh interesting. Thank you Pedro.

Like I said, we used to just verbally mention on CISA calls that X, Y, Z preferred term had not signaled in VAERS – but we also could leave it out if that this creates more hassle.

Thanks!
Allison

From: Moro, Pedro (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Saturday, November 26, 2022 7:49 PM
To: Lale, Allison (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: Weekly data mining

Hi Allison,

I think that because of the FOIAs we may have asked FDA to stop sending these weekly data mining outputs. I'll reach out to David Menschik and ask for the latest weekly report

Thanks

Pedro

From: Lale, Allison (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Saturday, November 26, 2022 6:28 PM
To: Moro, Pedro (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: FW: Weekly data mining

Hi Pedro,

I was just wondering if we still get these data-mining alerts from FDA? In the past, we have checked this list for our own verification before presenting a CISA consult.

For example, we have an upcoming case of Parsonage Turner syndrome (PT: Neuralgic Amytrophy) following COVID-19 vaccine. We performed a VAERS search with Elaine's help, but it could be nice to say this event has not preliminarily signaled in VAERS.

Thanks,
Allison

p.s. Hope you had a good holiday!

From: Menschik, David [redacted]
Sent: Tuesday, July 5, 2022 7:42 AM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]; Su, John (CDC/DDID/NCEZID/DHQP) [redacted]; Moro, Pedro (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Zinderman, Craig E (FDA/CBER) [redacted] Nair, Narayan (FDA/CBER) [redacted] Alimchandani, Meghna (FDA/CBER) [redacted] Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted]; McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted] Lale, Allison (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: Weekly data mining

Good morning all,

Attached please find a list of all (i.e., unvetted and regardless of notability) PTs with data mining alerts (i.e., EB05 ≥2) for all SARS-CoV-2 vaccine VAERS reports from our weekly 'US Signals Summary Table' ('as of date' 7/1/22). Please feel free to share this hypothesis generating output with your team/command chain, though this is not intended to be shared more broadly.

Thanks,
David

From: "Walsinsky, Sarah" [redacted]
To: "Edmonds, Amanda" [redacted], "Madni, Rubina" [redacted], "Osterman, Rachel" [redacted], "Marks, Peter" [redacted] "Hussain, Sana" [redacted], "Devore, Nicolette" [redacted], "Agnihothram, Sudhakar" [redacted], "Fink, Doran" [redacted], "Finn, Theresa" [redacted], "Farizo, Karen" [redacted]
Subject: Moderna adolescent declination
Date: Fri, 18 Feb 2022 22:14:49 +0000
Importance: Normal
Attachments: unnamed; 0191-cover.pdf; PONE-S-21-47379_(002).pdf; Response_to_Moderna.docx
Embedded: RE:_Moderna_adolescent_EUA_request_response; [EXTERNAL]_Clarification_request
Inline-Images: image00001.png; image00001(1).png; image00001(2).png; image00001(3).png

---

Walinsky, Sarah has shared a OneDrive for Business file with you. To view it, click the link below.

Response to Moderna.docx

Hopefully this works!

Discussing best way forward on the Moderna adolescent response letter.

Hi there,

Sarah.Walinsky [redacted] is inviting you to a scheduled ZoomGov meeting.

Join Zoom Meeting

One tap mobile: [redacted]

Meeting URL: [redacted]

Meeting ID: [redacted]
Passcode: [redacted]

Join by Telephone

For higher quality, dial a number based on your current location.
Dial: [redacted]

Meeting ID: [redacted]

Passcode: [redacted]

International numbers

Join from an H.323/SIP room system

H.323: 161.199.138.10 (US West)
161.199.136.10 (US East)

Meeting ID: [redacted]

Passcode: [redacted]

SIP: [redacted]

Passcode: [redacted]

From: "Edmonds, Amanda" [redacted]
To: "Walinsky, Sarah" [redacted], "Osterman, Rachel" [redacted], "Madni, Rubina" [redacted]
Cc: "Hussain, Sana" [redacted], "Devore, Nicolette" [redacted], "Agnihothram, Sudhakar" [redacted]
Subject: RE: Moderna adolescent EUA request response
Date: Fri, 18 Feb 2022 14:44:42 +0000
Importance: Normal
Inline-Images: image001.png

Sarah,

We recommend that this letter be redrafted so that it is more clear that FDA is applying the factors (or at least some of the factors) laid out in the guidance for when the Agency will exercise discretion to decline to issue an EUA for a product (or here, for an amendment to expand use of the product to a new population). The factors are laid out in section V of this guidance on EUAs for COVID vaccines, https://www.fda.gov/media/142749/download, and are also discussed at a high level in the overarching guidance on EUAs for medical products, https://www.fda.g.ov/media/97321/download. It seems the reasoning here is that there is not an emergency need for the Moderna vaccine for this pediatric population, especially given the data suggesting an increased myocarditis risk compared to the currently available vaccine for this population (Pfizer).

I don't think this was intentional at all, but as written, the current draft reads as if CBER is suggesting the company would be better off submitting a BLA supplement because CBER might not need to take a supplement to the VRBPAC, whereas this step would be needed for an EUA.

We haven't provided line edits because this would involve substantial redrafting.

Amanda

From: Walinsky, Sarah [redacted]
Sent: Thursday, February 17, 2022 12:22 PM
To: Edmonds, Amanda [redacted]; Osterman, Rachel [redacted]; Madni, Rubina [redacted]
Cc: Hussain, Sana [redacted]; Devore, Nicolette [redacted]; Agnihothram, Sudhakar [redacted]
Subject: Moderna adolescent EUA request response

Hi all,

Moderna is pushing for action on their adolescent EUA and we are hoping to respond with the attached letter pushing them towards a BLA submission instead of an EUA submission. Could you please review and provide us with edits/comments/thoughts? We are hoping to get this out before the long weekend, if possible.

Also – as a heads-up we are working on Covaxin/Ocugen decline to issue memo and letter and are hoping to get that to you soon for review and clearance before the long weekend as well.

Thanks,

Sarah

Sarah Walinsky, JD

Acting Chief of Staff

Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
[redacted]

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Stephen Hoge [redacted]
To: "Marks, Peter" [redacted], "Agnihothram, Sudhakar" [redacted]
Cc: Charbel Haber [redacted], Carla Vinals [redacted]
Subject: [EXTERNAL] Clarification request
Date: Wed, 9 Feb 2022 02:11:39 +0000
Importance: Normal
Inline-Images: image002.jpg

Dear Dr. Marks,

Moderna has appreciated the guidance and oversight we have had from the FDA throughout the pandemic. We have worked with the agency to follow the science where it leads us in the interests of both individual and public health. However, we disagree with FDA's decision on Friday evening not to reconsider authorization 100 mcg of mRNA-1273 in adolescents 12-17 in light of recent relevant data and long-awaited analysis clearly demonstrating that the benefits of mRNA-1273 far outweighs the risks, even in adolescents.

At this point, Moderna does not understand the scientific basis for the FDA's position. We request a meeting with the FDA to discuss the evidence FDA is relying on to support the agency's position that a 50 mcg primary series dose represents a more favorable benefit-risk profile than 100 mcg for adolescents, and also align on a path forward regarding the adolescent and pediatric indications.

Our current understanding of the facts are thus:

1. A quantitative benefit-risk comparison of Moderna and Pfizer by the CDC working group (presented to ACIP last Friday) has concluded that per 1 million second doses in 18-39 yo males, mRNA-1273 (vs. BNT162b2) will result in 104 fewer hospitalizations for COVID-19, and 21 incremental cases of myocarditis. For both genders combined, the comparison mRNA-1273 (vs. BNT162b2) would result in 162 fewer hospitalizations for COVID-19 and 9 incremental cases of myocarditis per million second doses (see figure below). The net incremental benefit-risk ratio between the two vaccines is 18 COVID-19 hospitalizations prevented for everyone 1 case of myocarditis in 18-39 year-olds. The risk and benefit are consistent with multiple prior reports, including peer-reviewed articles from other agencies (US VAMC NEJM, UK Nature Medicine).

2. On February 4th, CDC ACIP also reviewed analyses (VSD, MOVING) on the clinical course of cases of myocarditis, which were generally noted to be mild and recover rapidly. The VSD summary concluded "*Among 18 to 39 year-olds there were no noticeable clinical differences between cases after Moderna and those after Pfizer*". Moderna is not aware of any data or reports that concludes differently.

3. The CDC working group concluded that: "*Benefits for both mRNA COVID-19 vaccines far outweigh risk of myocarditis*". The ACIP unanimously endorsed mRNA-1273 for adults 18+.

4. FDA scientists recently submitted the updated BEST analysis for peer reviewed publication. The conclusion of the FDA analysis is: "*An increased risk of myocarditis/pericarditis was observed following COVID-19 mRNA vaccination, being highest in males aged 18–25 years following second dose. These results do not indicate a risk difference between mRNA-1273 and BNT162b2*." The BEST analysis reported a non-significant trend towards higher rates in 18-25 yo males for mRNA-1273 that was consistent with the numbers used in the CDC's favorable benefit-risk assessment.

5. FDA had previously indicated to Moderna that the rates of myocarditis reported in younger adults in other geographies (Scandinavia, Canada, France) were the basis of waiting for additional data to accrue in the more relevant US population. Of note, no regulatory action has been taken outside of the US as a consequence of these international observational studies. The recently completed VSD and BEST analyses cited above now include populations that are collectively larger than the previously cited international analyses, in the relevant US population, and following a more relevant dosing schema (i.e., homologous vaccination with 4-week interval for mRNA-1273). Moderna believes these larger, methodologically more relevant, US-based populations should be preferably weighed.

The findings summarized above have been repeatedly validated by international agencies or in published peer-reviewed articles. Moderna believe the conclusions are approaching broad scientific consensus.

Using a 50 mcg dose in the primary series introduces uncertainty concerning the magnitude and durability of the strong efficacy of the vaccine as demonstrated with 100 mcg, while at the same time we question the presumption that the 50 mcg dose will reduce the rate of myocarditis. Moderna is not aware of any data that suggest a lower (50 mcg) dose will provide a more optimal benefit-risk profile. Based on the CDC analysis, assuming the effectiveness and myocarditis rates of a 50 mcg dose of mRNA-1273 were to approach levels comparable to BNT162b2, then lowering the dose will result in 153 more preventable hospitalizations per million doses (162 hospitalizations for COVID-19 less 9 incremental cases of myocarditis). In the current public health emergency the FDA has seen fit to authorize multiple drugs, vaccines and diagnostics for the same indication as long as the known and potential benefits outweighs the known and potential risks, without regard to each product's *relative* efficacy or safety to other products. We believe the incremental difference between BNT162b2 and mRNA-1273 in a rare AE without significant sequalae, such as myocarditis, or the

incremental superiority of efficacy of mRNA-1273 over BNT162b2 in prevention of hospitalization, do not materially alter the overwhelmingly positive benefit/risk balance of both vaccines.

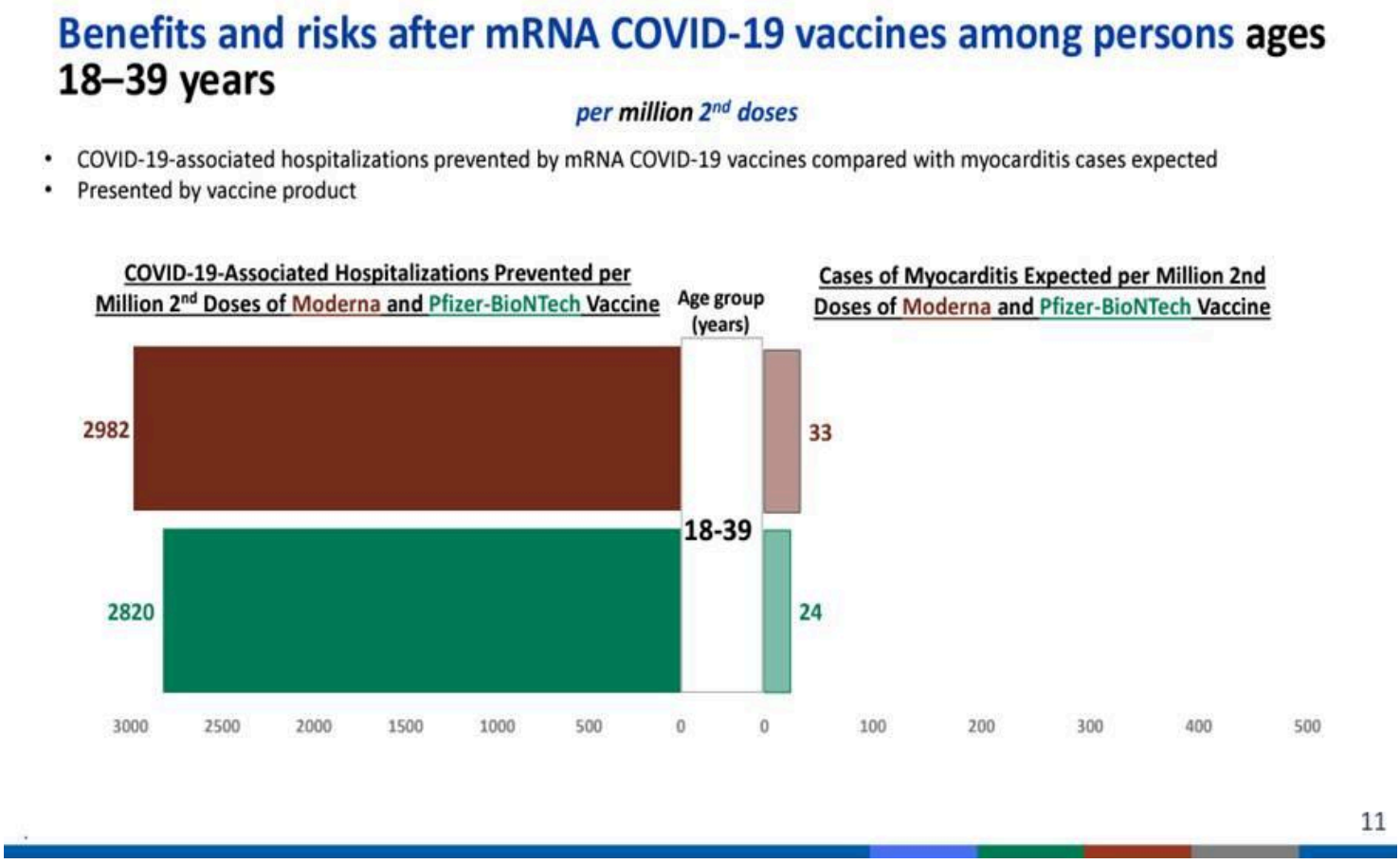
Given this scientific consensus regarding the positive benefit-risk profile, Moderna is concerned that FDA's decision not to consider authorization of mRNA-1273 for adolescents is inconsistent with its previous actions to authorize alternative products to address the same indications. We do not understand the scientific basis for this decision, with unclear implications, if any, for BLS's for the pediatric indication which we intend to file. We respectfully request a meeting with the FDA to understand what evidence the FDA is relying upon to supports its determination that (1) the known and potential benefits for vaccination with mRNA-1273 at 100 mcg do not exceed the known and potential risks for adolescents (age 12-17), and (2) a lower dose of mRNA vaccine represents a more favorable benefit-risk profile for adolescents. We believe a better understanding of the agency's position is required if Moderna is to respond correctly.

Moderna believes this discussion is urgent as there are currently over 11 million unvaccinated adolescents in the US. In addition, should SARS-CoV-2 evolve to require boosting, a highly effective and durable vaccine may be needed for adolescents, particularly those at higher risk. We will make ourselves available at any time that is convenient for the FDA.

Very respectfully,

Stephen Hoge, M.D.
President
Moderna, Inc.

Slide 11. Oliver, Summary of Working Group Interpretations. CDC ACIP, February 4th, 2022



Event: Moderna adolescent declination

Start Date: 2022-02-22 19:30:00 +0000

End Date: 2022-02-22 20:00:00 +0000

Organizer: Walinsky, Sarah [redacted]

Location: https://fda.zoomgov.com/j/1616041093?pwd=bzd4c1dub3ppNFQxTko0ZXpJdEJzUT09

Class: X-PERSONAL

Date Created: 2022-07-02 00:27:23 +0000

Date Modified: 2024-09-05 09:58:46 +0000

Priority: 5

DTSTAMP: 2022-02-18 22:14:26 +0000

Attendee: Edmonds, Amanda [redacted]; Madni, Rubina [redacted]; Osterman, Rachel [redacted]; Marks, Peter [redacted]; Hussain, Sana [redacted]; Devore, Nicolette [redacted]; Agnihothram, Sudhakar [redacted]; Fink, Doran [redacted]; Finn, Theresa [redacted]; Farizo, Karen [redacted]

Alarm: Display the following message 15m before start

> Reminder

Walinsky, Sarah has shared a OneDrive for Business file with you. To view it, click the link below.

Response to Moderna.docx

ic

on

Hopefully this works!

Discussing best way forward on the Moderna adolescent response letter.

Hi there,

Sarah.Walinsky [redacted] is inviting you to a scheduled ZoomGov meeting.

Join Zoom Meeting

One tap mobile: [redacted]

Meeting URL: [redacted]

Meeting ID: [redacted]
Passcode: [redacted]

Join by Telephone

For higher quality, dial a number based on your current location.
Dial: [redacted]

Meeting ID: [redacted]

Passcode: [redacted]

International numbers

Join from an H.323/SIP room system

H.323: 161.199.138.10 (US West)
161.199.136.10 (US East)

Meeting ID: [redacted]

Passcode: [redacted]

SIP: [redacted]

Passcode: [redacted]

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200 Technology Square • Cambridge, MA 02139
phone [redacted] • fax [redacted]

EUA Number 27073
Sequence No. 0191

June 9, 2021

Marion Gruber, PhD
Director, Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
[redacted]
Silver Spring, MD 20993-0002

Submission Type: Emergency Use Authorization (EUA) - Moderna COVID-19 VACCINE Adolescent (Aged 12 through <18 years old)

Dear Dr. Gruber:

Reference is made to pre-assigned submission tracking number (STN) EUA 27073 for the initial Emergency Use Authorization (EUA) for Moderna COVID-19 Vaccine (mRNA-1273, a novel lipid nanoparticle (LNP)-encapsulated messenger RNA (mRNA)-based vaccine against the 2019 novel coronavirus (CoV; SARS-CoV-2)).

Further reference is made to IND 019745, submitted to FDA on 27Apr 2021, and EUA 27073 authorized on 18Dec2020 for Emergency Use for Moderna COVID-19 Vaccine under Sections 564, 564A, and 564B of the Federal Food, Drug, and Cosmetic Act as amended or added by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 in Adults, aged 18 years and older.

The purpose of this submission is to submit an EUA Amendment to the authorized indication of the Moderna COVID-19 Vaccine to extend the indication to adolescents aged 12 through <18 years old.

The content of the submission package is described in Table 1.

Table 1 – Contents of Submission

Module	Document
1.1	Form 1571
1.2	Cover Letter
	Note to Reviewer
1.3.4	Financial Certification and Disclosure
1.4.4	Letter of Cross Reference

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200 Technology Square • Cambridge, MA 02139
phone [redacted] • fax [redacted]

1.14.1.3	Draft Fact Sheet
1.6	Meeting Materials
1.16	RMP
1.19	EUA submission document
5.3.1.4	Validation Assay Reports
5.3.5.1	mRNA-1273-p203: TFLs, CBER Tables, Narratives, CRFs, SAP and Datasets
5.3.5.1	mRNA-1273-p301: TFLs, CBER Tables, Narratives, CIOMS and Datasets
5.4	Literature references

If FDA has any questions, please do not hesitate to contact me directly at [redacted] or at [redacted].

This eCTD submission has been prepared by PPD Development, Inc. in full compliance with ICH and FDA guidance. The eCTD has been verified and confirmed to be virus and spyware free. PPD utilizes [redacted]. All technical questions should be directed to Mr. Eric Malamutt at PPD [redacted] or email at [redacted]

Sincerely,

Carlota Vinals
Digitally signed by Carlota Vinals
Date: 2021.06.09 08:15:41 -04'00'

Carla Vinals, Ph.D.
VP, Regulatory Affairs – Infectious Disease
ModernaTX, Inc.
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

PLOS ONE

Signaling COVID-19 Vaccine Adverse Events

--Manuscript Draft--

Manuscript Number:	
Article Type:	Research Article
Full Title:	Signaling COVID-19 Vaccine Adverse Events
Short Title:	Signaling COVID-19 Vaccine Adverse Events
Corresponding Author:	Rave Harpaz, Ph.D. Oracle Corp UNITED STATES
Keywords:	Covid-19; Adverse Events; Signal Detection
Abstract:	Statistical signal detection is a crucial tool for rapidly identifying potential risks associated with pharmaceutical products. The unprecedented environment created by the COVID-19 pandemic for vaccine surveillance predisposes signal detection to missed or delayed signals, which may limit our understanding of the risks associated with these vaccines. Based on data underlying the Vaccine Adverse Event Reporting System, we assess the current state and utility of signal detection for COVID-19 vaccine surveillance. To this end, we investigate the temporal evolution of signals corresponding to six largely recognized adverse events, and a newly discovered emerging adverse event. The results demonstrate that signals of adverse events related to COVID-19 vaccines may indeed be missed or delayed when generated by methodologies currently utilized by pharmacovigilance organizations . The results also suggest that a possible source of these missed signals is the notorious masking effect, and that properly identifying and addressing this effect exposes strong statistical associations that would otherwise be deemed uninteresting. Finally, the results demonstrate that a class of advanced methodologies can partially alleviate the problem of missed signals.
Order of Authors:	Rave Harpaz, Ph.D.
	William DuMouchel William
	Robbert Van Manen
	Alexander Nip
	Steve Bright
	Ana Szarfman
	Joseph Tonning
	Magnus Lerch
Opposed Reviewers:	
Additional Information:	
Question	**Response**
Financial Disclosure Enter a financial disclosure statement that describes the sources of funding for the work included in this submission. Review the submission guidelines for detailed requirements. View published research articles from *PLOS ONE* for specific examples.	The author(s) received no specific funding for this work

This statement is required for submission and **will appear in the published article** if the submission is accepted. Please make sure it is accurate. **Unfunded studies** Enter: *The author(s) received no specific funding for this work.* **Funded studies** Enter a statement with the following details: • Initials of the authors who received each award • Grant numbers awarded to each author • The full name of each funder • URL of each funder website • Did the sponsors or funders play any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript? • **NO** - Include this sentence at the end of your statement: *The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.* • **YES** - Specify the role(s) played. * typeset	
Competing Interests Use the instructions below to enter a competing interest statement for this submission. On behalf of all authors, disclose any competing interests that could be perceived to bias this work—acknowledging all financial support and any other relevant financial or non-financial competing interests. This statement is required for submission and **will appear in the published article** if the submission is accepted. Please make sure it is accurate and that any funding sources listed in your Funding Information later in the submission form are also declared in your Financial Disclosure statement. View published research articles from *PLOS ONE* for specific examples.	The authors have declared that no competing interests exist

NO authors have competing interests Enter: *The authors have declared that no competing interests exist.* Authors with competing interests Enter competing interest details beginning with this statement: *I have read the journal's policy and the authors of this manuscript have the following competing interests: [insert competing interests here]* * typeset	
Ethics Statement Enter an ethics statement for this submission. This statement is required if the study involved: • Human participants • Human specimens or tissue • Vertebrate animals or cephalopods • Vertebrate embryos or tissues • Field research Write "N/A" if the submission does not require an ethics statement. General guidance is provided below. Consult the submission guidelines for detailed instructions. **Make sure that all information entered here is included in the Methods section of the manuscript.**	analysis of public data from the U.S. Vaccine Adverse Event Reporting System

Format for specific study types **Human Subject Research (involving human participants and/or tissue)** • Give the name of the institutional review board or ethics committee that approved the study • Include the approval number and/or a statement indicating approval of this research • Indicate the form of consent obtained (written/oral) or the reason that consent was not obtained (e.g. the data were analyzed anonymously) **Animal Research (involving vertebrate animals, embryos or tissues)** • Provide the name of the Institutional Animal Care and Use Committee (IACUC) or other relevant ethics board that reviewed the study protocol, and indicate whether they approved this research or granted a formal waiver of ethical approval • Include an approval number if one was obtained • If the study involved *non-human primates*, add *additional details* about animal welfare and steps taken to ameliorate suffering • If anesthesia, euthanasia, or any kind of animal sacrifice is part of the study, include briefly which substances and/or methods were applied **Field Research** Include the following details if this study involves the collection of plant, animal, or other materials from a natural setting: • Field permit number • Name of the institution or relevant body that granted permission	
Data Availability Authors are required to make all data underlying the findings described fully available, without restriction, and from the time of publication. PLOS allows rare exceptions to address legal and ethical concerns. See the PLOS Data Policy and FAQ for detailed information.	Yes - all data are fully available without restriction

A Data Availability Statement describing where the data can be found is required at submission. Your answers to this question constitute the Data Availability Statement and **will be published in the article**, if accepted. **Important:** Stating 'data available on request from the author' is not sufficient. If your data are only available upon request, select 'No' for the first question and explain your exceptional situation in the text box. Do the authors confirm that all data underlying the findings described in their manuscript are fully available without restriction?	
Describe where the data may be found in full sentences. If you are copying our sample text, replace any instances of XXX with the appropriate details. • If the data are **held or will be held in a public repository**, include URLs, accession numbers or DOIs. If this information will only be available after acceptance, indicate this by ticking the box below. For example: *All XXX files are available from the XXX database (accession number(s) XXX, XXX.*). • If the data are all contained **within the manuscript and/or Supporting Information files**, enter the following: *All relevant data are within the manuscript and its Supporting Information files.* • If neither of these applies but you are able to provide **details of access elsewhere**, with or without limitations, please do so. For example: *Data cannot be shared publicly because of [XXX]. Data are available from the XXX Institutional Data Access / Ethics Committee (contact via XXX) for researchers who meet the criteria for access to confidential data.* *The data underlying the results presented in the study are available from (include the name of the third party*	research based on public data from the U.S. Vaccine Adverse Event Reporting System and calculated values supplementary materials

and contact information or URL). • This text is appropriate if the data are owned by a third party and authors do not have permission to share the data. * typeset	
Additional data availability information:	

Dear Editor,

We are pleased to submit a manuscript entitled, “Signaling COVID-19 Vaccine Adverse Events” for consideration by PLOS ONE as a Research Article.

As the world contends with ending the COVID-19 pandemic, understanding the risks associated with COVID-19 vaccines is critically urgent, and signal detection is a crucial tool for rapidly identifying such risks. Unfortunately, the unprecedented environment created by the COVID-19 pandemic predisposes traditional signal detection to missed or delayed signals, which can limit our understanding of the risks associated with COVID-19 vaccines and the timeliness of their identification.

This manuscript investigates the current state and utility of signal detection for COVID-19 vaccines. We investigate the temporal evolution of signals corresponding to seven distinct and partially recognized adverse events with various degrees of evidence linking them to the vaccines. This temporal evaluation led to several findings, which we believe will be of interest to the readers of PLOS ONE and of importance to drug safety organizations. Notably, we demonstrate that signals of adverse events related to COVID-19 vaccines can be missed or delayed when generated by methodologies currently utilized by drug safety organizations. We identify some of the causes for this problem and propose a solution to partially alleviate the problem.

Our manuscript does not assume readers’ familiarity with drug safety surveillance or signal detection. It introduces the topic of vaccine surveillance and signal detection, and provides the statistical concepts needed to understand one of the sources of missed signals and our proposed remediation.

We confirm that this work is original and has not been published elsewhere nor is it currently under consideration for publication elsewhere.

Thank you for your consideration.

Sincerely,

Rave Harpaz
Senior Director
Oracle Health Science

Signaling COVID-19 Vaccine Adverse Events

Rave Harpaz[1], William DuMouchel[1], Robbert Van Manen[1], Alexander Nip[1], Steve Bright[1], Ana Szarfman[2], Joseph Tonning[3], Magnus Lerch[1,4]*

[1] Oracle Health Sciences, Burlington, MA, United States

[2] U.S. FDA, Silver Spring, MD, United States

[3] U.S. Public Health Service/U.S. FDA retired

[4] Lenolution GmbH, Berlin, Germany

[*] Corresponding author

E-mail: [redacted]

Abstract

Statistical signal detection is a crucial tool for rapidly identifying potential risks associated with pharmaceutical products. The unprecedented environment created by the COVID-19 pandemic for vaccine surveillance predisposes signal detection to missed or delayed signals, which may limit our understanding of the risks associated with these vaccines. Based on data underlying the Vaccine Adverse Event Reporting System, we assess the current state and utility of signal detection for COVID-19 vaccine surveillance. To this end, we investigate the temporal evolution of signals corresponding to six largely recognized adverse events, and a newly discovered emerging adverse event. The results demonstrate that signals of adverse events related to COVID-19 vaccines may indeed be missed or delayed when generated by methodologies currently utilized by pharmacovigilance organizations. The results also suggest that a possible source of these missed signals is the notorious masking effect, and that properly identifying and addressing this effect exposes strong statistical associations that would otherwise be deemed uninteresting. Finally, the results demonstrate that a class of advanced methodologies can partially alleviate the problem of missed signals.

1. Introduction

As the world contends with ending the COVID-19 pandemic, understanding the risks associated with COVID-19 vaccines is critically urgent. The Vaccine Adverse Event Reporting System (VAERS), co-administered by the U.S. Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC), is one of several systems used to monitor adverse events (AEs) that occur after vaccination, including the COVID-19 vaccines. Like other safety surveillance

systems, VAERS offers the opportunity to rapidly identify potential risks associated with vaccines–a process usually known as signal detection.

Computational methodologies for signal detection have been routinely applied to safety surveillance systems for over 20 years and have become a de facto standard[1]. These methodologies are designed to compute surrogate measures of statistical association between specific pharmaceutical products and AEs that are reported into safety surveillance systems[2]. The measures are typically interpreted as signal scores, with larger values representing stronger statistical associations that are assumed more likely to represent true causal associations. A signal score threshold is often used to screen associations that warrant further attention.

Signal detection methodologies currently deployed by safety surveillance organizations are largely based on disproportionality statistics. These methodologies use frequency analysis of 2x2 contingency tables to quantify the degree to which a product-AE combination co-occurs disproportionately as compared with that expected if there were no statistical association. To illustrate, we use the Relative Reporting Ratio (RRR), which is a disproportionality statistic underlying several signal detection methodologies. The relative reporting ratio is defined as the ratio of the number of reports mentioning a specific (target) product-event combination to an expected number of reports for the same combination under the assumption that the product and AE occur independently. Based on the values displayed in Table 1, the relative reporting ratio is formally given by

$$RRR = \frac{(a+b+c+d)\cdot a}{(a+b)\cdot(a+c)} \quad (1)$$

and a number of enhancements, such as Bayesian smoothing and stratification, lead to several signal detection methodologies currently utilized by safety surveillance organizations[2].

Table 1. 2x2 contingency table used to compute disproportionality statistics for signal detection

	reports with target AE	reports without target AE	
reports with target product	a	b	a+b
reports without target product	c	d	
	a+c		a+b+c+d

Given its impact on public health, signal detection is still an active area of research and, since its inception, multiple guidances[3-6] have been published with practice recommendations as well as admonitions concerning data and methodological limitations.

Missed/delayed signals and false alerts are the two primary concerns with signal detection, and two objective measures with which the reliability of signal detection can be evaluated. Missed or delayed signals are especially disconcerting given their direct impact on public health, and in the context of the current pandemic can limit our understanding of the risks associated with COVID-19 vaccines and the timeliness of their identification.

Missed signals can stem from several sources. Incomplete data and the voluntary nature of reporting to surveillance systems are the primary sources of missed signals. However, missed signals can also stem from methodological limitations, and in particular a widely acknowledged problem called 'masking'[4, 7, 8].

Masking and, similarly, confounding are artifacts of conventional disproportionality statistics used for signal detection that rely on the analysis of 2x2 contingency tables as illustrated above. By virtue of being two-dimensional, other factors that may confound, mask, or more generally bias the relationships between products and AEs cannot be properly accounted for.

A masked relationship between a target product and target AE can emerge when one or multiple products are frequently reported with the target event while making the background rate for the target event considerably large. This larger background rate can then make the relationship between the target product and the target event appear less unusual, hence masking the true relationship. A possible solution to masking, albeit practically infeasible, is to first identify the 'offending' products and then remove cases/reports containing those products from the calculation of disproportionality statistics.

To illustrate, consider the values displayed in Tables 2-3, which build on the example provided in Table 1 and eq. 1. Tables 2-3 display values used for disproportionality analysis of 2x2 contingency tables capturing a hypothetical target AE and a hypothetical target product labeled 'A'. Table 2 introduces a product labeled 'B', which serves as the 'offending' product that masks the true relationship between the target product 'A' and the target AE. Table 2 shows that most of the reports (80/93) mentioning the target AE are associated with product 'B', which leads to masking. Applying the relative reporting ratio (eq. 1) yields a masked $RRR = (393 \times 3)/(93 \times 13) = 0.98$ indicating that there is no statistical association. However, removing the reports that mention product 'B', yields the counts displayed in Table 3, and an unmasked $RRR = (233 \times 3)/(13 \times 13) = 4.14$ that indicates a strong statistical association between the target AE and target product 'A'.

Table 2. contingency table used to compute disproportionality statistics with the inclusion of product 'B' that masks the association of product 'A' with the target AE

	reports w target AE	reports without target AE	
reports with target product A	3	10	13
reports with product B	80	80	160
reports without product A or B	10	210	220
	93	300	393

Table 3. contingency table used to compute disproportionality statistics with the exclusion of product 'B' that would mask the association of product 'A' with the target AE

	reports with target AE	reports without target AE	
reports with target product A	3	10	13
reports without product A	10	210	220
	13	220	233

Conditions that make signal detection especially vulnerable to masking effects include: smaller safety databases such as VAERS, relationships involving rare events, and relationships involving newer products. As such, the novelty of COVID-19 vaccines, coupled with ongoing vaccination programs, and the relatively early stages of COVID-19 vaccine surveillance makes signal detection especially susceptible to masking.

The aim of this manuscript is to assess the current state and utility of signal detection for COVID-19 vaccines with emphasis on the issue of missed or delayed signals and the potential of masking effects. To this end, we investigate the evolution of signals corresponding to seven distinct AEs with various degrees of evidence linking them to the vaccines. Six of these seven AEs are part of a list of adverse events deemed to be of special interest for COVID-19 vaccine surveillance by the CDC, FDA, and other health organizations[9-11], and the other is an emerging AE that is yet to be fully recognized but which has accumulated thousands of reports in VAERS and elsewhere. In

addition, we center the evaluation on the messenger RNA (mRNA) vaccines from Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273), which account for the vast majority of COVID-19 vaccine reports in VAERS.

2. Materials and Methods

2.1 Data

The investigation was performed using all VAERS reports available at the time of writing this manuscript (1990 to October 01, 2021). This data represents a total of 1,599,958 reports, including 39 weeks of COVID-19 vaccine reports, which are publicly released on a bi-weekly cadence from January 01, 2021 to October 01, 2021. Of those, 778,681 reports include the COVID-19 vaccine from three manufacturers: Pfizer-BioNTech (53%), Moderna (39%), and Janssen (8%). The investigation was based on AEs in VAERS coded at the MedDRA Preferred Term (PT) level, and products at the 'manufacturer' level, e.g., 'COVID19_PFIZER/BIONTECH'.

2.2 Adverse Events of Interest (AEOI)

The seven AEs investigated in this manuscript and their associated MedDRA PTs are listed below. The MedDRA PTs associated with each of the seven AEs were used to identify VAERS reports mentioning a given AE:

1. ***Bell's palsy*** (PT='Facial paralysis' or 'Bell's palsy')
2. ***Herpes zoster*** (PT='Herpes zoster')
3. ***Myocarditis*** (PT='Myocarditis')

4. ***Pericarditis*** (PT='Pericarditis')
5. ***Appendicitis*** (PT='Appendicitis' or 'Appendicitis perforated' or 'Complicated appendicitis')
6. ***Pulmonary embolism*** (PT='Pulmonary embolism')
7. ***Tinnitus*** (PT='Tinnitus')

As noted in the Introduction, the first six of these AEs are part of a list of adverse events deemed to be of special interest for COVID-19 vaccine surveillance by the CDC, FDA, and other health organizations[9-11]. The last (tinnitus), is an emerging AE that is yet to be fully recognized and characterized.

2.3 Signal Detection Methodologies

We evaluated disproportionality statistics produced by four signal detection methodologies. Three of these methodologies – MGPS[12], BCPNN[13], and PRR[14] – are well-established and are currently deployed by various organizations worldwide for routine safety surveillance. However, these three methodologies belong to the class of bi-variate signal detection methodologies, and as such were not designed to control masking and certain confounding effects. The fourth methodology, called Regression-Adjusted GPS (RGPS)[15], is a multi-variate signal detection methodology powered by regression that is designed to produce disproportionality statistics with adjusted background rates that can control masking and more extensive confounding effects. It operates by fitting separate Bayesian logistic regression models to each target AE and by automatically selecting predictors (e.g., vaccines) to be included in each

regression model. Additional details on the RGPS methodology are provided in the Supporting Information (S1), and complete details of the RGPS methodology in reference[15].

Stratification categories used for RGPS, MGPS, and BCPNN were age and gender. Stratification by 'report year' was not applied because the vast majority of COVID-19 VAERS reports represent a single year of reporting (2021). We applied the canonical version of PRR, which does not require stratification. For RGPS and MGPS, we generated both the point estimates, labeled ERAM and EBGM respectively, and their associated credible intervals labeled ER05-ER95 and EB05-EB95 respectively. Unless specified otherwise, signal scores are represented by the point estimates. The generation of signal scores for the three methodologies and analysis thereof was done using Oracle Empirica Signal 9.1[16].

2.4 Capturing the Evolution of Signals

The evolution of signal scores for each AE was captured by a time series of signal statistics. The time series starts from a period at which initial reports for an AE were available to the latest batch of reports available at the time of writing this manuscript. Each time point corresponds to a bi-weekly public release of VAERS reports, starting from week 3 (W3) January 22, 2021 and ending in week 39 (W39) October 01, 2021, for a total of 19 time points. The signal statistics computed for each time point include the signal score point estimate and its credible interval, e.g., *ER05-ERAM-ER95* for RGPS and *EB05-EBGM-EB95* for MGPS. These were computed based on all data available in VAERS, and not only the COVID 19 reports or data within the range of dates underlying the time series.

2.5 Analysis & Evaluation

The comparison of signal detection methodologies for the time series centers on the RGPS and MGPS methodologies. These were chosen as representatives of the two classes of methodologies described in the Introduction and above (bi-variate vs. multi-variate signaling methodologies). The IC statistic[13] computed by the BCPNN methodology produces signal scores that are almost identical to those produced by MGPS and therefore redundant in many parts of our evaluation. The PRR signal statistic in its canonical application does not include smoothing or signal score adjustments for small counts as do the other methodologies, and therefore does not protect against false alarms as well as the other methodologies. For this reason, a direct comparison against PRR (in its canonical form) would not have allowed us to isolate and explain sources of missed signals. Nonetheless, our results include notes on both the PRR and IC signal statistics.

We used the following concepts/conditions to describe our findings in the Results section:

(1) The ***signaling threshold*** used to evaluate signals is defined as the value 1.0, i.e., the boundary of no statistical association.

(2) For a given AE and methodology, a ***signal is present/detected*** if a positive statistical association for the AE is detected. This in turn occurs when the signal score produced by the methodology for the AE exceeds the signaling threshold, more specifically, if the lower limit of the signal score's credible interval exceeds the signaling threshold defined in (1). For example, ER05 > 1.0 for RGPS and EB05 > 1.0 for MGPS.

(3) For a given AE and methodology, a **signal is *not present/detected*** if the signal score's credible interval contains or falls below the signaling threshold, e.g., ER05 < 1.0 for RGPS and EB05 < 1.0 for MGPS.

(4) For a given association, a ***signal score difference*** between two methodologies is ***statistically significant*** if their credible intervals do not overlap. Likewise, we say that there is ***no difference*** in signal scores between two methodologies if their credible intervals overlap, e.g., ER05 < EB95 < ER95.

(5) A **candidate association for *masking*** is defined as one whose signal statistics satisfy the following condition:

$$ER05 > EB95 \text{ and } ER05 > 1 \text{ and } EB05 \leq 1$$

That is, an association where RGPS and MGPS disagree by producing signal scores that are statistically significant (non-overlapping credible intervals, *ER05 > EB95*) with RGPS's interval above the signaling threshold (*ER05 > 1*) and that of MGPS below or including the threshold (*EB05 ≤ 1*).

(6) The ***masking effect size*** is defined as the ratio of RGPS's and MGPS's signal scores, i.e.,

$$\frac{ERAM}{EBGM} - 1$$

In the following, the masking effect size will be averaged across the time series to produce a summary statistic and represented as a percentage.

Having generated the time series of signal scores for each AE of interest, we investigate and attempt to validate masking sources based on the following:

(1) We select two time periods: an earlier point in the evolution of signals when masking starts to take effect, and the end period (W39). Doing so allows us to examine the origin of the masking sources and whether the sources change over time. The earlier time point corresponds to the earliest point in the time series (for both the Pfizer-BioNTech and Moderna vaccines) for which the RGPS and MGPS signals scores were significantly different, and RGPS's signal score exceeded the signaling threshold as defined above.

(2) For each time point we evaluate the predictors that are automatically selected by RGPS to be included in the regression model for the target AE. Based on the regression coefficients, we then identify the strongest predictors (vaccines) as potential sources of masking.

(3) As mentioned in the Introduction, once masking sources have been identified, the conventional approach to control masking is to remove all reports containing the maskers, and re-compute signal scores. We use this conventional approach to confirm our findings. That is, we remove reports containing the potential maskers (vaccines) identified by RGPS and re-compute signal scores for the bi-variate signaling methodologies (MGPS, PRR, BCPNN). Substantial increases in these signal scores as well as their convergence toward the original RGPS signal score is a strong indication that the sources of masking have been correctly identified, and a likely explanation for missed or delayed signals.

3. Results

Figures 1 and 2 depict our findings for each of the seven AEs investigated in this manuscript. The figures display the evolution of signal scores for each AE–captured as a time series of signal scores. As described in the Materials and Methods (Section 2.4), the time series ranges from week 3 (W3) to week 39 (W39) of COVID-19 reports, for a total of 19 time points in two-week intervals corresponding to the bi-weekly public release of VAERS reports.

Figure 1. The evolution of signal scores for Bell's palsy, Herpes zoster, Myocarditis, and Pericarditis

Figure 2. The evolution of signal scores for Appendicitis, Pulmonary embolism, and Tinnitus

Rows in the figures correspond to AEs, and columns to vaccines (Pfizer/BioNTech vs Moderna). Figure 1 covers the AEs: Bell's palsy, Herpes zoster, Myocarditis, and Pericarditis, whereas Figure 2 the AEs: Appendicitis, Pulmonary embolism, and Tinnitus. Each figure displays a time series of signal scores for the RGPS and MGPS methodologies. Each point corresponds to the signal score point estimate and its credible interval (shaded region), i.e., *ER05-ERAM-ER95* for RGPS and *EB05-EBGM-EB95* for MGPS. Supporting information (S2) provides signal statistics, for all combinations of AE/vaccine/signaling methodology.

The figures clearly show several trends:

(1) The time series curves of signal scores produced by RGPS are always above those of MGPS, i.e., the RGPS signal scores are always larger than those of MGPS. This is not an expected pattern and is indicative of masking effects for the AEs of interest. This also suggests that the RGPS

methodology would have been able to detect signals missed by MGPS or identify signals at an earlier time point than MGPS.

(2) Signal scores for the Pfizer-BioNTech vaccine are generally larger than those of the Moderna vaccine, regardless of the signaling methodology used.

(3) For most AEs, RGPS and MGPS initially agree on their signals scores (statistically insignificant differences) and then diverge in their signal scores. The divergence is likely due to the influence of masking effects, the evolution of VAERS data, and possibly changes in reporting practices.

(4) For several AEs, the time series exhibits aberrations. The aberrations are likely explained or coincide with external events, such as the availability of a vaccine to certain age groups, and the influence of publications.

(5) For certain AEs at certain time points the signal scores fall below the signaling threshold. This indicates that at those time points signals would have been missed and that signaling qualification may be time-sensitive.

(6) As more data accumulates signal scores expectedly stabilize. Larger fluctuations are seen for RGPS indicating that it is sensitive to masking and confounding effects, and that the data may still be evolving.

The following describes our findings for each AE of interest.

3.1 Bell's Palsy

Bell's palsy is a form of acute facial paralysis with a weakening and a drooping appearance of the facial muscles usually on just one side of the face. In most cases the paralysis resolves spontaneously within several weeks. Bell's palsy is due to swelling of the facial nerve, and Type I interferons have been proposed as the potential mechanism[17]. Incidents of Bell's palsy were

reported in clinical trials for both the Pfizer-BioNTech and Moderna vaccines, and it has also been documented with the Influenza vaccine[18, 19]. The FDA currently recommends its surveillance with larger populations globally. In addition, there have been multiple case reports of Bell's palsy associated with the mRNA vaccines[18, 20-22], and several studies that investigated the association[23-25].

As of week 39, there are 7795 reports of Bell's palsy for the mRNA vaccines (5684 Pfizer-BioNTech, 2111 Moderna). The time series in Figure 1 shows that the signal scores produced by each methodology differ by a small amount, with RGPS and MGPS diverging (non-overlapping credible intervals) around weeks 7-9. The figure also shows that a mild masking effect is present (40% averaged across the time series). Regardless of masking, all methods agree early on that the reported co-occurrence of the mRNA vaccines with Bell's palsy is unlikely due to chance (signal scores exceeding the signaling threshold). However, towards the end period (W33) the MGPS signal scores fall below the signaling threshold for the Moderna vaccine. On average the signal scores for the Pfizer-BioNTech vaccine are 46% larger than those of the Moderna vaccine for RGPS, and 43% larger for MGPS.

3.2 Herpes zoster

Herpes zoster (shingles) is a painful rash that develops on one side of the face or body. The rash consists of blisters that typically clear within 2 to 4 weeks[26]. Multiple reports of patients who developed herpes zoster shortly after COVID-19 vaccination have been recently published, suggesting a potential link with the mRNA COVID-19 vaccines[27-32]. Possible mechanisms that explain the pathogenic link are related to the stimulation of innate immunity through toll-like receptors 3,7 by mRNA-based vaccines[28].

As of week 39, there are 8228 reports of herpes zoster for the mRNA vaccines (5637 Pfizer-BioNTech, 2591 Moderna). Figure 1 shows a substantial difference between RGPS and MGPS, with MGPS indicating that there is no statistical association between herpes zoster and the vaccines (signal scores below the signaling threshold), versus RGPS indicating the contrary (signal scores exceeding the signaling threshold) from week 13 (Pfizer-BioNTech) and week 17 (Moderna) through the remaining time periods. Although the value of the RGPS signal score is not large relative to the other AEs, it indicates that the association is unlikely due to chance. Averaged across the time series, RGPS signal scores for the Pfizer-BioNTech vaccine tend to be 31% larger than for the Moderna vaccine, and 33% larger for MGPS.

Interestingly, the size of the masking effect for herpes zoster was the largest among the AEs of interest. Averaged across the time series, the size of the masking effect was 230% for both mRNA vaccines. The sources of masking were evaluated and validated based on the process described in Section 2.5. The two time periods examined were W17 and W39. RGPS automatically selected 67 (W17) and 44 (W39) vaccine predictors for the herpes zoster regression model. The strongest predictors were the Varicella (chickenpox) and the VARZOS (a combination Varicella and Zoster) vaccines, for a total of six vaccine predictors at the manufacturer level. Although the risk is low, there are documented cases and studies of herpes zoster following Varicella and VARZOS vaccination[33-35]. Upon removal of all reports containing the Varicella and VARZOS vaccines we found that the PRR, EBGM, and IC signal scores indeed reverted to larger signal scores close in magnitude to RGPS's original signal score. For example, the PRR signal score for the Pfizer-BioNTech vaccine increased from 0.37 to 1.47 (297%) on W17, and 0.76 to 2.3 (202%) on W39. Similarly, the EBGM signal score increased from 0.35 to 1.47 (320%) on W17, and 0.66 to 1.48

(124%) on W39. In addition, we found that these masking sources (i.e., the Varicella and VARZOS vaccines) did not change over time and remained consistent at both time periods that were evaluated.

3.3. Myocarditis and Pericarditis

Myocarditis and pericarditis refer to inflammation of the heart muscle, and outermost layer of the heart respectively. Myocarditis and pericarditis are both thought to be caused by viral infections, and symptoms include chest pain, shortness of breath, and irregular heartbeat appearing within several days after the second dose of the mRNA vaccines. Several case reports of myocarditis and pericarditis developing rapidly after the first and second doses of the mRNA vaccines have been published[36-40], as well as several retrospective studies[11, 41-44] identifying it as a rare complication of the vaccines. One study on mice suggests that inadvertent intravenous injection of COVID-19 mRNA vaccines may induce myopericarditis[45].

The risk of myocarditis following vaccination has been observed to be highest among young males. The CDC has recognized the association with the COVID-19 mRNA vaccines[2], and both myocarditis and pericarditis now appear on the product labels (warning section) of the vaccines[46, 47].

As of week 39, there are 4690 reports of myocarditis for the mRNA vaccines (3515 Pfizer-BioNTech, 1175 Moderna), and 3079 reports of pericarditis for the mRNA vaccines (2408 Pfizer-BioNTech, 671 Moderna) in the VAERS system. Relative to the total number of cases for these AEs, 87% of myocarditis cases, and 83% of pericarditis cases are associated with the mRNA COVID-19 vaccines.

The changing age distribution of COVID-19 vaccine recipients can be observed in the progression of the time series. Figure 1 shows that both the RGPS and MGPS signal scores for myocarditis were initially not indicative of a safety signal, but around weeks 19-21 (week ending May 30, 2021) as the COVID-19 vaccines were made available in the U.S. to people under 65, a substantial increase in both signal scores can be observed. At this point RGPS and MGPS start diverging, with MGPS remaining on point and RGPS showing a gradual increase from a signal score of 2.3 to above 9.0 (Pfizer-BioNTech) and 1.5 to above 5.0 (Moderna). Similar trends of signal score progression are observed for pericarditis, with a slight decrease in RGPS signal scores around weeks 31-33 onwards. Averaged across the time series, signal scores for myocarditis tend to be 24% larger for the Pfizer-BioNTech vaccine than for the of Moderna vaccine, and 35%-38% larger for pericarditis.

The size of the masking effect for myocarditis is ranked second for the AEs of interest with an average value around 190%. For pericarditis the effect size is 70%. Like the herpes zoster evaluation, the sources of masking for myocarditis were evaluated based on the process described in Section 2.5. The two time periods examined were W19 and W39. RGPS automatically selected 20 (W19) and 39 (W39) vaccine predictors for the myocarditis regression model. The strongest predictors for both time points were a set of three Smallpox vaccines (at the manufacturer level), which is consistent with published reports recognizing myocarditis as a rare AE of the Smallpox vaccine[48-50].

Upon removal of all reports containing the Smallpox vaccines on W19, the PRR, EBGM, and IC signal scores indeed reverted to larger signal scores close in magnitude to RGPS's original signal score. The PRR signal score for the Pfizer-BioNTech vaccine increased from 1.44 to 2.48 (72%),

and for the Moderna vaccine from 0.8 to 1.34 (67%). Similarly, the EBGM signal score for the Pfizer-BioNTech vaccine increased from 1.44 to 2.17 (51%), and from 0.94 to 1.42 (51%) for the Moderna vaccine. As more data accumulated in VAERS, the Pfizer-BioNTech and Moderna COVID-19 vaccines were also identified by RGPS as potential maskers. In this case masking each other for the myocarditis AE. On W39 the Pfizer-BioNTech vaccine was identified by RGPS as the strongest masker. Removing all reports containing the Pfizer-BioNTech vaccine led to a substantial increase in signal scores for the Moderna-myocarditis association. The PRR signal score increased from 1.2 to 4.98 (315%), and the EBGM score increased from 1.32 to 2.13 (61%). This demonstrates how the Pfizer-BioNTech vaccine is masking the Moderna vaccine, and how masking sources may evolve over time. In addition to the COVID-19 vaccines, the Smallpox vaccines were still identified by RGPS as strong sources of masking on W39. Removing both Smallpox and Pfizer-BioNTech vaccines led to the following additional increases for the Moderna association: PRR increased from 4.98 to 8.14 (63%), and EBGM increased from 2.13 to 2.4 (13%). Similarly, removing the Smallpox and Moderna vaccines led to the following increases for the Pfizer-BioNTech-myocarditis association: PRR increased from 5.42 to 10.96 to 17.94 (230%), and EBGM increased from 1.94 to 2.02 to 2.12 (9%).

3.4 Appendicitis

Appendicitis is an inflammation of the appendix usually caused by an obstruction of the appendiceal lumen; however, the exact etiology of acute appendicitis is often unknown. Appendicitis is the most common cause of acute abdominal pain requiring surgery. If left untreated, acute appendicitis can result in serious complications, such as peritonitis or abscess formation[51, 52]. According to the Pfizer-BioNTech COVID-19 Vaccine Fact Sheet for Healthcare

Providers, appendicitis was reported as a serious AE in a clinical trial for 8 vaccine participants and 4 placebo participants (Pfizer-BioNTech COVID-19 Vaccine = 10,841; placebo = 10,851), but not during post-authorization experience[46]. The Moderna COVID-19 Vaccine Fact Sheet for Healthcare Providers does not mention appendicitis as an AE in clinical trials or in post-authorization experience[47]. However, both the Pfizer-BioNTech and Moderna Fact Sheets for Healthcare Providers mention lymphadenopathy as reported adverse events during clinical trials. Barda et al demonstrated an elevated risk ratio for appendicitis (risk ratio, 1.40; 95% CI, 1.02 to 2.01) with the Pfizer-BioNTech COVID-19 Vaccine in a mass nationwide vaccination setting[53]. As of week 39, there are 725 reports of appendicitis for the mRNA vaccines (537 Pfizer-BioNTech, 188 Moderna) in the VAERS system. As shown in Figure 2, both MGPS and RGPS showed extremely large signal scores early on that attenuated over time but remained high for RGPS with values above 3.7 for Pfizer-BioNTech and above 1.7 for Moderna. This early signaling by week 3 appeared even when the numbers of reports were small (15 Pfizer-BioNTech, 6 Moderna). RGPS and MGPS started diverging around week 11 likely due to masking. The figure shows a relatively large masking effect. Averaged across the time series, the size of the masking effect was high and around the value of 100% for both vaccines. Differences between the signal scores of the Pfizer-BioNTech and Moderna vaccines were highest among the AEs of interest with the Pfizer-BioNTech scores on average roughly 71% larger than those for the Moderna vaccine. This difference is consistent with the evidence from clinical trials and publications mentioned above.

3.5 Pulmonary embolism

Pulmonary embolism (PE) is a sudden blockage in a lung artery. It usually happens when a blood clot breaks loose and travels through the bloodstream to the lungs. PE is a serious condition that

can cause permanent damage to the lungs, low oxygen levels in the blood, and damage to other organs in the body from not getting enough oxygen. PE can be life-threatening, especially if a clot is large, or if there are many clots[54].

Systematic reviews and meta-analyses showed high incidences of PE in COVID-19 patients[55, 56]. Barda et al. reported an elevated risk ratio for PE (risk ratio, 12.14; 95% CI, 6.89 to 29.20) for SARS-CoV-2-infected compared to uninfected persons [53].

Besides COVID-19 itself, it appears that COVID-19 vaccines increase the risk for PE: several authors reported the occurrence of PE, often in combination with vaccine-induced thrombotic thrombocytopaenia (VITT), following COVID-19 vaccination, mainly for adenovirus-based COVID-19 vaccines[57-63]. Although no increased risk for PE was found by Klein et al. for mRNA vaccines[10] and by Barda et al. for Pfizer-BioNTech[53], some case reports described the occurrence of PE following vaccination with Pfizer-BioNTech[64-66]. To date, PE is not mentioned in the vaccine labels of the Pfizer-BioNTech and the Moderna COVID-19 vaccines.

As of week 39, there are 5869 reports of PE for the mRNA vaccines (4394 Pfizer-BioNTech, 1475 Moderna) in the VAERS system. Figure 2 shows that both MGPS and RGPS exceed the signal threshold for PE already in W3 for both vaccines. In the following weeks, starting on week 9, RGPS departs from MGPS and stays on a value level about three-fold that of MGPS. Averaged across the time series, the size of the masking effect was high and around the value of 170% for both vaccines. The MGPS time series for Moderna decreases to below the signaling threshold in week 39, whereas RGPS remains well above the threshold. For Pfizer-BioNTech, MGPS and RGPS remain above the signaling threshold, with RGPS at times about three times the value of MGPS.

Compared to Moderna, signal scores for Pfizer-BioNTech are on average 17% (RGPS) and 12% (MGPS) larger.

3.6 Tinnitus

Tinnitus is described as the sensation of hearing ringing, hissing, or other noises in one or both ears that is not caused by an external sound. Tinnitus can be intermittent or continuous and can vary in pitch and intensity. Prolonged exposure to loud sounds and a variety of other conditions can lead to tinnitus, however the mechanism responsible for tinnitus is unclear.

Tinnitus has been linked to other vaccines such as hepatitis, rabies, measles, and H1N1 vaccines[67]. In COVID-19 vaccine trials prior to the release of the Pfizer-BioNTech and Moderna vaccines, no mention was made of the onset of tinnitus or worsening tinnitus for either vaccine. As early as March 2021, in a report from the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA), 196 tinnitus cases among 33,207 vaccinated persons were recorded for the Pfizer-BioNTech vaccine[68], and since then several case reports linking tinnitus to the mRNA vaccines as well as to the Janssen and AstraZeneca vaccines have been published[68-71]. In addition, due to an apparently increased number of individuals experiencing tinnitus during the pandemic period, the connection between the vaccines and tinnitus received special attention in various media outlets and professional associations dedicated to tinnitus[72, 73]. To date, tinnitus is not mentioned in the vaccine labels. As mentioned in the Introduction, tinnitus is not contained in the set of AEs of interest recognized by various health organizations as do the previous six AEs.

As of week 39, there are 12296 reports of tinnitus for the mRNA vaccines (7649 Pfizer-BioNTech, 4647 Moderna) in the VAERS system. Interestingly, the number of reports for tinnitus is larger by a substantial amount than for any of the other AEs covered in this manuscript. Figure 2 shows that both MGPS and RGPS exceed the signal threshold early on for both vaccines and remain above the signaling threshold through the remaining time periods (excluding a brief crossing for MGPS and Moderna on weeks 9-15). On average the signal scores for the Pfizer-BioNTech vaccine are 30% larger than those for the Moderna vaccine. RGPS and MGPS start diverging on weeks 15-17, with RGPS rapidly increasing to signal score values twice as large in a short amount of time. This appears correlated with the increase in the number of reports available throughout the period, and likely the dynamics of masking effects.

Averaged across the time series, the size of the masking effect was high and around the value of 80% for both vaccines. Based on the process described in Section 2.5 we evaluated the sources of masking for tinnitus. The two time periods examined were W17 and W39. RGPS automatically selected 21 (W17) and 25 (W39) vaccine predictors for the tinnitus regression model. For W17 the strongest predictors and potential maskers identified by RGPS were the HPV4 (papilloma virus) vaccine, and the Janssen and Pfizer-BioNTech COVID-19 vaccines. Hence, on W17 two COVID-19 vaccines were already masking other associations; Janssen masking the Pfizer-BioNTech and Moderna COVID-19 vaccines, and the Janssen and Pfizer-BioNTech vaccines masking the Moderna vaccine. Removing all reports containing these three vaccines (HPV4, Janssen, and Pfizer-BioNTech) resulted in expected signal score increases for the Moderna-tinnitus association, with PRR increasing from 1.79 to 2.5 (40%), and EBGM increasing from 1.13 to 1.43 (27%). Expectedly, on W39 as more data accumulated in VAERS, the Pfizer-BioNTech and

Moderna vaccines were identified by RGPS as the strongest maskers (masking each other) in addition to the Janssen vaccine. On W39 the HPV4 vaccine was no longer identified as a strong masker. Removing reports containing the Janssen and Pfizer-BioNTech vaccines led to the following signal score changes for the Moderna-tinnitus association: PRR increasing from 1.8 to 5.5 (205%), and EBGM increasing from 1.18 to 1.69 (43%). Similarly, removing reports containing the Janssen and Moderna vaccines led to the following signal score changes for the Pfizer-BioNTech-tinnitus association: PRR increasing from 2.75 to 6.67 (143%), and EBGM modestly increasing from 1.57 to 1.71 (9%). This demonstrates that the Pfizer-BioNTech and Moderna vaccines may mask each other to varying degrees, in this case Pfizer-BioNTech having a larger effect on Moderna than vice versa.

3.7 Masking Statistics at the Database Level

Table 4 displays counts for the number of potentially masked associations in VAERS categorized by vaccine type. The conditions that define a potentially masked association are provided in the Materials and Methods (Section 2.5 - *candidate association for masking*). The table shows that the likelihood of a masked association for the COVID-19 vaccines is 2.3%, which is roughly eight times larger than for non-COVID-19 vaccines (0.3%). This result clearly demonstrates the increased potential and susceptibility of VAERS COVID-19 vaccine surveillance to the problem of missed signals due to masking effects.

Table 4. VAERS counts of masked associations

	Num Associations	Num Masked Associations	
All Vaccines	265987	1330	0.50%
Non-COVID-19 Vaccines	241016	753	0.31%
COVID-19 Vaccines	24971	577	2.31%
Pfizer-BioNTech/Moderna	18588	458	2.46%

4. Discussion:

The unprecedented dynamic and extent of reporting into VAERS for the novel class of COVID-19 vaccines, compounded by methodological limitations, predisposes signal detection to missed or delayed signals, which may limit our understanding of the risks associated with COVID-19 vaccines and delay their identification.

We investigated seven AEs with various degrees of reported and statistical evidence that link them to the Pfizer-BioNTech and Moderna vaccines. Six of the AEs are largely recognized by various health authorities. The investigation enabled us to discover a potentially new AE (tinnitus), which is yet to be recognized by health authorities, but which has overwhelming statistical support in VAERS, as well as external supporting materials.

In the investigation, we traced the evolution of signals related to the seven AEs during the course of the initial year of COVID-19 vaccination and the accompanying availability of COVID-19 vaccine AE reports made public in VAERS. This temporal evaluation led to several findings regarding the current state of signal detection for COVID-19 vaccine surveillance discussed in the following. We surmise that these findings are important not only for the COVID-19 vaccines currently approved

and investigated in this manuscript but are also important for any new COVID-19 vaccines which might be approved in the future, and likewise should also apply to any new vaccine (or drug) approved for use in the future.

The results overall suggest that signals for COVID-19 vaccines may indeed be missed when generated by conventional signal detection methodologies that are currently utilized by pharmacovigilance organizations. For example, the tinnitus signal may have been overlooked partly due to the low signal scores produced for it by conventional methodologies. Similarly, due to inaccurate lower signal scores produced by conventional methodologies, statistical signals for the other six AEs might have been delayed. Fortunately, these other six AEs had already been well characterized by the FDA, CDC, and other sources.

The findings demonstrate that one source of these missed or delayed signals is the notorious masking effect. Our investigation reveals that statistical masking is present, with varying degrees of strength (up to 300%), and that properly identifying and addressing this effect exposes strong statistical associations that would otherwise be deemed uninteresting. We found that masking is roughly eight times more likely to occur with COVID-19 vaccines than with other vaccines, which

can be explained by the novelty of these vaccines. We also found that masking sources may change over time. Expectedly, in earlier time periods of surveillance, other vaccines could mask signals associated with COVID-19 vaccines, whereas in later time periods, as more COVID-19 reports accumulate, the Pfizer-BioNTech and Moderna vaccines can mask each other and likely other vaccines. Masking effects have been traditionally addressed by removing cases containing the 'offending' product, by using stratification, or by employing regression techniques. However, each of these approaches requires to some extent identifying masking sources prior to signaling, which may limit the utility of signal detection in scenarios where masking and confounding is present. This investigation was made possible by using a methodology that automatically identifies and adjusts masking effects. The masking sources for three AEs identified by this methodology were verified using the traditional approach to address masking, i.e., by re-applying the conventional signaling approaches on data that excludes the masking sources.

The results suggest that different signaling approaches may lead to drastically different results—a conclusion that is especially disconcerting in the context of COVID-19 surveillance. Unfortunately, in the absence of an ultimate benchmark, the question of which methodology to

rely on is still in debate. Nonetheless, the findings highlight the utility of a more advanced class of signal detection methodologies for COVID-19 vaccine surveillance. Given present-day computational power and recognized analytic approaches such as regression, there are few reasons to avoid the utilization of these approaches, at the very least to address acknowledged problems with conventional approaches, such as masking.

The results also show that signal scores for the Pfizer-BioNTech vaccine are generally larger than those for the Moderna vaccine. These differences cannot be exclusively explained by the larger volume of reports available for the Pfizer-BioNTech vaccine. Neither do these larger signal scores suggest or provide evidence that the risk of AEs for the Pfizer-BioNTech vaccine is higher. However, it appears that the two vaccines mask each other and that the masking effect is larger in one direction (Pfizer-BioNTech) than the other (Moderna).

It also appears that the VAERS data for COVID-19 vaccine surveillance is still evolving and susceptible to external influences, such as vaccination policies, publication influences, reporting practices, and updates to the MedDRA terminology. This in turn could contribute to signal score fluctuations resulting in time-dependent signaling uncertainty.

The mRNA Pfizer-BioNTech and Moderna vaccines have demonstrated to be highly effective in preventing infection and severe illness from COVID-19. They also appear to have acceptable safety profiles, suggesting that the benefits of COVID-19 vaccination outweigh the potential risk of AEs. Consequently, AEs such as those highlighted in this manuscript, which are also rare as far as we know, cannot be used to argue against vaccination. Moreover, signal detection is inherently an exploratory process. Therefore, associations flagged by signaling approaches do not imply causal relationships and always warrant further scrutiny, including those named in this manuscript. Notwithstanding, signal detection has the advantage of being fast and performed in "real time". Analyses can be easily "tailored" to a specific age group or gender, time frame, and product type. Signal detection also has the advantage of casting a much wider net for AE reporting from millions or hundreds of millions of people and may identify rare AEs not seen in clinical trials. These advantages are critical in the "real time" and the "real world" environment of COVID-19 vaccine surveillance.

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Disclaimer

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Competing financial interests

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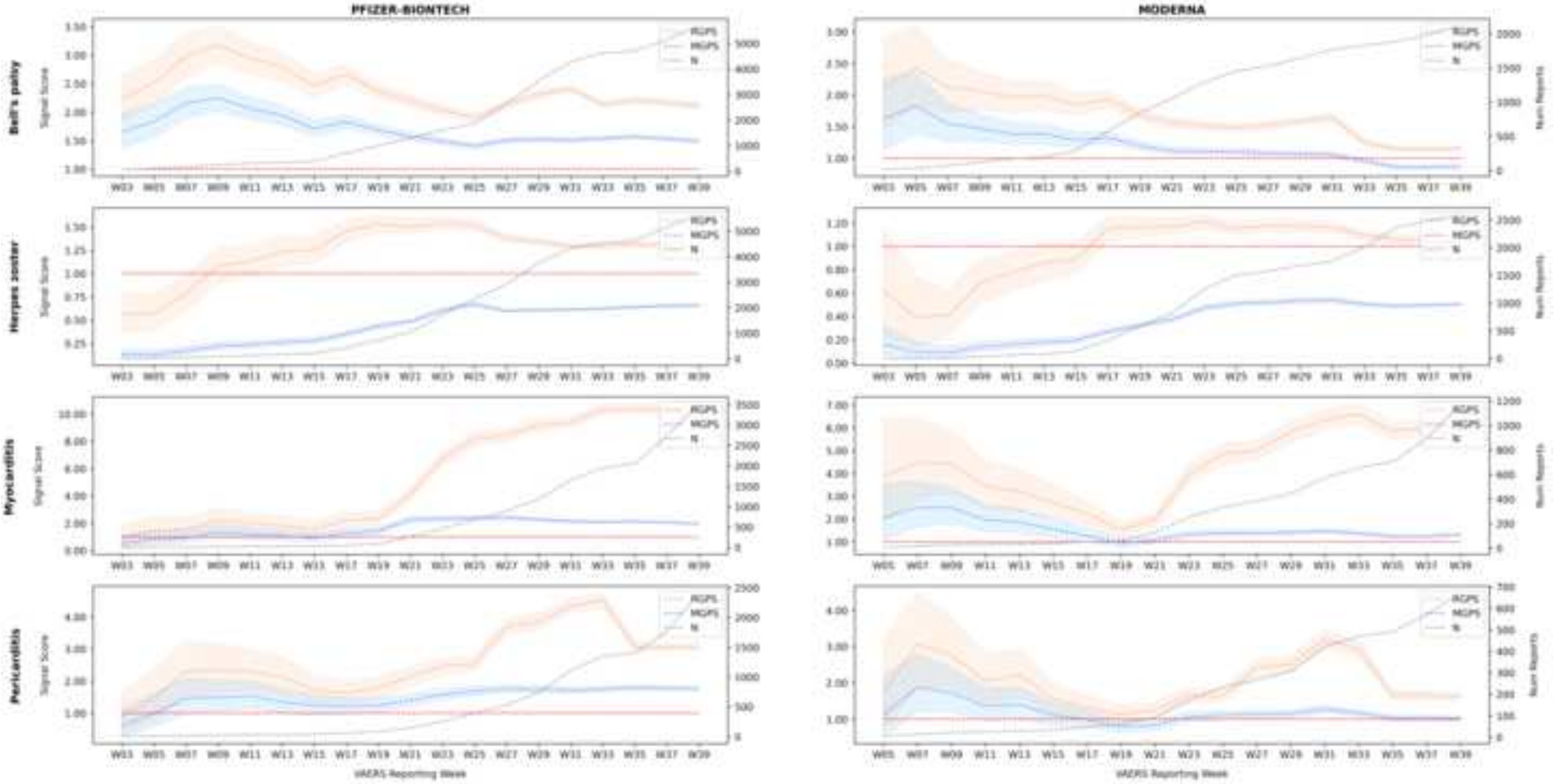
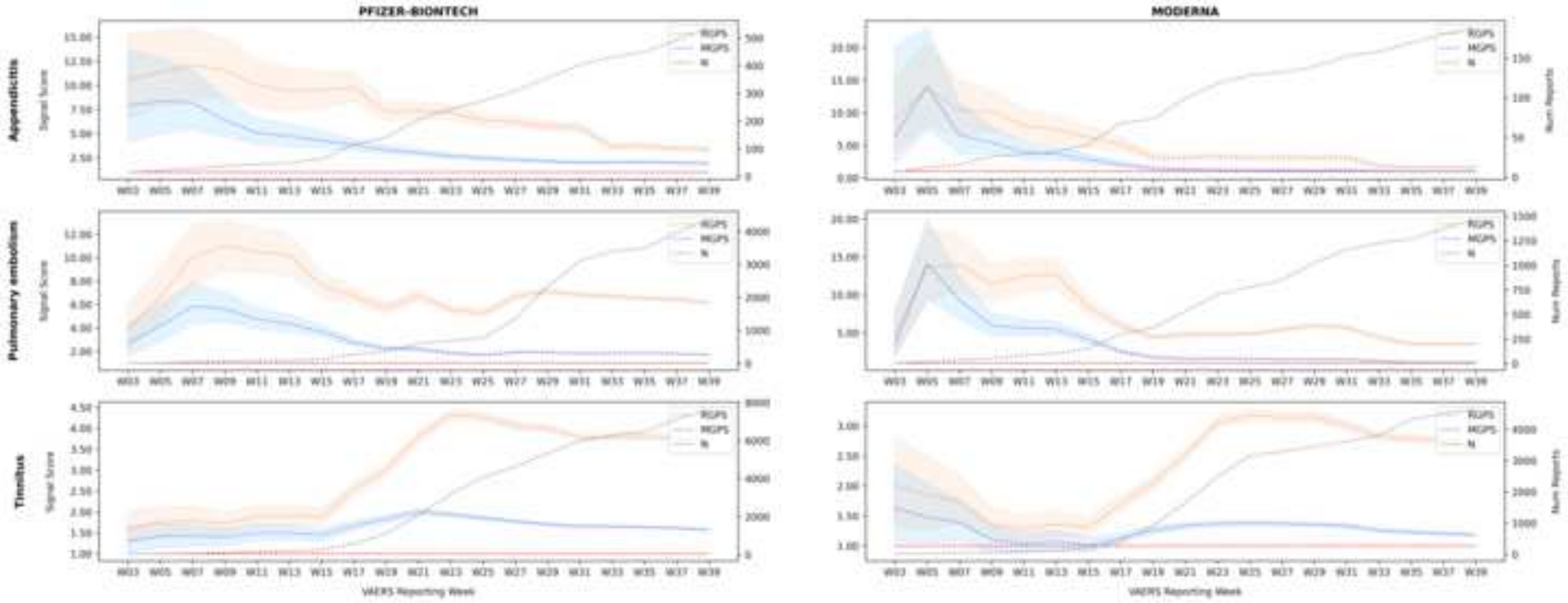
Supporting information

S1 File. Description of the Regression-Adjusted GPS (RGPS) signal detection methodology

S2 File. Excel table with all signal statistics referenced and evaluated in the manuscript. This includes the time series of signal statistics used in Figures 1 and 2, and other statistics underlying additional combinations of AE/vaccine/signaling methodology referenced in the manuscript.





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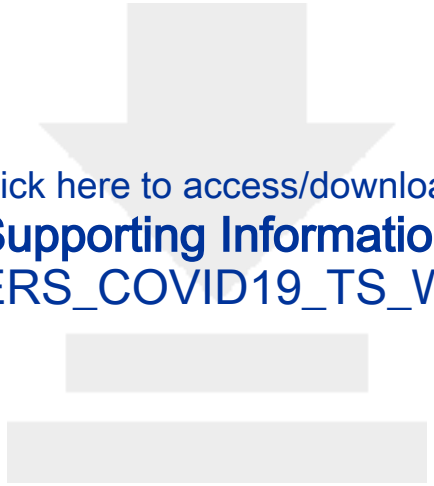
Supporting Information
S1 RGPS Method Description.docx



Click here to access/download
Supporting Information
S2_VAERS_COVID19_TS_W39.xlsx

Attachment by reference: https://fda-my.sharepoint.com/personal/sarah_walinsky_fda_gov/Documents/CBER/Response%20to%20Moderna.docx?web=1

From: "Unger, Ellis" [redacted]
To: "Farizo, Karen" [redacted]
Subject: FW: COVID-19 paper
Date: Mon, 7 Jun 2021 17:12:31 +0000
Importance: Normal
Attachments: PDS_-_COVID19_safety_surveillance_and_masking.docx; CDER_Clearance_Request_for_Articles_Speeches_and_Other_Publications__Masking_Associated_with_Early_COVID-19_Vaccine_Safety_Surveillance.pdf
Inline-Images: image001.png

Hi Karen,

I hope all things are improving for you and yours.

I received this paper to clear for a woman who works in one of the divisions in my office. We have two types of FDA disclaimers—the usual one where we say that the views expressed are not those of the FDA, etc., and an unusual disclaimer that says that the principles may not be consistent with FDA policy. This paper is about surveillance of adverse events after COVID vaccines. Is there someone in CBER you could recommend to provide a quick general comfort level on this paper? This is not what we do in CBER.

Ellis

From: Szarfman, Ana [redacted]
Sent: Friday, June 4, 2021 11:24 AM
To: Unger, Ellis [redacted]
Subject: FW: COVID-19 paper

Hi Ellis, Please refer to the attached paper and form for your clearance.

Many thanks.

--Ana

Ana Szarfman, MD, PhD, FAMIA,
Diplomate by the American Board of Pathology in both, Clinical Pathology (1984) and Clinical Informatics (2017), and Fellow of the American Medical Informatics Association (2020)
Medical Officer, Safety Data Mining Developer and Medical Informatics Analyst,
Celebrating nearly a quarter of a century of successful implementation of safety data mining, interactive patient profiles, and other automated analytical tools.
Division of Cardiology and Nephrology, OCHEN, Center for Drug Evaluation and Research, Food and Drug Administration
[redacted]

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Stockbridge, Norman L [redacted]
Sent: Friday, June 4, 2021 7:14 AM
To: Szarfman, Ana [redacted]
Subject: RE: COVID-19 paper

I marked a few suggested edits.
Good luck,
Norman

From: Szarfman, Ana [redacted]
Sent: Thursday, June 3, 2021 2:30 PM
To: Stockbridge, Norman L [redacted]
Subject: RE: COVID-19 paper

Many thanks Norman. Please refer to the attached paper and OND clearance form.

From: Stockbridge, Norman L [redacted]
Sent: Tuesday, May 25, 2021 9:00 AM
To: Szarfman, Ana [redacted]
Subject: RE: COVID-19 paper

Fine with me. When it is ready to submit, send it to me with the OND clearance form.
Thanks,
Norman

From: Szarfman, Ana [redacted]
Sent: Tuesday, May 25, 2021 7:48 AM
To: Stockbridge, Norman L [redacted]
Subject: COVID-19 paper

Hi Norman, Will it be OK with you if I am a co-author of the attached paper?

Many thanks,

Ana

Masking Associated with Early COVID-19 Vaccine Safety Surveillance

DuMouchel W.[1], Harpaz R.[1], Szarfman A.[2], Van Manen R.[1], Nip A.[1], Bright S.[1], Al-Ansari M[1].*

[1] Oracle Health Sciences, Bedford, MA, United States
[2] U.S. FDA, Silver Spring, MD, United States
[*] Corresponding author

Abstract:

Purpose*: raise awareness to the problem of masking associated with early stage VAERS COVID-19 vaccine surveillance, which can lead to missed signals. Provide a preliminary investigation of these masking effects.*

Methods*: three signal detection methodologies: MGPS, PRR, and a new methodology called RGPS that can control masking were applied to six years of VAERS reports, consisting of 17 weeks of COVID-19 vaccine reports.*

Results*: several statistically masked associations are identified, some of which are also listed in the product labels and reported in clinical trials. The most extreme case of masking is statistically verified by removing reports containing the 'offending' masker. RGPS appears to provide a reasonable middle ground between MGPS and PRR with respect to the veracity and number of signals produced by each methodology.*

Conclusions*: statistical masking is present and should be considered in the context of early stage COVID-19 signal detection. RGPS can address masking and confounding effects, which cannot be properly controlled by conventional signal detection methodologies.*

Purpose:

As the world contends with rolling out massive scale vaccination programs to end the COVID-19 pandemic, identifying and studying adverse events related to these vaccines is critically urgent. The Vaccine Adverse Event Reporting System (VAERS), co-administered by the US Food and Drug Administration and the Centers for Disease Control and Prevention (CDC), is one of several systems used to monitor adverse events that occur after vaccination, including the COVID-19 vaccine. Like other safety surveillance systems, VAERS offers the opportunity to rapidly flag potential safety issues related to vaccines–a process usually known as signal detection.

Computational methodologies for signal detection have been routinely applied to safety surveillance systems for over 20 years and have become a de facto standard[1]. Given its impact on public health, signal detection is still an active area of research, and since its conception multiple guidances[2-5] have been published with practice recommendations as well as admonitions concerning data and methodological limitations.

In particular, 'masking' is a problem that may result in missed signals. Masking[3, 6, 7] is an artifact of conventional disproportionality statistics used for signal detection that are based on 2x2 contingency tables. A masked relationship between a target product and target adverse event can emerge when another product/s is frequently reported with the target event while making the background rate for the target event considerably large. This larger background rate can then make the relationship between the

target product and the target event appear less unusual, hence masking the true relationship. Conditions that make signal detection especially vulnerable to masking effects include: smaller volume of cases such as in VAERS, relationships involving rare events, and relationships involving newer products (i.e., emerging signals). As such, the early stages of COVID-19 vaccine surveillance make signal detection especially susceptible to masking.

Masking effects can be ameliorated by removing cases containing the 'offending' product, by using stratification, and by employing regression techniques, all of which require to some extent identifying masking sources prior to signaling.

Regression-Adjusted GPS (RGPS)[8] is a signal detection methodology that is designed to combine the application simplicity of conventional signal detection methodologies with the power of regression to produce disproportionately statistics with adjusted background rates. Among other, these adjusted background rates can control masking effects.

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The purpose of this report to raise awareness to masking in the context of early stage VAERS COVID-19 vaccine surveillance and provide a preliminary investigation of these masking effects using the RGPS methodology.

Methods:

Data: The investigation was done using VAERS reports from Jan. 01, 2015 to May 01, 2021–the latest public release of VAERS data available at the time of writing. This data represents 17 weeks of COVID-19 vaccine reports, and 6 years of other vaccine reports used as background. In total 466,401 reports were used. Of those 145,300 reports included the COVID-19 vaccine from three manufacturers: Pfizer/BionTech (39.6%), Moderna (45.9%), and Janssen (14.5%). Events were represented at the MedDRA Preferred Term (PT) level. To investigate adverse events commonly reported across the three manufacturers, products were represented at the 'vaccine type', e.g., 'COVID19' rather than at the 'manufacturer' level, e.g., 'COVID19_PFIZER/BIONTECH'.

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Methods: The RGPS methodology operates by fitting separate Bayesian logistic regression models to each target adverse event. RGPS automatically selects two types of predictors to be included in each regression model: (1) products that are statistically associated with the target event, which are represented as indicator variables, and (2) stratification categories grouped by target event rates, which are represented as multiple regression intercepts. Rather than using the fitted regression coefficients to compute signal scores (disproportionalities), RGPS computes observed to expected ratios of counts similar to conventional methodologies. The expected counts are computed by summing the regression predicted probabilities of the target event across all reports mentioning the target product under the null hypothesis of no association between the target product and target event. The null hypothesis probabilities are computed by setting the coefficient of the target product to zero if selected as a model predictor. This results in adjusted expected counts (background rates) that can address masking. The final signal score (and its intervals) are computed using Bayesian shrinkage of observed to expected counts similar to MGPS[9]. Complete details of the RGPS methodology are presented in reference[8].

The results of RGPS were compared against those of the MGPS and the PRR[10] methodologies. Stratification categories used for RGPS and MGPS were: age (10 levels) and gender (3 values). Stratification by 'report year' could not be applied because COVID-19 VAERS reports dominate reporting from

December 2020. We applied the canonical version of PRR, which does not require stratification. For RGPS and MGPS we generated both the point estimates, labeled ERAM and EBGM respectively, and their associated credible intervals labeled ER05-ER95 and EB05-EB95 respectively. Unless specified otherwise, signal scores are represented by the point estimates. The generation of signal scores for the three methodologies and analysis thereof was done using Oracle Empirica Signal 9.1[11].

Results:

Figure 1 provides a high-level comparison of signal scores generated by RGPS, MGPS, and PRR for COVID-19 vaccine-related adverse events. The comparison is illustrated by means of sector (heat) maps.

The figure positions RGPS as a compromise between PRR and MGPS with respect to the number of signals produced by each methodology. Setting the signal score cutoff to 2, PRR produced 3,695 signals, whereas RGPS 467 signals, and MGPS 74. Setting the cutoff to 5, PRR produced 1,492 signals, whereas RGPS 74 signals, and MGPS only 7. The canonical version of PRR is generally known to produce more signals at the expense of possibly a larger number of false alerts compared to MGPS, but as a result may miss fewer signals than MGPS. Which of the methods provides a better tradeoff is still a subject of debate, and beyond the scope of this report.

We conjecture that the larger number of signals produced by RGPS compared to MGPS is due to masking. Both RG*PS and PRR show a 'hot' zone of cardiac events some of which were recently highlighted by the CDC[12].

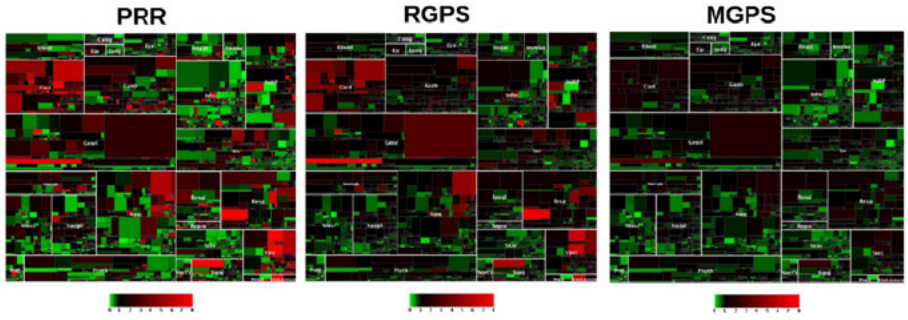

Figure 1. Sector-map comparison of signal scores generated by RGPS, MGPS, and PRR for COVID-19 vaccine-related adverse events. The major rectangular areas represent system-organ-classes (SOCs) and the smaller interior rectangles represent preferred terms (PTs). The box sizes represent the number of cases, and colors represent the size/scale of signal scores, ranging from green-smaller scores to red-larger scores.

Table 1 provides signal statistics for the top 20 masked COVID-19 vaccine associations flagged by RGPS. A candidate association for masking is defined as one whose signal statistics satisfy the following condition:

$$ER05 > EB95 \text{ and } ER05 > 1 \text{ and } EB05 < 1$$

That is, an association where RGPS and MGPS disagree by producing non-overlapping credible intervals (*ER05 > EB95*) with RGPS' interval above the boundary of no association (*ER05>1*) and that of MGPS below

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or including the boundary of no association (*EB05 < 1*). The associations are ranked by the magnitude of the masking effect, which we define as the ratio of RGPS' and MGPS' signal scores, i.e., *ERAM/EBGM*. The table also provides signal scores for the IC statistic[13], which were close to those of MGPS.

Several of the adverse events listed in Table 1 have been listed in the product labels and reported in clinical trials[14], and others are known issues associated with vaccine administration. While the size of the signal scores in Table 1 would normally not be considered large enough to warrant immediate action, they nonetheless clearly illustrate the masking effect. Herpes zoster (shingles, 903 reports) was ranked highest in terms of the masking ratio equal to 1.20/0.31=3.91. PRR produced a signal score of 0.17 for the same association. RGPS automatically selected 39 product predictors and 16 stratification groups for the Herpes zoster regression model (the 'COVID19' vaccine type was not one of the predictors). The strongest predictor and likely the culprit for masking was the VARZOS vaccine--a combination vaccine of Varicella and Zoster. Upon removal of all reports containing the VARZOS vaccine (the alternative approach for controlling masking) the PRR and EBGM signal scores reverted to 1.76 and 1.12 respectively, supporting RGPS' finding of the offending masker. Herpes zoster has also been reported in an observation study[15].

Table 1.Top 20 masked COVID-19 vaccine associations flagged by RGPS. N: number of reports with the adverse event and COVID-19. E_RGPS: adjusted expected counts produced by RGPS. ERAM: signal score produced by RGPS. ER05/ER95: lower and upper bounds of RGPS' credible intervals. E_MGPS: adjusted expected counts produced by MGPS. EBGM: signal score produced by MGPS. EB05/EB95: lower and upper bounds of MGPS' credible intervals. PRR: signal score produced by PRR. 2^IC: 2 to the power of the signal score produced by the IC calculation. Masking ratio: ERAM/EBGM.

Event (MedDRA PT)	N	E_RGPS	ER05	ERAM	ER95	E_MGPS	EB05	EBGM	EB95	PRR	2^IC	Masking Ratio
Herpes zoster	903	752.2	1.14	1.20	1.27	2940.2	0.29	0.31	0.33	0.17	0.31	3.91
Numb chin syndrome	10	1.8	2.63	4.79	7.46	5.2	0.96	1.58	2.49	41.28	1.85	3.03
Cholecystitis acute	10	1.8	2.64	4.80	7.48	5.1	0.96	1.58	2.50	41.28	1.86	3.03
Influenza virus test negative	354	303.6	1.07	1.17	1.27	497.4	0.65	0.71	0.78	0.52	0.71	1.64
Pneumonia	612	462.3	1.24	1.32	1.41	712.6	0.80	0.86	0.92	0.60	0.86	1.54
White blood cell count increased	491	432.6	1.05	1.14	1.22	619.3	0.74	0.79	0.85	0.62	0.79	1.43
Underdose	468	345.8	1.25	1.35	1.46	488.1	0.89	0.96	1.03	0.70	0.96	1.41
Syringe issue	313	209.9	1.35	1.49	1.63	289.0	0.98	1.08	1.18	1.11	1.08	1.38
Oral herpes	247	188.0	1.18	1.31	1.45	259.1	0.86	0.95	1.06	1.28	0.95	1.38
Sepsis	192	127.5	1.33	1.50	1.68	175.3	0.97	1.09	1.23	0.82	1.10	1.37
Product administered to patient of inappropriate age	1132	908.9	1.19	1.25	1.31	1158.6	0.93	0.98	1.03	0.38	0.98	1.27
Abdominal discomfort	1262	1038.9	1.16	1.21	1.27	1272.1	0.95	0.99	1.04	1.41	0.99	1.22
Head injury	344	274.0	1.15	1.25	1.37	333.3	0.94	1.03	1.13	0.83	1.03	1.22
Seizure	884	818.0	1.02	1.08	1.14	986.4	0.85	0.90	0.95	0.42	0.90	1.21
Disturbance in attention	431	382.2	1.04	1.13	1.22	454.8	0.87	0.95	1.02	0.95	0.95	1.19
Pallor	1171	1029.9	1.08	1.14	1.19	1219.7	0.92	0.96	1.01	0.58	0.96	1.18
Vaccination site swelling	569	516.3	1.03	1.10	1.18	609.5	0.87	0.93	1.00	0.96	0.93	1.18
Syncope	2666	2292.0	1.13	1.16	1.20	2681.5	0.96	0.99	1.03	0.87	0.99	1.17
Rash pruritic	1838	1640.8	1.08	1.12	1.16	1880.6	0.94	0.98	1.02	1.39	0.98	1.15
Loss of consciousness	2259	1947.6	1.12	1.16	1.20	2213.4	0.99	1.02	1.06	0.97	1.02	1.14

Conclusion:

The novelty and early stages of COVID-19 vaccine surveillance, compounded by the size of the VAERS database predisposes signal detection to the notorious masking effect. Left unattended masking could lead to costly missed signals. This report demonstrates that statistical masking is indeed present and at the very least should be considered in the context of COVID-19 signal detection. The report also demonstrates the potential utility of a new signal detection methodology called RGPS that can address masking and confounding effects that cannot be properly controlled by conventional signaling methodologies. Signal detection is inherently exploratory, therefore the associations named in this report do not imply causal relationships.

Disclaimer:

The findings and conclusions expressed in this report are those of the authors and do not necessarily represent the views of the U.S. FDA or the federal government.

Competing financial interests:

The authors declare no competing financial interests. DuMouchel W., Harpaz R., Van Manen R., Nip A., Bright S., Al-Ansari M. are employed by Oracle Health Sciences.

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Date of Request: 06/03/2021

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1. Person to Contact	2. Phone Number	3. Email address
Ana Szarfman	[redacted]	[redacted]

4. Title of Article, Speech, or Other Publication

Masking Associated with Early COVID-19 Vaccine Safety Surveillance

5. Authors

DuMouchel W.1, Harpaz R.1*, Szarfman A.2, Van Manen R.1, Nip A.1, Bright S.1, Al-Ansari M1.

6. Author Affiliations

1. Oracle Health Sciences, Bedford, MA, United States; 2. Division of Cardiology and Nephrology, OCHEN, OND, CDER, FDA

7. Details of Article or Speech

☑ **Journal Article**	☐ Regulatory Summary ☐ Letter ☐ Review Article ☐ Editorial ☑ Peer Reviewed Research	Journal: 'Pharmacoepidemiology and Drug Safety'		
☐ **Book Chapter**	Chapter Title	Book Title		
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10. If the article or speech is reporting the results of CDER research, all of the methodological details, analytical procedures, and underlying source data supporting the conclusions are documented and available for inspection? ◉ Yes ○ No

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12. To the best of my knowledge, the statements and conclusions in this article or speech conform with FDA policy. ◉ Yes ○ No

13. The following divisions and offices have reviewed this article or speech:

14. Submitter Signature (digital) Ana Szarfman -S

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Date: 2021.06.03 14:28:16 -04'00'

Review and Clearance

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15. Second Line Reviewer (optional - by office)	Free of non-public information Select Conforms with FDA policy Select	Name	Signature (digital)	Date
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Name	Signature (digital)	Date

CLEAR FORM | SAVE FORM | PRINT FORM

From: "Szarfman, Ana" [redacted]
To: "Marks, Peter" [redacted], "Anderson, Steven" [redacted], "Forshee, Richard" [redacted], "Dal Pan, Gerald" [redacted], "Witten, Celia (CBER)" [redacted], "Stockbridge, Norman L" [redacted]
Subject: RE: NYT - As Millions Get Shots, F.D.A. Struggles to Get Safety Monitoring System Running
Date: Mon, 1 Mar 2021 19:08:29 +0000
Importance: Normal
Attachments: Ana_Szarfman_-_Briefing_of_Dr_Peter_Marks_-_March_1_2021_at_100_PM..pdf; IBMs_Retreat_From_Watson_Highlights_Broader_AI_Struggles_in_Health_-_WSJ.pdf
Inline-Images: image003.png

Hi All,

I enjoyed the opportunity to have this discussion with you.

I have attached an updated presentation and the WSJ article on IBM retreating from Watson.

Warmest regards,

--Ana

Ana Szarfman, MD, PhD, FAMIA,
Diplomate by the American Board of Pathology in both, Clinical Pathology (1984) and Clinical Informatics (2017), and Fellow of the American Medical Informatics Association (2020)
Medical Officer, Safety Data Mining Developer and Medical Informatics Analyst,
Celebrating nearly a quarter of a century of successful implementation of safety data mining, interactive patient profiles, and other automated analytical tools.
Division of Cardiology and Nephrology, OCHEN, Center for Drug Evaluation and Research, Food and Drug Administration
[redacted]

FDA U.S. FOOD & DRUG ADMINISTRATION

-----Original Appointment-----
From: Marks, Peter [redacted]
Sent: Wednesday, February 17, 2021 6:50 PM
To: Marks, Peter; Anderson, Steven; Forshee, Richard; Szarfman, Ana; Dal Pan, Gerald; Ball, Robert; Witten, Celia (CBER); Stockbridge, Norman L
Subject: NYT - As Millions Get Shots, F.D.A. Struggles to Get Safety Monitoring System Running
When: Monday, March 1, 2021 1:00 PM-2:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: WebEX
Importance: High

From: Szarfman, Ana [redacted]
Sent: Sunday, February 14, 2021 9:31 AM
To: Marks, Peter [redacted]
Cc: Stockbridge, Norman L [redacted]
Subject: NYT - As Millions Get Shots, F.D.A. Struggles to Get Safety Monitoring System Running

Hi Peter.

Thanks so much for your work.

Regarding the NYT article, I am quite concerned that the distributed network of EHRs that the Sentinel System uses does not have mortality data, and that they (and we) are not clamoring to fix this problem. It still takes several years to collect mortality data. Indeed there are no incentives to update electronic health records with mortality data.

https://www.nytimes.com/2021/02/12/health/covid-vaccine-how-safe.html?referringSource=articleShare

→ Let me know if you want Bill DuMouchel and I to discuss our proposal for more effective monitoring, including the need to use an updated algorithm by DuMouchel for data mining spontaneous reports at CDER and CBER.

Many thanks,

--Ana

Ana Szarfman, MD, PhD, FAMIA,
Diplomate by the American Board of Pathology in both, Clinical Pathology (1984) and Clinical Informatics (2017), and Fellow of the American Medical Informatics Association (2020)
Medical Officer, Safety Data Mining Developer and Medical Informatics Analyst,
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Division of Cardiology and Nephrology, OCHEN, Center for Drug Evaluation and Research, Food and Drug Administration
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I am humbled and thankful for the tremendously difficult and amazingly hard work you are all doing and for all your successes

Many thanks for your invitation to exchange thoughts

Mortality data to address the COVID-19 public health and analytical needs of the users of the information

More timely detection of adverse events and associated risk factors that we may not know how to formulate *a priori*

Ana Szarfman, MD, PhD, FAMIA, Medical Officer, Diplomate by the American Board of Pathology in both, Clinical Pathology (1984) and Clinical Informatics (2017), Safety Data Mining Developer and Medical Informatics Analyst, Division of Cardiology and Nephrology, CDER, FDA

Dr. Peter Marks Briefing, February 29, 2021

Mortality data linked to EHRs and Claims data

- **There is no universal tool to CENTRALLY capture mortality data in the U.S.**
- Multiple surveillance and analytical systems cannot easily access data on *DEATHS OCCURRING IN AN OUT-OF-HEALTHCARE SETTING* using EHRs or claims data.
- If a patient *DIES WHILE IN THE HOSPITAL, the death will be coded as such in the EHR*, but *not if the death occurs with patients being discharged to hospice care, to a nursing home, or to their home.*
- When such information is needed for RESEARCH or to be linked to CLAIMS data (such as BCBS), it is typically obtained from *PRIVATE SERVICES* who collect the information from various sources like *FUNERAL HOMES AND OBITUARIES IN LOCAL NEWSPAPERS.* **(a very time consuming and very inefficient process)**

- Deaths occurring at home, on the street, or when the subject is homeless, as well as autopsies are not treated as medical clinical service events.
- The death certificate information does not get back to the medical record.
- Death certificates are notoriously sparse and incomplete.
  - They are collected by a multitude of governing localities, and then gathered by the State. The types of reportable deaths are determined by federal, state or local laws.

- The States receive the certificates and submit them to the National Death Index (NDI) where they get adjudicated and added to the NDI final file annually.
- The NDI website provides death information to researchers; but the process requires funding support*:*
  https://www.cdc.gov/nchs/data/ndi/ndi_application.pdf
  https://www.cdc.gov/nchs/ndi/portal.htm
- These requests are usually applied to 500 patients in a research project or clinical trial.

→We need mortality data for over 300 million individuals

- Clinical trials contain COMPREHENSIVE AUTOPSY information but not the EHRs.
- Registries, like cancer registries or transplant registries systematically collect death information, but they represent relatively small siloes of information disjoined from EHRs.
- CMS and DoD and VA hospitals GET FEEDBACK SEEDS from the SSA of *DEATHS THAT NEED TO BE REMOVED FROM THEIR BENEFICIARY LIST.*
  - *NOT SURE HOW OPTIMIZED THESE SYSTEMS ARE FOR INCLUDING DEATHS IN THEIR ANALYSES OF CLINICAL DATA.*
- Outside these Federal systems, the SSA STOPPED MAKING THIS INFORMATION AVAILABLE 5 YEARS AGO because of a potential for fraud (people applying for loans using fake Social Security codes) and would only typically provide an answer for a specific person, and inform when and how they died.

- Death information IS NOT CONSIDERED PRIVATE HEALTH INFORMATION. IT IS PUBLIC INFORMATION.
  - Family members, life insurance companies, and voter registrations are granted such access.
- The key problem is that this information is not collected and made available in a timely way.
- If there is a time, it is now for the Federal Government to act and improve the ability to centrally collect death information or to expedite the link of NDI information to address the necessary research and public health needs of all the analysts of the information.
  - The government can define the requirements and precautions that the receiving parties will need to put in place to avoid fraud.
  - The government can also monitor and prevent fraud activity.
- Correction of this situation will require awareness of this problem, know-how, efforts, funding, and regulatory support.

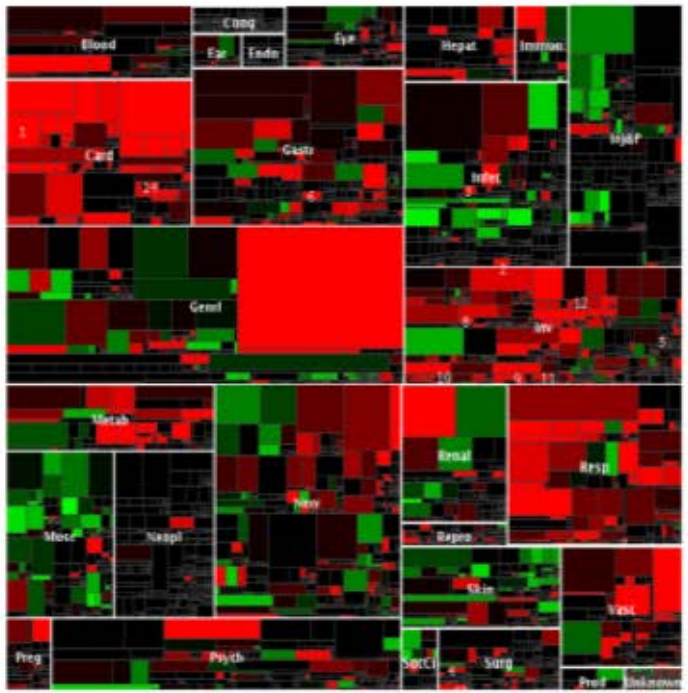
The superior performance of the RGPS algorithm for data mining spontaneous reports, currently only available outside the FDA and CDC

There is a contracting mechanism in place at the FDA to solve this problem quickly

SECTOR MAPS FOR COVID19 VACCINES IN VAERS, RESTRICTED TO AGES 18-75, FDA YEARS 2019-2021, FROM 3 DISPROPORTIONALITY ALGORITHMS

PRR

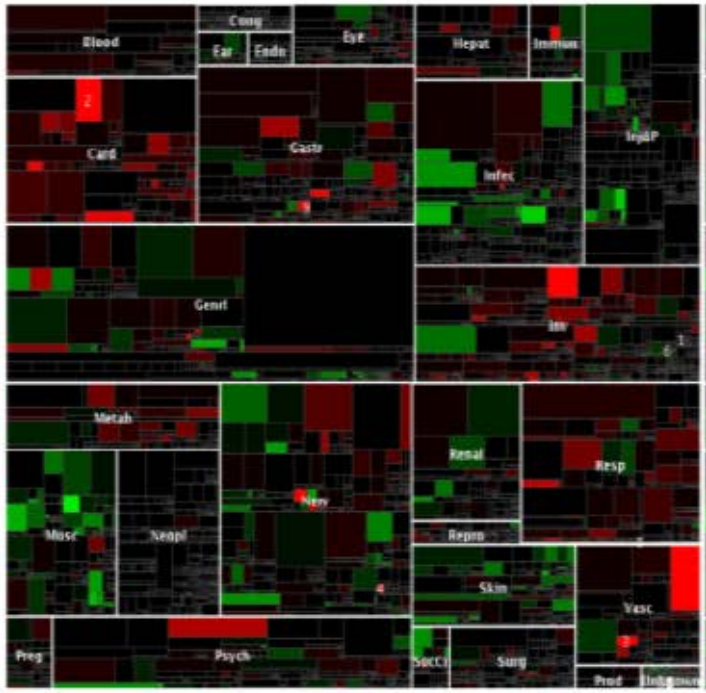
Drug=COVID19



Rank	SOC	Term (PT)	PRR
1	Card	Cardio-respiratory arrest	164.466
2	Infec	COVID-19 pneumonia	164.466
3	Infec	Appendicitis	102.248
4	Surg	Appendicectomy	93.204
5	Inv	SARS-CoV-2 test positive	84.463
6	Gastr	Small intestinal obstruction	48.895
7	Resp	Throat clearing	42.972
8	Inv	Activated partial thromboplastin time prolonged	40.005
9	Inv	Blood magnesium decreased	40.005
10	Inv	Blood pH increased	40.005

RGPS: ERAM

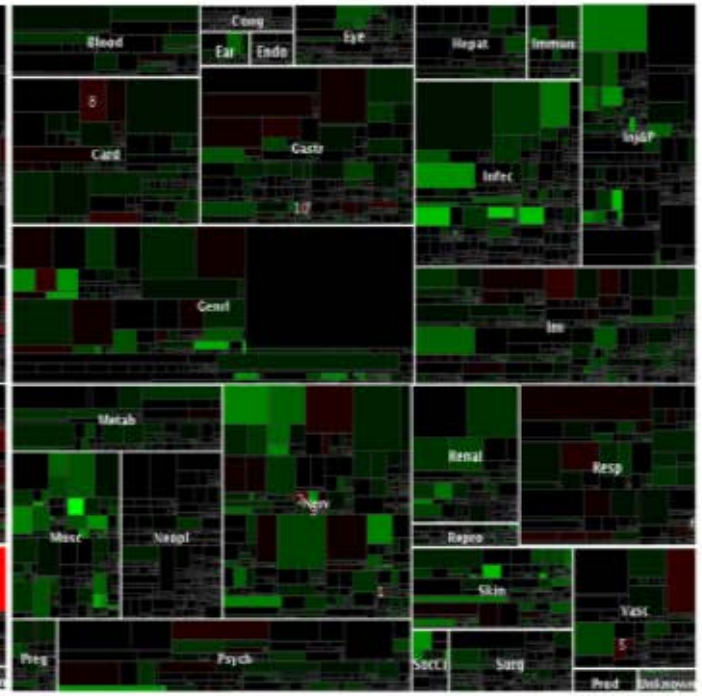
Drug=COVID19



Rank	SOC	Term (PT)	ERAM
1	Inv	SARS-CoV-2 test positive	13.728
2	Card	Tachycardia	7.770
3	Vasc	Flushing	6.754
4	Nerv	Anosmia	6.470
5	Resp	Throat clearing	6.316
6	Inv	Procalcitonin increased	5.795
7	Unknown	Hypertension [SMQ] [broad]	5.766
8	Unknown	Hypertension [SMQ] [narrow]	5.695
9	Gastr	Paraesthesia oral	5.670
10	Unknown	Gastrointestinal perforation [SMQ] [broad]	5.590

MGPS: EBGM

Drug=COVID19

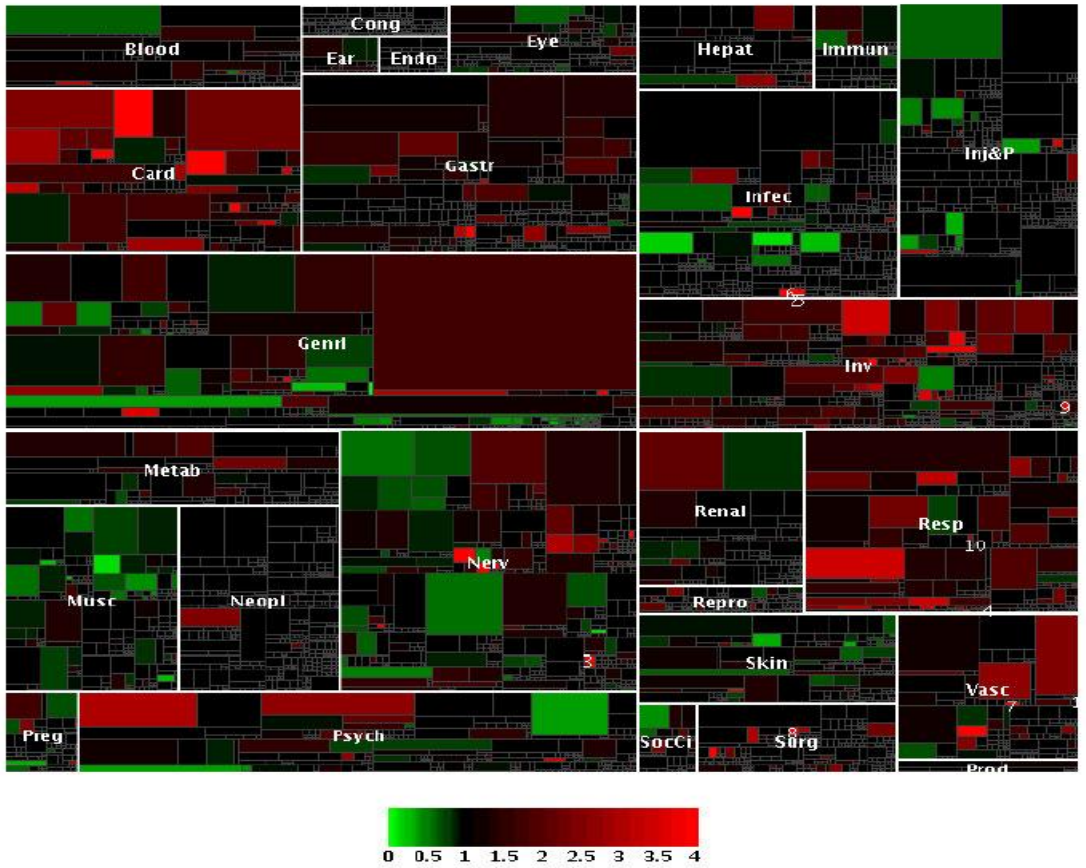


Rank	SOC	Term (PT)	EBGM
1	Nerv	Anosmia	1.991
2	Nerv	Dysgeusia	1.941
3	Unknown	Taste and smell disorders [SMQ] [broad]	1.915
4	Unknown	Taste and smell disorders [SMQ] [narrow]	1.915
5	Vasc	Flushing	1.863
6	Resp	Pharyngeal paraesthesia	1.811
7	Gastr	Paraesthesia oral	1.773
8	Card	Tachycardia	1.770
9	Nerv	Agnosia	1.746
10	Gastr	Hypoaesthesia oral	1.715

The graph showing the signals of 3 Sector Maps next to each other is quite interesting

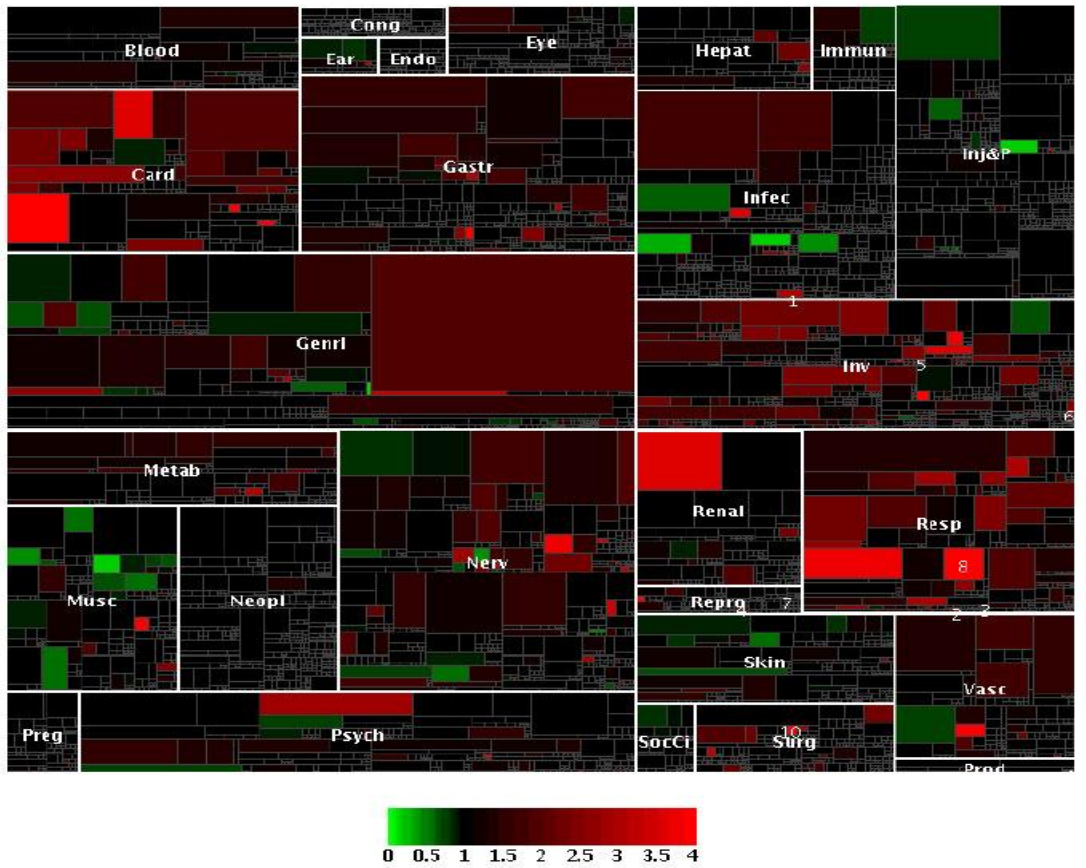
- The PRR on the left highlights almost everything
- The MGPS on the right is flat (you are not getting useful information with such low counts)
- The RGPS in the middle looks more informative for follow-up evaluation
  - This is because RGPS can better adjust for both, masking (false negatives) and confounding (false positives).

Drug=COVID19_PFIZER/BIONTECH



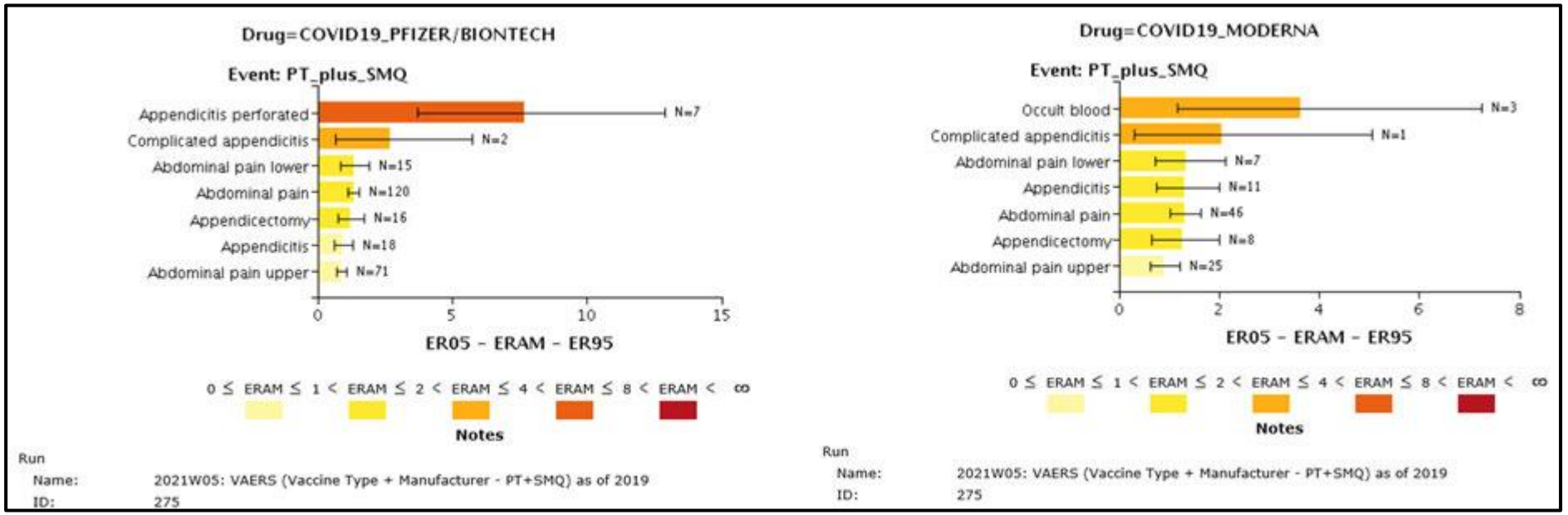
Rank	SOC	Term (PT)	ERAM
1	Vasc	Hypertensive emergency	31.164
2	Infec	COVID-19 pneumonia	24.861
3	Nerv	Anosmia	13.750
4	Resp	Throat clearing	11.520
5	Infec	Suspected COVID-19	10.500
6	Infec	COVID-19	9.619
7	Vasc	Pelvic venous thrombosis	9.439
8	Surg	Hospice care	8.551
9	Inv	Forced expiratory volume decreased	7.781
10	Resp	Respiratory tract irritation	7.746

Drug=COVID19_MODERNA



Rank	SOC	Term (PT)	ERAM
1	Infec	COVID-19 pneumonia	58.246
2	Resp	Lung opacity	13.824
3	Resp	Throat clearing	7.832
4	Repro	Uterine spasm	6.756
5	Inv	Electrocardiogram PR shortened	6.021
6	Inv	Computerised tomogram thorax abnormal	5.917
7	Repro	Suppressed lactation	5.719
8	Resp	Chronic obstructive pulmonary disease	5.595
9	Prod	Product container issue	5.258
10	Surg	Hospice care	5.229

Only to highlight an "Appendicitis, perforated" signal with the Pfizer vaccine that may require follow-up evaluation



For the seven Pfizer cases the onset times for appendicitis perforated are as follows:

VAERS_ID from Demo	Onset days	Onset period	Onset period
0951817	1	Days: 0-6	Days: 0-6
0952318	1	Days: 0-6	Days: 0-6
0955762	0	Days: 0-6	Days: 0-6
0961503	2	Days: 0-6	Days: 0-6
0962110	0	Days: 0-6	Days: 0-6
0974009	3	Days: 0-6	Days: 0-6
0979690	2	Days: 0-6	Days: 0-6

The MGPS data mining method currently in use at the Agency and at the CDC is not the state of the art

RGPS is the state of the art:

- Is a regression-based extension of MGPS that incorporates more information into the signal generation process. This leads to a lower rate of missed signals and less false alerts.
  - Removes the effect of products whose strong signals in the background are overwhelming the signals of the product of interest and thus uncovers signals of products being masked (the false negatives.)
  - Adjusts for the concomitant products in the same reports having strong signals to remove the confounding that generates false positives with innocent bystander products.

VAERS doesn't code concomitant medications, while FAERS does

- If we would also adjust for the concomitant meds in the narratives of VAERS reports, we could improve the estimate of confounding (false alerts or false positives) even better.
- Bill DuMouchel, who developed both, MGPS and RGPS is planning to extract and code the drugs in the narratives of VAERS reports to reduce confounding.

- Note also that REPORTS FOR THE ASTRA ZENECA VACCINE IN USE IN THE U.K. *arrive to the FAERS data instead of arriving to the VAERS data.*

Simultaneous, automated identification of adverse events and risk factors from multiple products in multiple clinical trials, that we may not know how to specify *a priori*

This is a new analytical approach by Dr. Bill DuMouchel that will require funding

Analysis of adverse event data (as opposed to efficacy) from studies of medical products involve several difficult problems

- Pre-specification of analysis end points are rarely possible for adverse events, leading to a multiple comparisons challenge whenever many different adverse events show up.
- Rare adverse event issues often show up with small counts that could be grave dangers to public health.
- Data from many clinical trials and observational studies may need to be analyzed jointly, such as for many newly developed products.

Risk prediction for diseases for which we do not understand the trajectory of individual patients is low

- There is a need for a statistical method capable of identifying rare, unbalanced risk factors that not only occur during or after treatment, **but also, more importantly, at baseline.**
- Consistent efficacy and safety signals may remain hidden in disjoined clinical trial applications or by analyses that do not properly adjust for multiplicity and small counts across all the data being generated.
- We need to implement a solution that will allow for display of the adverse event information and results of analyses in an interactive and user-friendly way that will not require a continuous and impossible-to-document customizations of the complex data and the analytical tools.

Advantages of having this automated, intuitive, and interactive analytical program in place

- Can perform of analysis of patient level data from many clinical trials and many applications at once.
- The addition or removal of some data will generate a quick analysis WITHOUT HAVING TO DO A LOT OF INTERMEDIATE ANALYSES and redo a meta-analysis based on the new summary statistics.
- Can provide TRANSPARENCY to the decision-making process and enable RAPID RE-ASSESSMENT OF THE DATA FOR INCREASED COMPREHENSION of new and evolving issues of interest

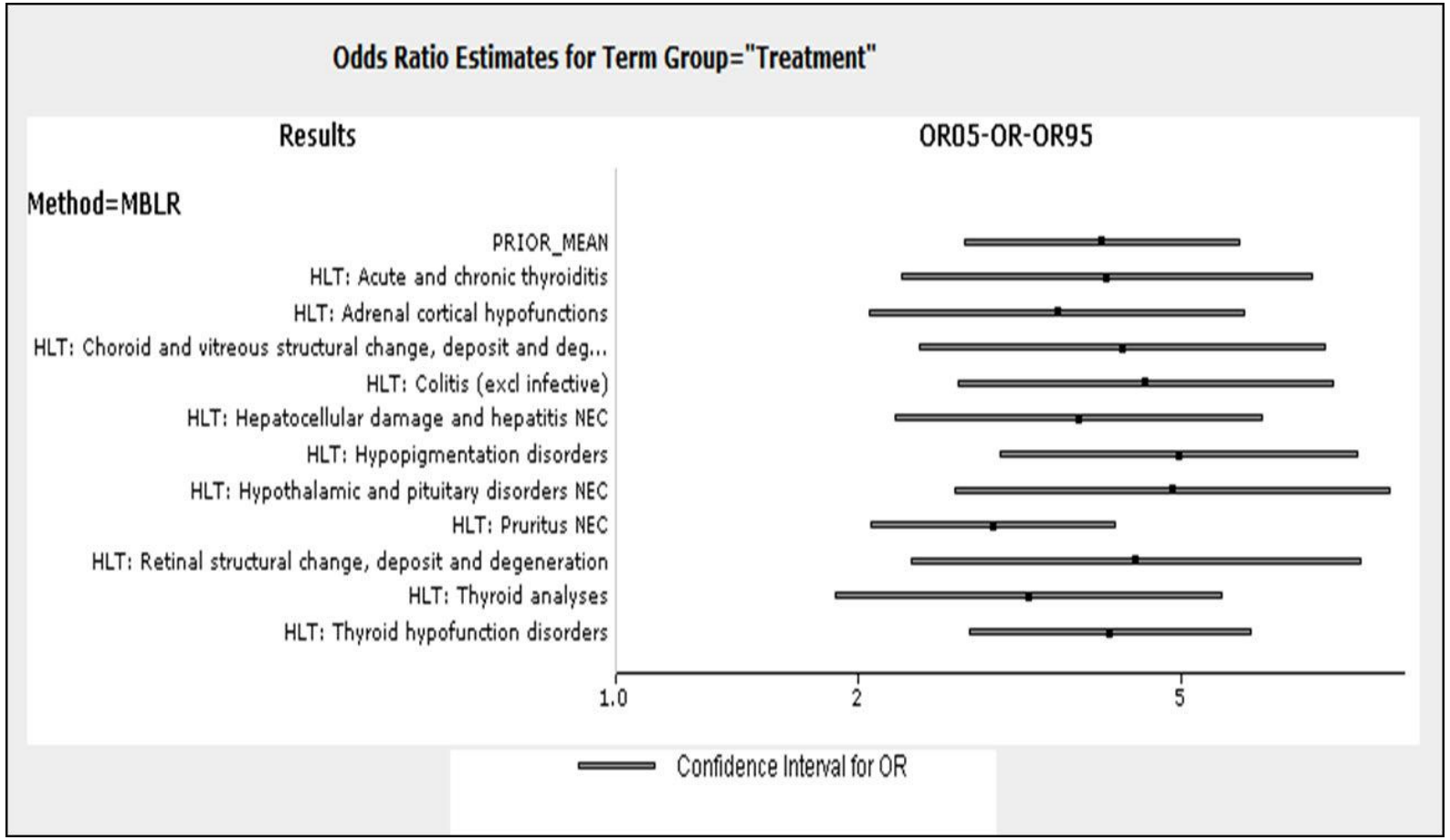
Comparing different treatments that do not all appear in any one study

- This approach will compare subgroups based on multiple treatment arms, covariates, and endpoints measured on each patient.
- All this would usually require an analysis of the patient level data in order to fit the Bayesian shrinkage model.
- **THESE ACTIVITIES NEED TO BE DONE EXPEDITIOUSLY, IN A TRANSPARENT WAY TO AVOID PUBLIC CONFUSION**
- **WE HAVE NEVER BEEN ABLE TO CONDUCT SUCH ASSESSMENTS, AND EVEN LESS TO CONDUCT SUCH ASSESSMENTS IN AN INTUITIVE AND AUTOMATED MANNER.**

Eight Studies of the ICPI Nivolumab versus other Active Comparators -- How to compare the various treatment effects?

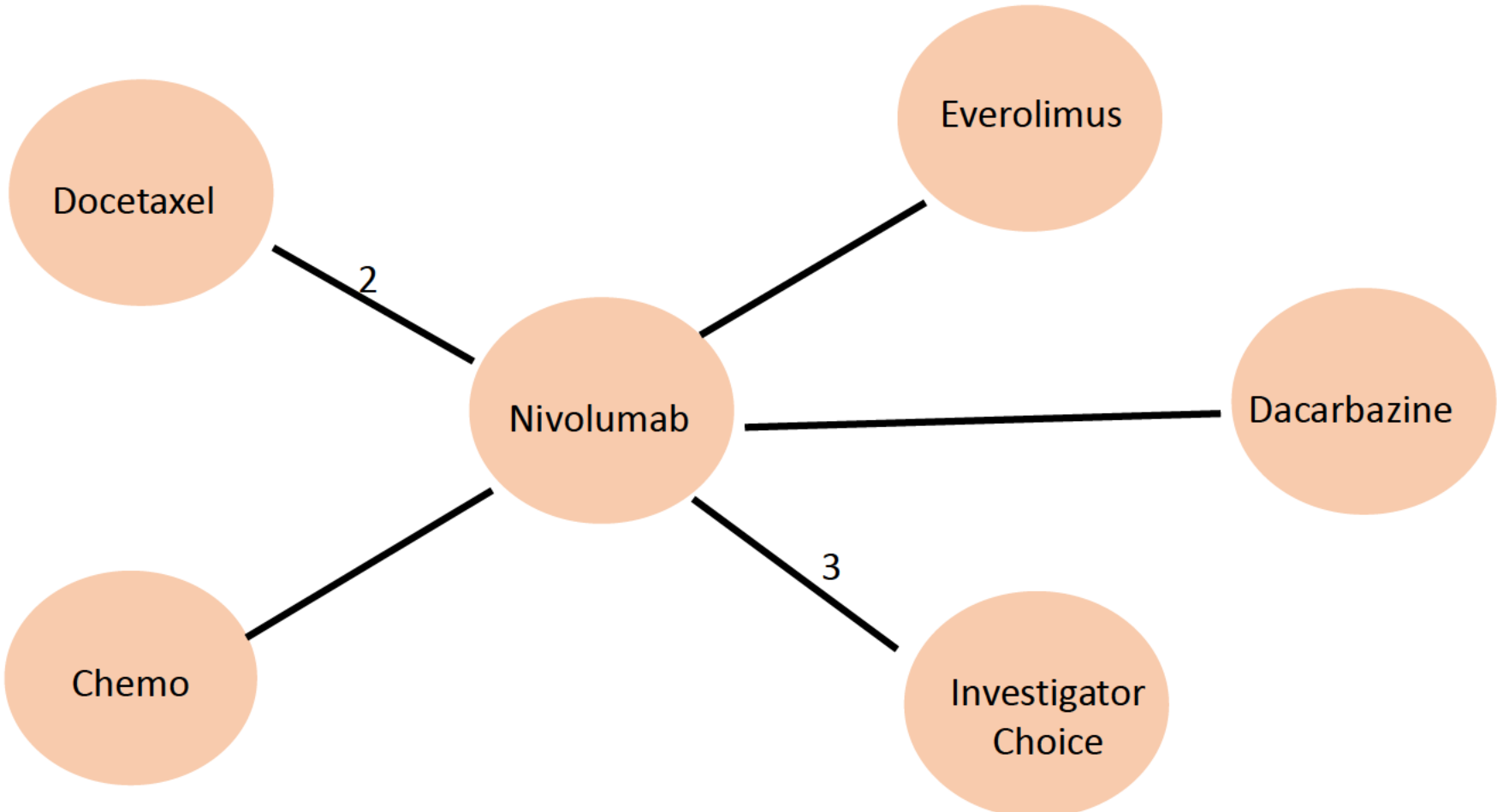
Study	ARM 1	Arm 2
37	NIVOLUMAB	INVESTIGATOR CHOICE
17		DOCETAXEL
25		EVEROLIMUS
57		DOCETAXEL
66		DACARBAZINE
26		INVESTIGATOR CHOICE
41		INVESTIGATOR CHOICE
27		CHEMO

Comparison: Pool All 8 Studies Into 1 Analysis For 11 Safety HLTs

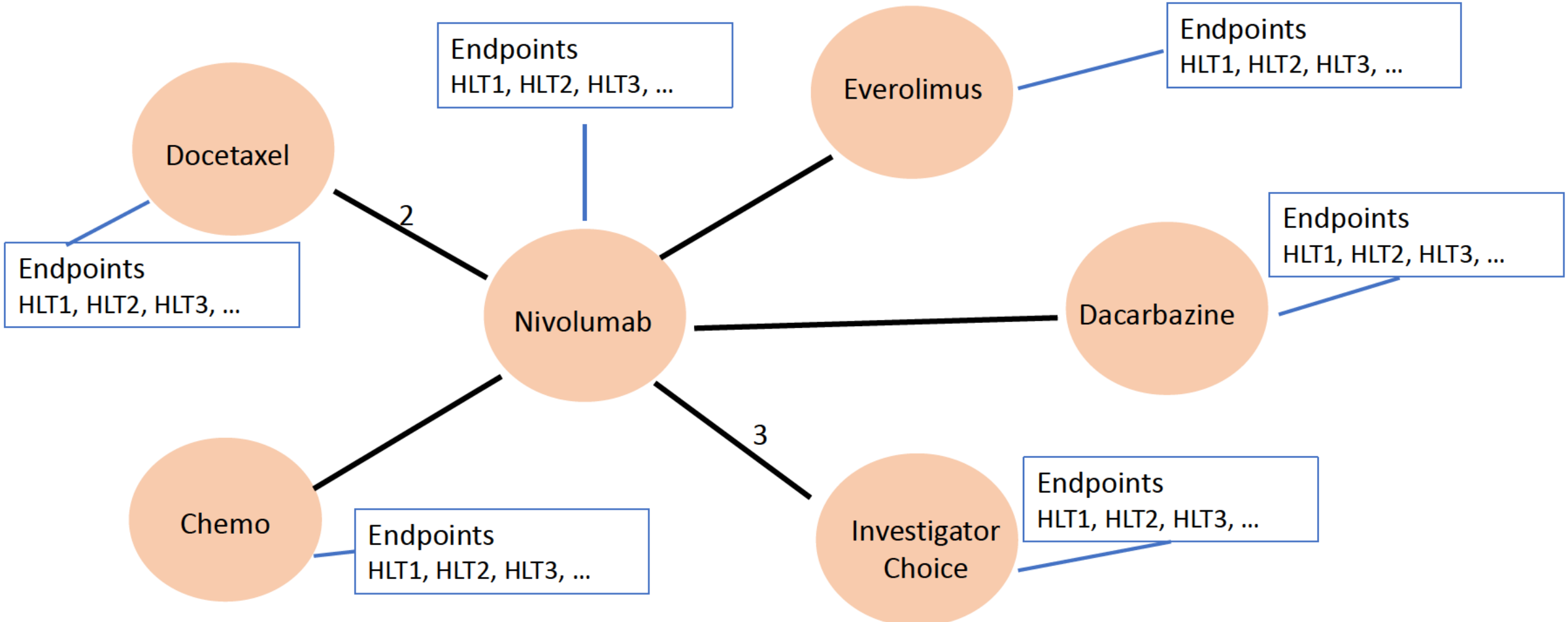


Representing a Pool of Studies as a Network

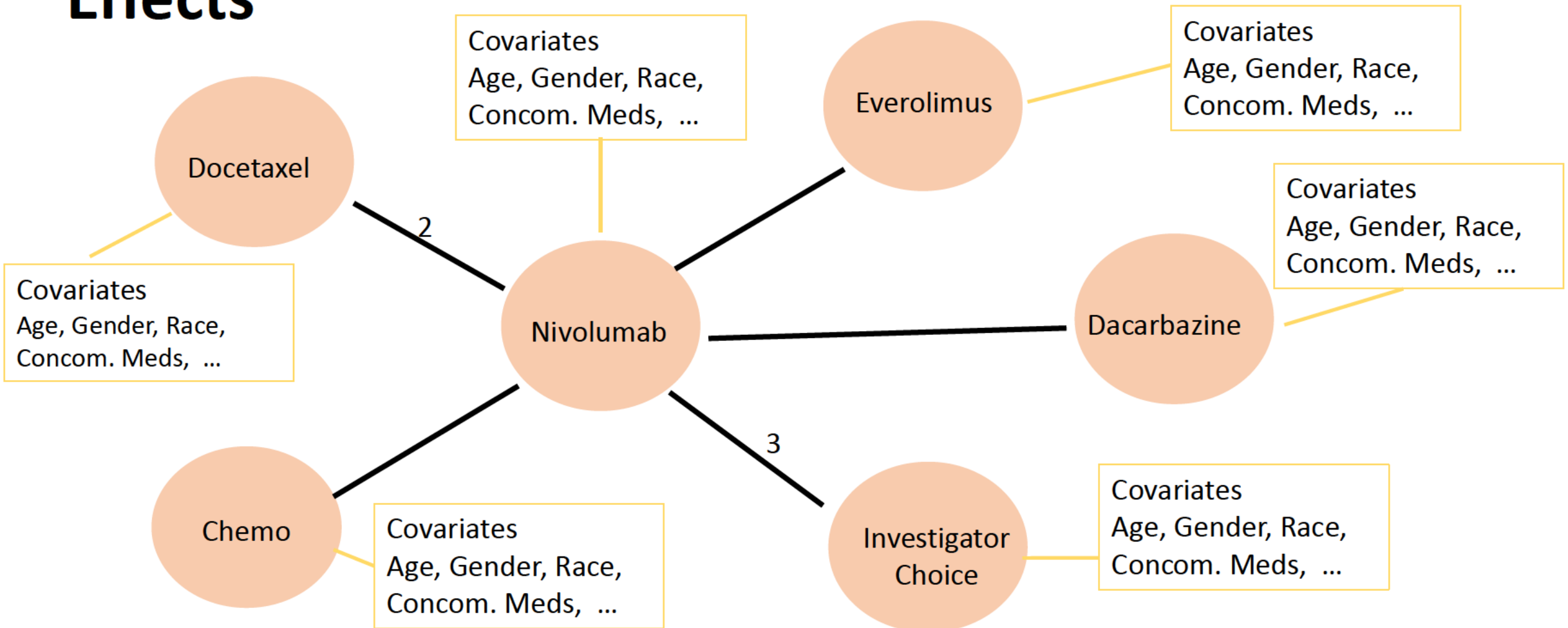
Lines Connecting Two Arms Represent within-Study Comparisons (numbers=study multiplicity)



Each Patient May Have Multiple Medically Similar Endpoint Measurements



Each Patient May Have Multiple Covariates Possibly Influencing Endpoints or Treatment Effects



Thanks to your work, there are now in place multiple approaches for passive and active surveillance for post-authorization safety signals assessments

Some critical roadblocks to consider:

- Claims not collecting vaccinations in a systematic way to understand who gets vaccinated and with which vaccine.
- No direct link/access to dead registries or EHRs to understand cause of death and underlying risk factors.
- **Viral variants need to be associated with particular clinical profiles,** a task that requires the maintenance of a high level of clinical data veracity. **However,**
- There is a lack of a **universal proactive definition and application of permissible variables and values in EHRs** and of **unique IDs for patients (linked to providers and health facilities)** that will simplify access to such data.
- There are **incomplete and not standardized data creation practices in place within and across systems** that unnecessarily delays the analytical processing.
- There are **no simple ways to follow individual patient progression in EHRs and in other sources of data**

Potential improvements:

- For passive surveillance:
  - RGPS will provide a big advantage over MGPS for signal detection
- For active surveillance:
  - The simultaneous automated assessment of safety data from multiple clinical trials and OD -- and associated risk factors that we may not be able correctly specify *a priori* -- will provide a great analytical advantage

BUSINESS | HEALTH CARE | HEALTH

IBM's Retreat From Watson Highlights Broader AI Struggles in Health

Watson Health was billed as a 'bet the ranch' move by Big Blue; now the company is prepared to throw in the towel

Watson Health has struggled for market share.
PHOTO: COLIN MILLER/AGENCE FRANCE-PRESSE/GETTY IMAGES

By [redacted] Daniela Hernandez *and* Asa Fitch
Feb. 20, 2021 11:46 am ET

Your browser does not support the audio tag.
[redacted] Listen to this article
8 minutes

Ten years ago, International Business Machine Corp.'s IBM +0.66% ▲ artificial intelligence system Watson bested humans at the quiz show "Jeopardy!"

The feat was supposed to herald a shift in the way machines served up answers to questions big and small, opening up new revenue streams for Big Blue specifically and Big Tech more generally. A key target:

healthcare, a trillion-dollar industry many say is saddled with inefficiencies that some tech advocates say AI could cure.

A decade later, reality has fallen short of that promise. IBM is now exploring the sale of Watson Health, a unit whose marquee product was supposed to help doctors diagnose and cure cancer.

IBM spent several billion dollars on acquisitions to build up Watson. Former senior IBM executive John Kelly once touted the initiative as a "bet the ranch" move. It didn't live up to the hype. Watson Health has struggled for market share in the U.S. and abroad and currently isn't profitable.

Alphabet Inc.'s GOOG Google DeepMind unit, which famously developed a Go-playing algorithm that vanquished a champion human player in 2016, later launched several healthcare-related initiatives focused on chronic conditions. It also has lost money in recent years and run into privacy concerns over how health data was being collected.

IBM computer Watson beat Ken Jennings, left, and Brad Rutter to the buzzer to answer a question during a practice round of 'Jeopardy' in 2011.
PHOTO: SETH WENIG/ASSOCIATED PRESS

The stumbles highlight the challenges of attempting to apply AI to treating complex medical conditions, healthcare experts said. The hurdles include human, financial and technological barriers, they said. Having access to data that represents patient populations broadly has been a challenge, the experts say, as have gaps in knowledge about complex diseases whose outcomes often depend on many factors that may not be fully captured in clinical databases.

Tech companies also sometimes lack deep expertise in how healthcare works, adding to the challenge of implementing AI in patient settings, according to Thomas J. Fuchs, Mount Sinai Health System's dean of artificial intelligence and human health.

"You truly have to understand the clinical workflow in the trenches," he said. "You have to understand where you can insert AI and where it can

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be helpful" without slowing things down in the clinic.

For IBM, the retreat underscores the difficulties new CEO Arvind Krishna faces in restoring growth at the iconic tech company. Mr. Krishna has said AI, along with cloud-computing, would be pivotal for IBM's prospects.

Watson Health was one of IBM's first and the largest AI efforts, said Toni Sacconaghi, an analyst at Bernstein Research. IBM initially promoted it as an engine for growth, but more recently has given it less prominence amid mounting business struggles, leadership changes and layoffs, he said.

"Watson may be very emblematic of a broader issue at IBM of taking good science and finding a way to make it commercially relevant," Mr. Sacconaghi said.

Even as Watson Health ran into problems, the company's research arm has continued to give priority to AI and healthcare. IBM Research and Pfizer developed speech tests last year to predict the onset of Alzheimer's disease, the company said last year.

IBM wouldn't comment about the sale, but said Watson Health has had successes over the years. "This work began nearly 10 years ago, at the beginning of the AI revolution, and we explored groundbreaking space in helping physicians advance healthcare through AI," the company said. "IBM is continuing to evolve the Watson Health business, based on our decade of experience, to meet the needs of patients and physicians."

A sale would mark Mr. Krishna's second major move to exit struggling businesses in less than a year at the helm. IBM last year said it planned to spin off its managed IT services division, which generated about $19 billion of annual revenue, or about a quarter of its total sales.

By slimming IBM down, Mr. Krishna expects IBM to deliver consistent mid-single-digit growth following a decade filled with revenue declines. IBM had $73.6 billion in sales last year, down from almost $100 billion in 2010.

IBM's climb down also serves as a warning to the wider tech industry that sees healthcare as a promising growth market. Watson Health and some other tech-industry AI projects that have struggled were overly ambitious, trying to answer broad, complicated health-related questions, experts said. Watson Health, for instance, was marketed broadly as finding answers to all kinds of cancer, they said.

"When the notion is, 'Well, we can answer any question in cancer care with this data,' it's too overwhelming. We don't have the power to do

4. Biden Declares a Major Disaster in Texas, Triggering Aid

5. Tesla Quality Issues Threaten Its Dominance in China EV Market

that right now," said David Agus, the chief executive of the Ellison Institute for Transformative Medicine at the University of Southern California and an early tester of the Watson system.

Another challenge is the lack of data-collection standards, which makes taking an algorithm that was developed in one setting and applying it in others difficult, experts said. "The customization problem is severe in healthcare," said Andrew Ng, an AI expert and CEO of startup Landing AI, based in Palo Alto, Calif.

The most successful applications of AI in healthcare to date have been when the technology aims to solve discrete and narrow problems, according to Cynthia Burghard, research director at IDC Health Insights, a technology market research and advisory services firm. Such applications include alert systems that warn doctors which of their patients might be at risk for readmissions or severe outcomes and chatbots that help answer basic questions.

Recently, some healthcare providers and insurers also have married different data sources, including medical history and income-related information, to come up with risk scores for patients to identify those potentially more vulnerable to Covid-19 exposure to target outreach to them, she said. Such applications are easier to manage because they don't involve diagnoses.

Other areas where AI has seen some successes include radiology and pathology, disciplines where image-recognition software can be applied to answer specific questions, experts said.

"It's about incremental improvements. It's not about solving the most complex things in healthcare," she said. "We might get there someday, but [right now] it's crawl, walk, run."

Another area where the technology has had inroads is in streamlining business processes, like billing and charting, rather than in making diagnoses, experts said, because the stakes are lower, and there is better data to make these systems work. There are also clear financial incentives, they said.

"There's a lot of human capital invested in these things, and a lot of that could be markedly reduced with AI support." said Eric Topol, a cardiologist and executive vice president at Scripps Research.

Despite the challenges of applying AI in healthcare, experts said they expect investments to continue.

"The market size is infinite," said USC's Dr. Agus. "Healthcare is probably a trillion-dollar market and it's probably 40% to 60% inefficient. So the notion that you can make it dramatically better with something as elegant as a machine-learning algorithm, or AI, which is scalable, obviously is very enticing."

Write to Daniela Hernandez at daniela.hernandez@wsj.com and Asa Fitch at asa.fitch@wsj.com

Appeared in the February 22, 2021, print edition as 'IBM Retreat Highlights Hurdles for Health AI.'

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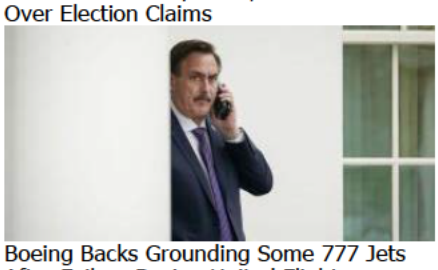

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Travel's Covid-19 Blues Are Likely Here to Stay—'People Will Go Out of Business'

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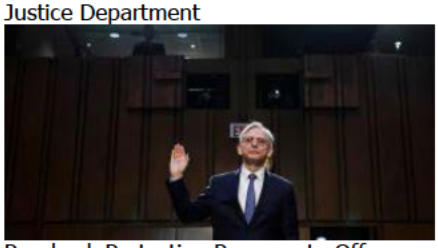

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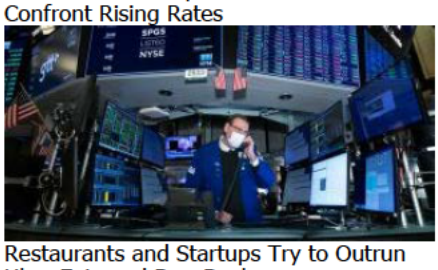
Bond Selloff Prompts Stock Investors to Confront Rising Rates



Restaurants and Startups Try to Outrun Uber Eats and DoorDash

Historic Gains in Small Stocks Highlight Investor Exuberance

Connecticut Governor Defends Refusal to Increase Taxes on Wealthy

China Deploys Covid-19 Vaccine to Build Influence, With U.S. on Sidelines

From: "Forshee, Richard" [redacted]
To: "Scott, John [redacted] " [redacted], "Lee, Shiowjen" [redacted]
Subject: FW: William DuMouchel_advanced meta-analysis (005).pptx
Date: Wed, 23 Dec 2020 19:48:33 -0000
Importance: Normal
Attachments: William_DuMouchel_advanced_meta-analysis_(005).pptx
Inline-Images: image001.png

Dear John and Shiowjen,

Ana Szarfman invited me to a lecture by Bill DuMouchel about his implementation of Network Meta-Analysis methods. Ana thinks it could be very helpful for vaccine safety and effectiveness studies, but I have my doubts. The methods are great for certain problems, but I'm not sure they will address our biggest concerns.

I've attached his presentation for your review. Let me know if you'd like to explore it further.

Thanks and happy holidays,
--Rich

From: Szarfman, Ana [redacted]
Sent: Wednesday, December 23, 2020 2:39 PM
To: Forshee, Richard [redacted]
Cc: bill.dumouchel [redacted]
Subject: William DuMouchel_advanced meta-analysis (005).pptx

Great talking with you Richard. Thanks for your participation.

Please refer to the latest version of Bill DuMouchel's presentation.

--Ana

Ana Szarfman, MD, PhD, FAMIA,
Diplomate by the American Board of Pathology in both, Clinical Pathology (1984) and Clinical Informatics (2017), and Fellow of the American Medical Informatics Association (2020)
Medical Officer, Safety Data Mining Developer and Medical Informatics Analyst,
Celebrating nearly a quarter of a century of successful implementation of safety data mining, interactive patient profiles, and other automated analytical tools.
Division of Cardiology and Nephrology, OCHEN, Center for Drug Evaluation and Research, Food and Drug Administration
[redacted]

FDA U.S. FOOD & DRUG ADMINISTRATION

Addressing the need for improving the comprehensiveness and transparency of our decision processes to address the COVID-19 pandemic

Introductory words to the presentation by Dr. William DuMouchel

by

Ana Szarfman, MD, PhD, FAMIA
Division of Cardiology and Nephrology, OCHEN, Center for Drug Evaluation and Research
Food and Drug Administration

The good news is that we now have new potential interventions for containing the pandemic.

These interventions are unprecedented for:

- The compressed time for their development and study
- The large number of potential new interventions (20 +)
- The enormous size of the global population impacted (hundreds of millions of people)

The usual review process for new vaccines and molecular entities at the Agency is designed at assessing a much smaller impacted population.

Hearing the summary options of scientists that helped control in the past much smaller outbreaks would not be sufficient.

- Consistent efficacy and safety signals may remain hidden in disjoined CT applications and observational studies or by analyses that do not properly adjust for multiplicity and small counts across all the data being generated.

We need an automated, interactive analytical process in place that can compare the data of all interventions being continuously collected in CTs and observational studies.

- The automated reanalysis of the data and identification of consistent signals by specific interventions that can be exhaustively examined by experts will provide transparency to the decision making process.

We have been encouraging Bill DuMouchel to implement a methodology that can assess multiple studies and applications at once (i.e., all vaccines for COVID-19, all anticoagulants) where the goal is to compare different treatments that don't all appear in any one study, which is the "Network Meta-Analysis" paradigm.

As Bill DuMouchel explained, this approach will compare subgroups based on several covariates and in addition where there are multiple endpoints measured on each patient.

All this would usually require an analysis of the patient level data in order to fit the Bayesian shrinkage model.

Finally, an advantage of having one program that can do an analysis of patient level data from many studies and many applications at once, is when we need to add or remove some data, we can get a quick re-analysis without having to do a lot of intermediate analyses and redo a meta-analysis based on the new summary statistics.

Bill DuMouchel:

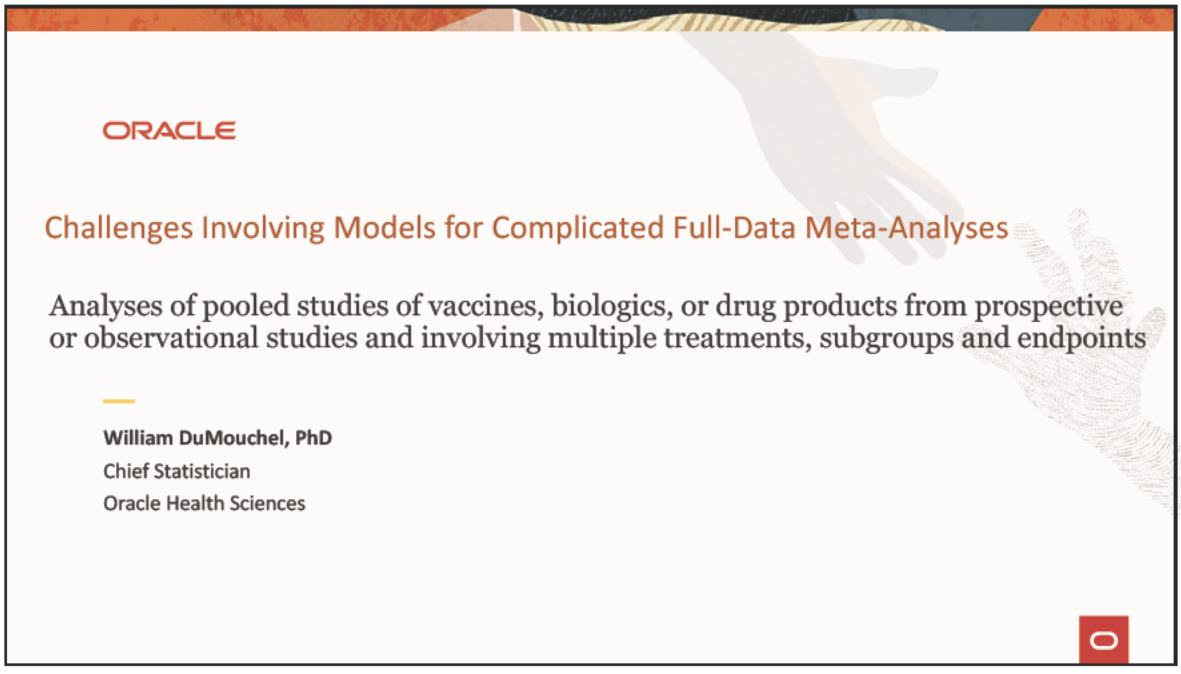
Invented the empirical Bayesian data mining algorithm known as Gamma-Poisson Shrinker (**GPS**) and its successor **MGPS**, which have been applied to the detection of safety signals in databases of spontaneous adverse drug event reports.

He was a senior member of the data mining research group at **AT&T (Bell) Labs** and Chief Statistical Scientist at **BBN Software Products,** and in the faculty of several institutions, including

- University of California at Berkeley,
- University of Michigan,
- MIT,
- Columbia University

Was an associate editor of

- Journal of the American Statistical Association,
- Statistics in Medicine,
- Statistics and Computing, and
- Journal of Computational and Graphical Statistics.



Many New Vaccines and Proposed Treatments for Covid-19 Are Being Tested

Comparisons of Efficacy and Safety Are Complicated

- Multiple Efficacy and Multiple Safety Endpoints
- Within-Study Comparisons of Treatment Arms
- Comparing Subsets Depending on Covariate Values (age, sex, concomitant meds, etc.)
- Combining Studies (Including Prospective and Observational Studies)
  - Studies May Differ by Indication, Populations or Medical History
  - Bayesian Approaches May Give Higher Weight to Certain Study Designs

8

Network Meta-Analysis

https://training.cochrane.org/resource/key-concepts-network-meta-analysis-nma

Several Products Need to Be Compared

- Each Study Typically Only Includes Two or a Few Products
- But a Chain of Within-Study Comparisons May Connect Every Pair of Products
- Pooled Studies Can Create Efficient Indirect Comparisons Among Them All
- Allowance Must Be Made for Population Differences Between Studies

Both Observational and Prospective Studies May Be In the Pool

- Bayesian Approaches May Give Higher Weight to Certain Study Designs

9

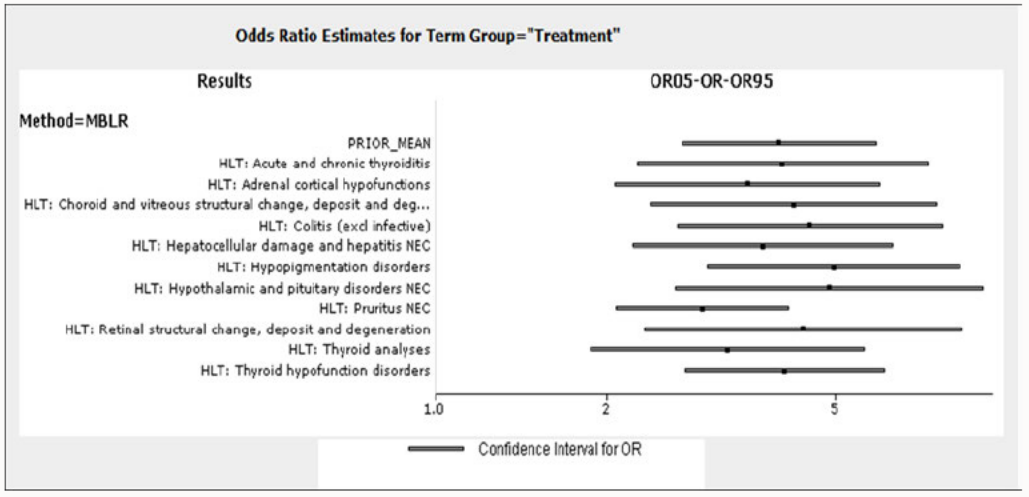
Eight Studies of the ICPI Nivolumab versus other Active Comparators

How to compare the various treatment effects?

Study	ARM 1	Arm 2
37	NIVOLUMAB	INVESTIGATOR CHOICE
17		DOCETAXEL
25		EVEROLIMUS
57		DOCETAXEL
66		DACARBAZINE
26		INVESTIGATOR CHOICE
41		INVESTIGATOR CHOICE
27		CHEMO

10

Comparison: Pool All 8 Studies Into 1 Analysis For 11 Safety HLTs



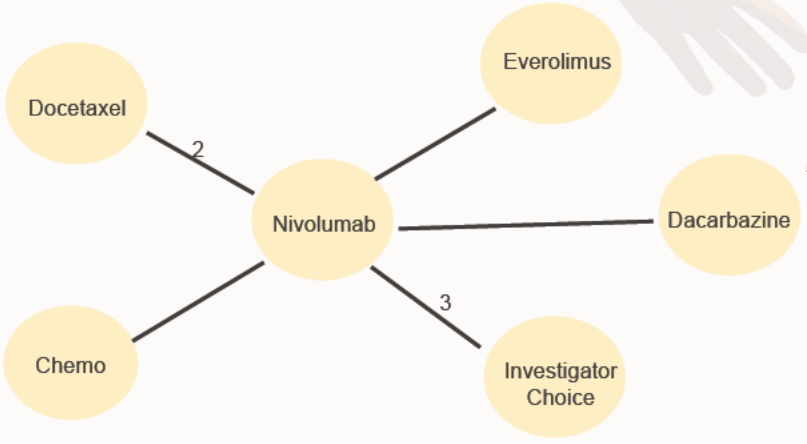
Multivariate Bayesian Logistic Regression (MBLR)

MBLR (also known as BLR) is similar to meta-analysis, but uses the whole data from each study. Adjusts for potentially biasing between-study differences and multiple comparisons. The results of a BLR run may help support any of the following conclusions:

An issue appears related to treatment in a screening analysis, but is not related to treatment when covariates are included in a BLR run, and these covariates show a strong relationship to issue outcome. This may indicate that a randomization error has occurred.

Representing a Pool of Studies as a Network

Lines Connecting Two Arms Represent within-Study Comparisons (numbers=study multiplicity)



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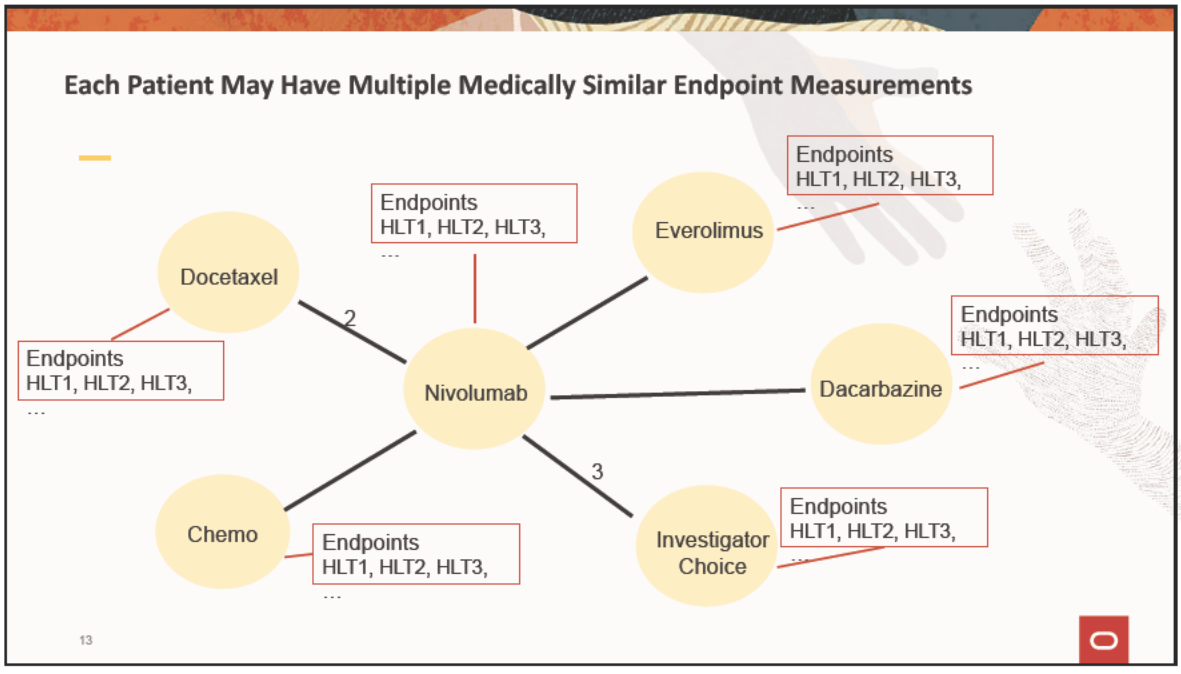

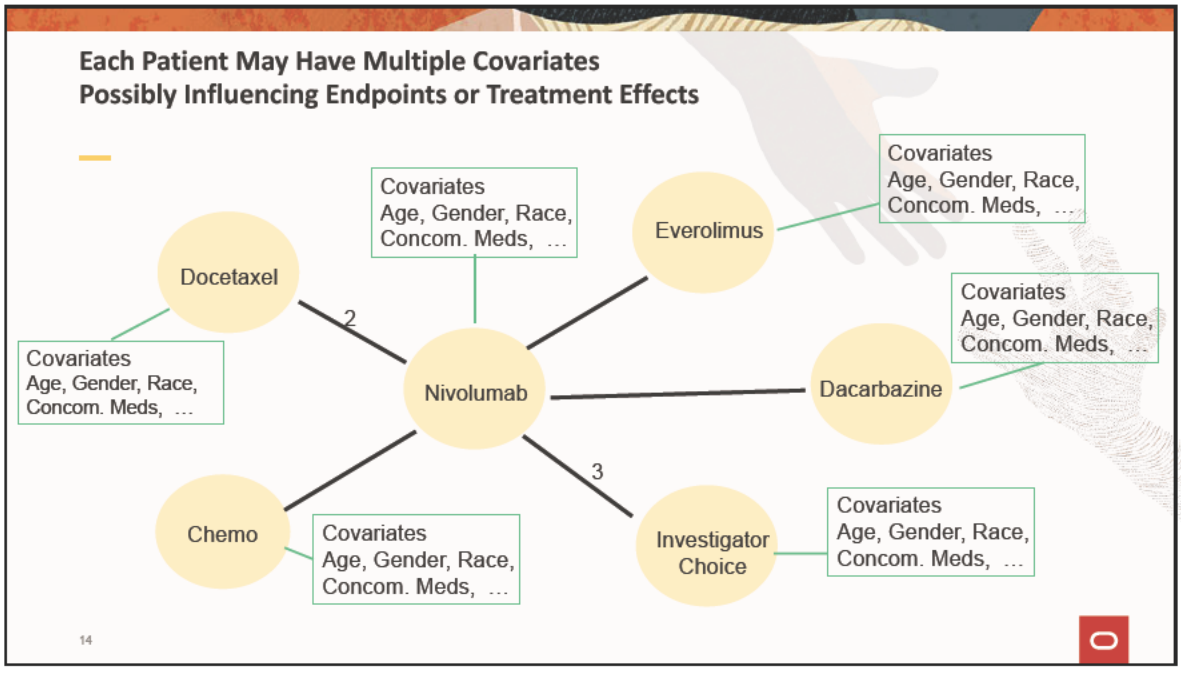

Hierarchical Bayesian Models and Multiple Comparisons

Selecting a "Best" Treatment, Covariate-Subgroup or Endpoint Post-hoc while Accounting for Random Variation

Standard Approach: Require Small p-Values or Wide Confidence Intervals

- When there are very many comparisons, these become too conservative
- True Positives Can Remain Hidden
- Very Large Datasets Can Generate too many False Positives

Hierarchical Bayesian Approach

- Fit Models that "Shrink" the Differences among the Estimates Being Compared
- Estimates typically Move toward the Average of all stand-alone Estimates
- But Error Bars typically become shorter, not longer and Effect strengths are more accurately ranked

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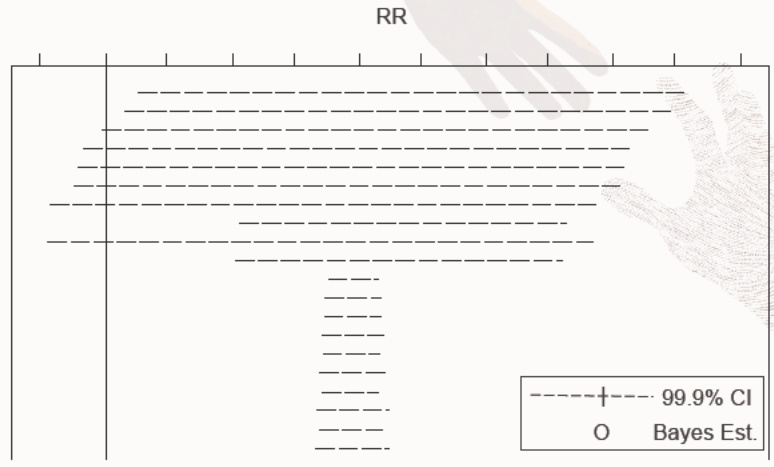
Example of Bayesian "Shrinkage": Spontaneous Report Disproportionalities

Drug-Event Combinations with large ratios of RR = N/E = Observed/Expected counts



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How Bayesian Models Decide How Much to Shrink

Shrinking Estimated Differences Provides Multiple Comparisons Protection

Requires Estimation of Variance Component or Prior Variability

- Compare Data Variation to that Expected by the Null Hypothesis
- Excess Data Variance Allows Estimate of Prior Variability
- Bayesian Calculations Produce the "Shrinkage" Estimates and Error Bars (Individual Values Move Toward Average of All Values)

Next: Two examples of advanced meta-analyses where estimation of excess data variance helped evaluate prediction accuracy

Meta-Regression for Extrapolating Across Biological Systems

DuMouchel W, Harris J (1983) Bayes methods for combining the results of cancer studies in humans and other species, *J Amer Stat Assoc* 78: 293-315 (w Discussion)

Filled cells are those BioSystem – Chemical combinations with data for fitting a dose-response model. Goal is to get better estimates of Human Lung Cancer Risk from Diesel Emissions.

y = log of dose-response slope

$$y_{kl} = \mu + \alpha_k + \gamma_l + \delta_{kl} + \epsilon_{kl},$$

$$Y = X\beta + \delta + \epsilon, \text{ where } \theta = X\beta + \delta$$

$$\sigma \sim \Pi,$$

$$(\beta \mid \sigma) \sim N(b, V),$$

$$(\theta \mid \beta, \sigma) \sim N(X\beta, \sigma^2 I),$$

$$(Y \mid \theta, \beta, \sigma) \sim N(\theta, C).$$

	1 ROOF TAR	2 COKE OVEN	3 GAS ENGINE	4 BaP	5 CIG	6 DIESEL A	7 DIESEL B	8 DIESEL C	9 DIESEL D	10 DIESEL E
LUNG CANCER	●	●			●	?	?	?	?	●
SKIN TUMOR INIT	●	●	●	●	●	●	●		●	
VIRAL TRANSFORM	●	●	●	●	●	●	●	●	●	
MUTAGENESIS -MA	●	●	●		●	●	●	●	●	
MUTAGENESIS +MA	●	●	●		●	●	●	●	●	

18

Biological Effects of Ionizing Radiation [B.E.I.R. Report IV]

from: Health Risks of Radon and other Internally Deposited Alpha-Emitters, 1988, Nat Acadamy Press [Annex 7A, by P Groer and W DuMouchel]

- *Making Better Use of Radium Dial Painters' Data by Combining Studies of Bone Cancer Risk from 4 Isotopes across 4 Biological Systems*

	ISOTOPE			
BIOLOGICAL SYSTEM	Ra-226	Ra-228	Pu-238	Pu-239
Human	●	●	?	?
Beagle Dog (Injection)	●	●		●
Beagle Dog (Inhalation)			●	
Rat			●	●

Plutonium Bone Cancer Risk Estimate:
300 Cancer Deaths per Million Person-Rad
95% Interval = (80, 1100)
5 to 10 times Larger than Risk from Radon

19

Complicated Problems Require Combining Several Shrinkage Calculations

Combining Multiple Studies Requires Estimating Random Study Effects

Multiple Treatment Effects Require a Separate Shrinkage Calculation

Covariate by Treatment Interactions Require More Shrinkage Parameters

Evaluating Multiple Endpoints: Choose Variables that Are Probably Correlated

- Ex: Safety ADRs—Choose Multiple MedDRA Preferred Terms within the Same Higher Level Grouped Term

Rationale for Use of Covariates

When Studies Are Randomized, Why Adjust for Covariates? Won't They all Balance Out Anyway?

- Depending on sample sizes, will not be perfect balance
- If covariates have strong effects, adjustment for them will reduce residual variance and therefore Treatment effect uncertainty
- Less focus on a single pre-specified model for safety analyses than for efficacy analyses

Main Rationale—Treatment by Covariate Interactions

- Estimating Treatment x Covariate interactions in a safety analysis is equivalent to searching for vulnerable subgroups
- MBLR– cross every Covariate with the Treatment effect

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Rationale for EB Model Across End Points

Coping with Fine Granularity of Adverse Event Data or Several Efficacy Measures

- Compare T vs. C on K potential AEs or Efficacy measures that are similar in meaning
- Approach 1—separate analyses of all K measures
  - Small counts lead to non significant comparisons
  - Adjustment for multiple comparisons further reduces sensitivity
- Approach 2—define a single measure as the union or mean of the K measures
  - Significant T vs C difference may be washed out by the pooling
  - Even if significant, little information about the original K measures

Compromise Approach—EB Hierarchical Model

- K individual estimates that "borrow strength" from each other
- Estimate separate vector of coefficients for each response measure
  - But a prior distribution shrinks corresponding coefficients across responses toward each other
  - The amount of shrinkage is controlled by certain prior variances that are also estimated from the data
  - Treatment-Covariate interaction effects, which are *apriori* less likely, are also shrunk toward the null hypothesis value of 0

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Bayesian Shrinkage Models

Statistical Validity of Searching for Extreme Differences

- Most significant adverse event or patient subgroup

Classical Approach to Post-Hoc Interval Estimates

- Maintain centers of CI at observed differences
- Expand widths of every CI
- Expansion is greater the more differences you look at
  - If you look at too many, the CI's are too wide to be useful

Bayesian Approach

- Requires a prior distribution for differences
  - Can estimate it from the multiple observed differences available
- Centers of CI's are "shrunk" toward average or null difference
  - High-variance differences shrink the most
- Widths of CI's usually shrink a little too
  - The more you look at, the better you can model the prior dist.

Safety Study Difficulties

Analysis of safety data versus studies of efficacy

1. Prespecification of end points is rarely possible for safety analyses
2. Sample sizes are typically inadequate for many safety issues
3. The optimal granularity of adverse event definitions is often uncertain
4. Subset analyses across subpopulations can rarely be prespecified
5. Pooled analyses of many studies are necessary to compare product safety profiles
6. Combining safety information from clinical trials and observational data may be necessary

All of the above issues can be thought of as variations on problems of multiple comparisons

Hierarchical Bayesian analysis methods analyze commonalities among the diverse effects Shrinkage techniques help the estimates "borrow strength" from each other

W DuMouchel, "Multivariate Bayesian Logistic Regression for Analysis of Clinical Study Safety Issues", *Statistical Science*, 2012, vol. 27, no. 3, 319-349). The cited pages include three invited discussions of the methodology.

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Robustness to Post-Hoc Selection

Simulation Study of Bayesian Estimation from Article Cited on last Slide

- Draw "true parameters" from the prior distributions 1000 times
- Estimate main and interaction effects each time
  - Get both MBLR and Standard "unshrunk" estimates

Focus on Estimating the "Most Significant" Interaction (Subset Difference)

- 80 Interactions (8 covariates x 10 response events)
- For each simulation, select β_{gk} that has *largest* b_{gk}/se_{gk}
- Compare accuracy of estimates and confidence limits

Note that Bayesian Shrinkage Eliminates Selection Bias!

	SIM.COEF	SD.SIMC	BIAS	RMSE	Z.SCORE	CI.05	CI.95
MBLR	1.7651	0.6094	0.0005	0.2923	-0.0052	0.067	0.056
Stnd	1.7445	0.5981	0.2184	0.4330	0.5794	0.008	0.135

25

Proposal for Enhancement of the Current MBLR Method

Use Network Meta-Analysis to Compare Multiple Interventions Across Studies

Add Estimation of a Study-Level Variance Component (Shrinkage Parameter)

- Allow Study-Level Variables such as *Prospective* vs *Observational*
- Incorporate Extra Uncertainty for Observational Studies

Allow Borrowing Strength Across Multiple Efficacy Endpoints

- Example: Multiple Values of Duration Since Vaccination

Explore Markov Chain Monte Carlo Computational Approach

Recommended Aspects of Analysis Methodology

Graphical Representation of Comparisons with Confidence Intervals

- Covariate selection and interpretation of subset analyses
- Comparison of results from different input assumptions—Sensitivity Analyses

Collaboration with statisticians from FDA and elsewhere during program development

Example pools of studies with their analysis results for training purposes

Not a Replacement for Study analyses, but a uniform methodology for comparing estimates across Treatments, Studies, Endpoints and Subsets

27

From: "Forshee, Richard" [redacted]
To: "Scott, John" [redacted], "Lee, Shiowjen" [redacted]
Subject: RE: William DuMouchel_advanced meta-analysis (005).pptx
Date: Mon, 04 Jan 2021 19:24:12 -0000
Importance: Normal
Inline-Images: image001.png

Thanks, John. I won't pursue this.

Best Regards,
--Rich

From: Scott, John [redacted]
Sent: Monday, January 4, 2021 12:53 PM
To: Forshee, Richard [redacted]; Lee, Shiowjen [redacted]
Subject: RE: William DuMouchel_advanced meta-analysis (005).pptx

Hi Rich,

Thanks for sharing - I really don't see any applicability at all of this to COVID vaccines, possibly to any vaccines.

Best,
John

From: Forshee, Richard [redacted]
Sent: Wednesday, December 23, 2020 2:49 PM
To: Scott, John [redacted]; Lee, Shiowjen [redacted]
Subject: FW: William DuMouchel_advanced meta-analysis (005).pptx

Dear John and Shiowjen,

Ana Szarfman invited me to a lecture by Bill DuMouchel about his implementation of Network Meta-Analysis methods. Ana thinks it could be very helpful for vaccine safety and effectiveness studies, but I have my doubts. The methods are great for certain problems, but I'm not sure they will address our biggest concerns.

I've attached his presentation for your review. Let me know if you'd like to explore it further.

Thanks and happy holidays,
--Rich

From: Szarfman, Ana [redacted]
Sent: Wednesday, December 23, 2020 2:39 PM
To: Forshee, Richard [redacted]
Cc: bill.dumouchel [redacted]
Subject: William DuMouchel_advanced meta-analysis (005).pptx

Great talking with you Richard. Thanks for your participation.

Please refer to the latest version of Bill DuMouchel's presentation.

--Ana

Ana Szarfman, MD, PhD, FAMIA,
Diplomate by the American Board of Pathology in both, Clinical Pathology (1984) and Clinical Informatics (2017), and Fellow of the American Medical Informatics Association (2020)
Medical Officer, Safety Data Mining Developer and Medical Informatics Analyst,
Celebrating nearly a quarter of a century of successful implementation of safety data mining, interactive patient profiles, and other automated analytical tools.
Division of Cardiology and Nephrology, OCHEN, Center for Drug Evaluation and Research, Food and Drug Administration
[redacted]

FDA U.S. FOOD & DRUG ADMINISTRATION

From: "Szarfman, Ana" [redacted]
To: "Forshee, Richard" [redacted]
Cc: "bill.dumouchel [redacted]
Subject: William DuMouchel_advanced meta-analysis (005).pptx
Date: Wed, 23 Dec 2020 19:38:32 +0000
Importance: Normal
Attachments: William_DuMouchel_advanced_meta-analysis_(005).pptx
Inline-Images: image003.png

Great talking with you Richard. Thanks for your participation.

Please refer to the latest version of Bill DuMouchel's presentation.

--Ana

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[redacted]

FDA U.S. FOOD & DRUG ADMINISTRATION

Addressing the need for improving the comprehensiveness and transparency of our decision processes to address the COVID-19 pandemic

Introductory words to the presentation by Dr. William DuMouchel

by

Ana Szarfman, MD, PhD, FAMIA
Division of Cardiology and Nephrology, OCHEN, Center for Drug Evaluation and Research
Food and Drug Administration

The good news is that we now have new potential interventions for containing the pandemic.

These interventions are unprecedented for:

- The compressed time for their development and study
- The large number of potential new interventions (20 +)
- The enormous size of the global population impacted (hundreds of millions of people)

The usual review process for new vaccines and molecular entities at the Agency is designed at assessing a much smaller impacted population.

Hearing the summary options of scientists that helped control in the past much smaller outbreaks would not be sufficient.

- Consistent efficacy and safety signals may remain hidden in disjoined CT applications and observational studies or by analyses that do not properly adjust for multiplicity and small counts across all the data being generated.

We need an automated, interactive analytical process in place that can compare the data of all interventions being continuously collected in CTs and observational studies.

- The automated reanalysis of the data and identification of consistent signals by specific interventions that can be exhaustively examined by experts will provide transparency to the decision making process.

We have been encouraging Bill DuMouchel to implement a methodology that can assess multiple studies and applications at once (i.e., all vaccines for COVID-19, all anticoagulants) where the goal is to compare different treatments that don't all appear in any one study, which is the "Network Meta-Analysis" paradigm.

As Bill DuMouchel explained, this approach will compare subgroups based on several covariates and in addition where there are multiple endpoints measured on each patient.

All this would usually require an analysis of the patient level data in order to fit the Bayesian shrinkage model.

Finally, an advantage of having one program that can do an analysis of patient level data from many studies and many applications at once, is when we need to add or remove some data, we can get a quick re-analysis without having to do a lot of intermediate analyses and redo a meta-analysis based on the new summary statistics.

Bill DuMouchel:

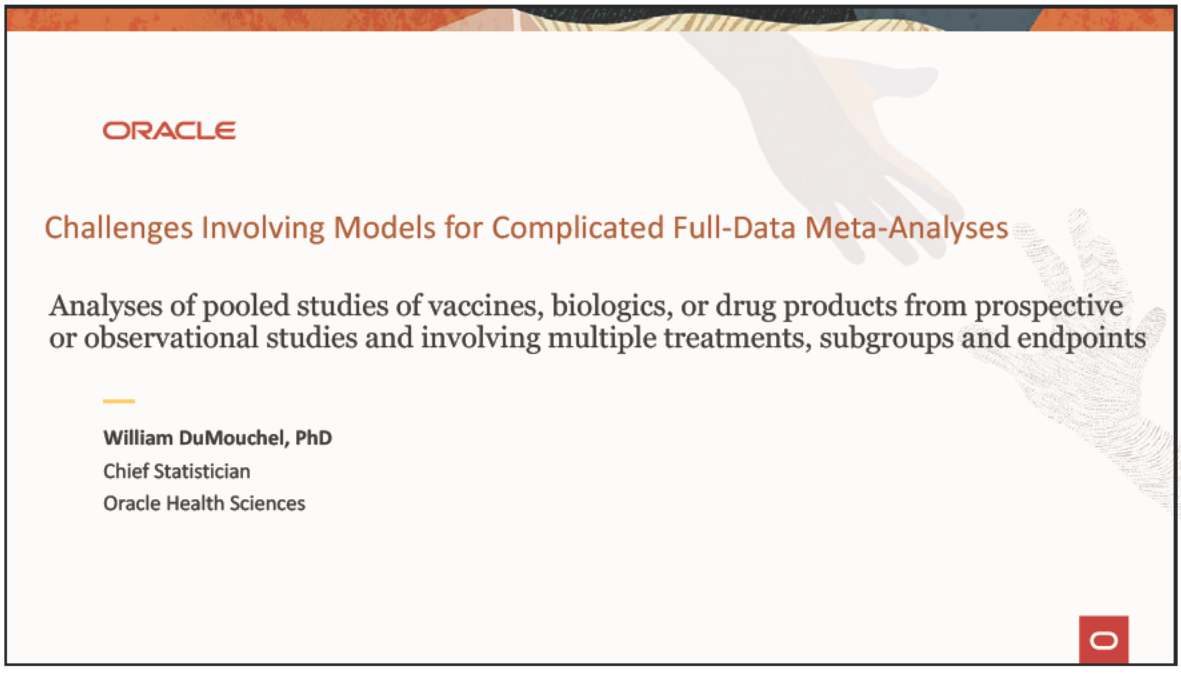
Invented the empirical Bayesian data mining algorithm known as Gamma-Poisson Shrinker (**GPS**) and its successor **MGPS**, which have been applied to the detection of safety signals in databases of spontaneous adverse drug event reports.

He was a senior member of the data mining research group at **AT&T (Bell) Labs** and Chief Statistical Scientist at **BBN Software Products,** and in the faculty of several institutions, including

- University of California at Berkeley,
- University of Michigan,
- MIT,
- Columbia University

Was an associate editor of

- Journal of the American Statistical Association,
- Statistics in Medicine,
- Statistics and Computing, and
- Journal of Computational and Graphical Statistics.



Many New Vaccines and Proposed Treatments for Covid-19 Are Being Tested

Comparisons of Efficacy and Safety Are Complicated

- Multiple Efficacy and Multiple Safety Endpoints
- Within-Study Comparisons of Treatment Arms
- Comparing Subsets Depending on Covariate Values (age, sex, concomitant meds, etc.)
- Combining Studies (Including Prospective and Observational Studies)
  - Studies May Differ by Indication, Populations or Medical History
  - Bayesian Approaches May Give Higher Weight to Certain Study Designs

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Network Meta-Analysis

https://training.cochrane.org/resource/key-concepts-network-meta-analysis-nma

Several Products Need to Be Compared

- Each Study Typically Only Includes Two or a Few Products
- But a Chain of Within-Study Comparisons May Connect Every Pair of Products
- Pooled Studies Can Create Efficient Indirect Comparisons Among Them All
- Allowance Must Be Made for Population Differences Between Studies

Both Observational and Prospective Studies May Be In the Pool

- Bayesian Approaches May Give Higher Weight to Certain Study Designs

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Eight Studies of the ICPI Nivolumab versus other Active Comparators

How to compare the various treatment effects?

Study	ARM 1	Arm 2
37	NIVOLUMAB	INVESTIGATOR CHOICE
17		DOCETAXEL
25		EVEROLIMUS
57		DOCETAXEL
66		DACARBAZINE
26		INVESTIGATOR CHOICE
41		INVESTIGATOR CHOICE
27		CHEMO

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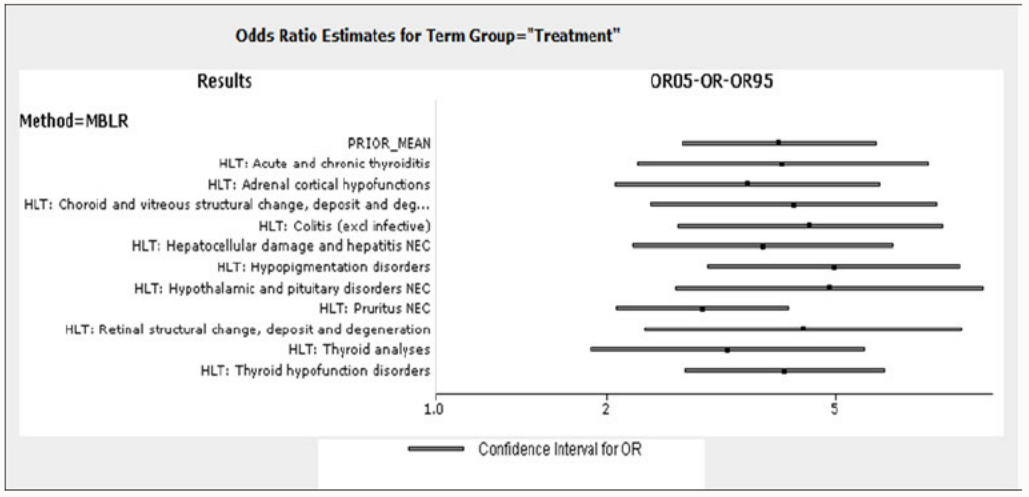
Comparison: Pool All 8 Studies Into 1 Analysis For 11 Safety HLTs



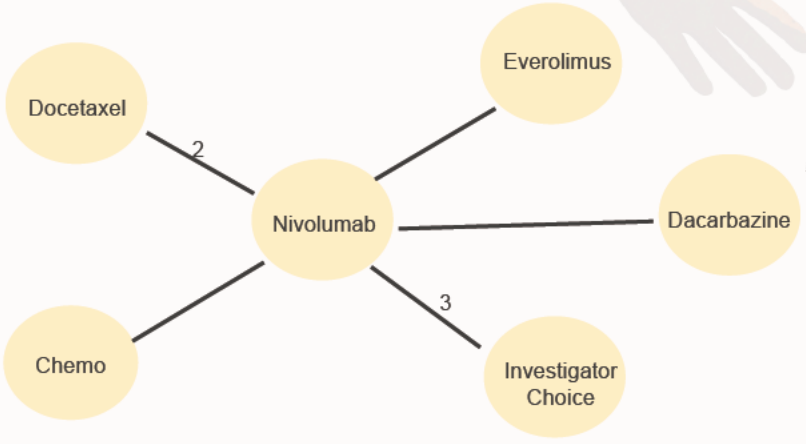
Multivariate Bayesian Logistic Regression (MBLR)

MBLR (also known as BLR) is similar to meta-analysis, but uses the whole data from each study. Adjusts for potentially biasing between-study differences and multiple comparisons. The results of a BLR run may help support any of the following conclusions:

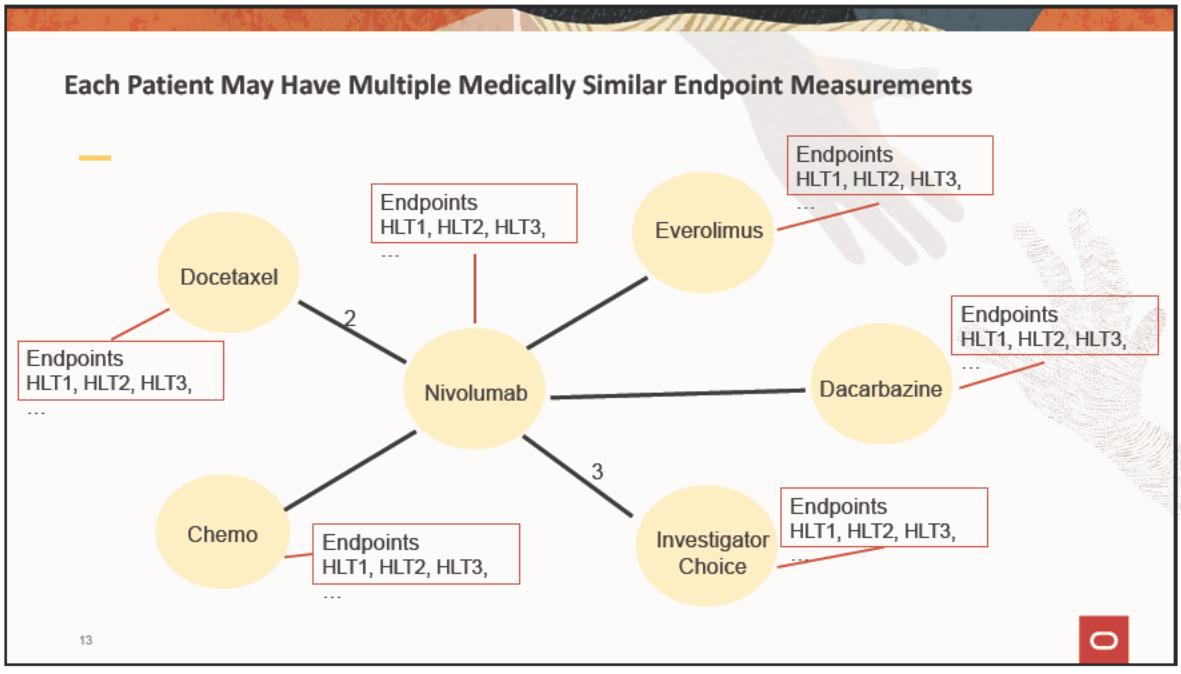
An issue appears related to treatment in a screening analysis, but is not related to treatment when covariates are included in a BLR run, and these covariates show a strong relationship to issue outcome. This may indicate that a randomization error has occurred.

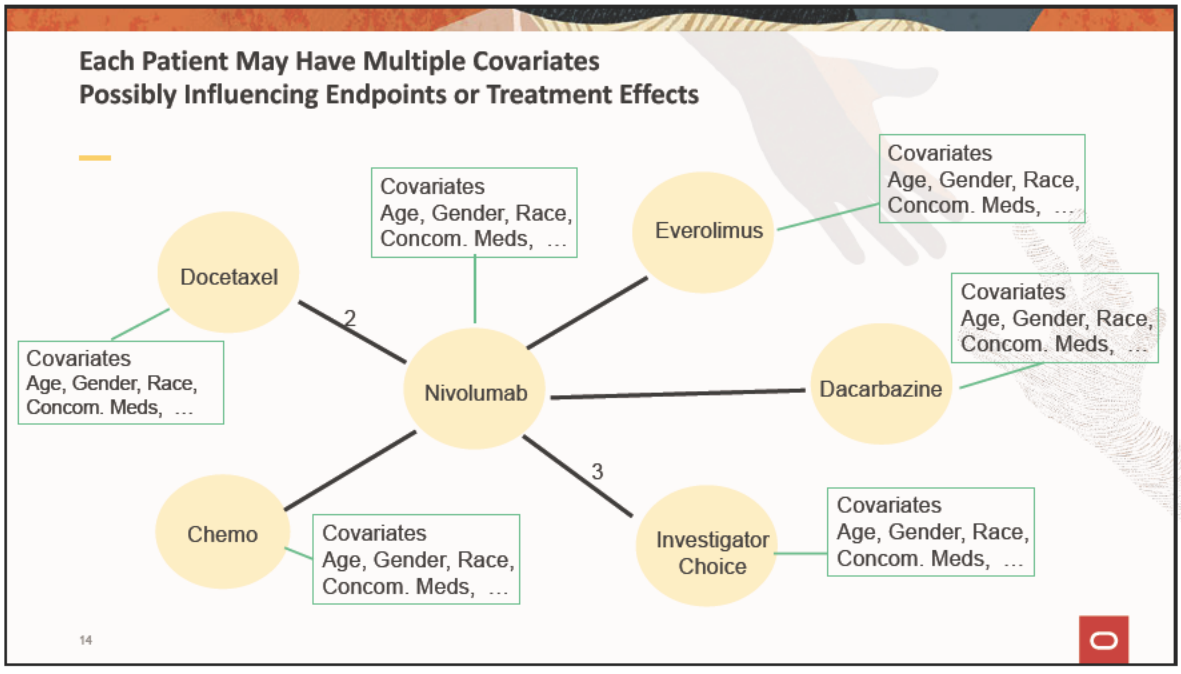
Representing a Pool of Studies as a Network

Lines Connecting Two Arms Represent within-Study Comparisons (numbers=study multiplicity)



12





Hierarchical Bayesian Models and Multiple Comparisons

Selecting a "Best" Treatment, Covariate-Subgroup or Endpoint Post-hoc while Accounting for Random Variation

Standard Approach: Require Small p-Values or Wide Confidence Intervals

- When there are very many comparisons, these become too conservative
- True Positives Can Remain Hidden
- Very Large Datasets Can Generate too many False Positives

Hierarchical Bayesian Approach

- Fit Models that "Shrink" the Differences among the Estimates Being Compared
- Estimates typically Move toward the Average of all stand-alone Estimates
- But Error Bars typically become shorter, not longer and Effect strengths are more accurately ranked

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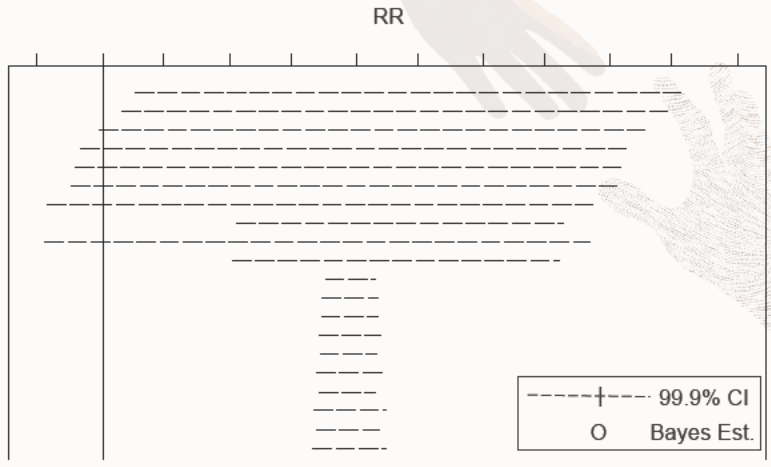
Example of Bayesian "Shrinkage": Spontaneous Report Disproportionalities

Drug-Event Combinations with large ratios of RR = N/E = Observed/Expected counts



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How Bayesian Models Decide How Much to Shrink

Shrinking Estimated Differences Provides Multiple Comparisons Protection

Requires Estimation of Variance Component or Prior Variability

- Compare Data Variation to that Expected by the Null Hypothesis
- Excess Data Variance Allows Estimate of Prior Variability
- Bayesian Calculations Produce the "Shrinkage" Estimates and Error Bars (Individual Values Move Toward Average of All Values)

Next: Two examples of advanced meta-analyses where estimation of excess data variance helped evaluate prediction accuracy

Meta-Regression for Extrapolating Across Biological Systems

DuMouchel W, Harris J (1983) Bayes methods for combining the results of cancer studies in humans and other species, *J Amer Stat Assoc* 78: 293-315 (w Discussion)

Filled cells are those BioSystem – Chemical combinations with data for fitting a dose-response model. Goal is to get better estimates of Human Lung Cancer Risk from Diesel Emissions.

y = log of dose-response slope

$$y_{kl} = \mu + \alpha_k + \gamma_l + \delta_{kl} + \epsilon_{kl},$$

$$Y = X\beta + \delta + \epsilon, \text{ where } \theta = X\beta + \delta$$

$$\sigma \sim \Pi,$$

$$(\beta \mid \sigma) \sim N(b, V),$$

$$(\theta \mid \beta, \sigma) \sim N(X\beta, \sigma^2 I),$$

$$(Y \mid \theta, \beta, \sigma) \sim N(\theta, C).$$

	ROOF TAR	COKE OVEN	GAS ENGINE	BaP	CIG	DIESEL A	DIESEL B	DIESEL C	DIESEL D	DIESEL E
LUNG CANCER	●	●			●	?	?	?	?	●
SKIN TUMOR INIT	●	●	●	●	●	●	●		●	
VIRAL TRANSFORM	●	●	●	●	●	●	●	●	●	
MUTAGENESIS -MA	●	●	●		●	●	●	●	●	
MUTAGENESIS +MA	●	●	●		●	●	●	●	●	
	1	2	3	4	5	6	7	8	9	10

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Biological Effects of Ionizing Radiation [B.E.I.R. Report IV]

from: Health Risks of Radon and other Internally Deposited Alpha-Emitters, 1988, Nat Acadamy Press [Annex 7A, by P Groer and W DuMouchel]

- *Making Better Use of Radium Dial Painters' Data by Combining Studies of Bone Cancer Risk from 4 Isotopes across 4 Biological Systems*

	ISOTOPE			
BIOLOGICAL SYSTEM	Ra-226	Ra-228	Pu-238	Pu-239
Human	●	●	?	?
Beagle Dog (Injection)	●	●		●
Beagle Dog (Inhalation)			●	
Rat			●	●

Plutonium Bone Cancer Risk Estimate:
300 Cancer Deaths per Million Person-Rad
95% Interval = (80, 1100)
5 to 10 times Larger than Risk from Radon

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Complicated Problems Require Combining Several Shrinkage Calculations

Combining Multiple Studies Requires Estimating Random Study Effects

Multiple Treatment Effects Require a Separate Shrinkage Calculation

Covariate by Treatment Interactions Require More Shrinkage Parameters

Evaluating Multiple Endpoints: Choose Variables that Are Probably Correlated

- Ex: Safety ADRs—Choose Multiple MedDRA Preferred Terms within the Same Higher Level Grouped Term

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Rationale for Use of Covariates

When Studies Are Randomized, Why Adjust for Covariates? Won't They all Balance Out Anyway?

- Depending on sample sizes, will not be perfect balance
- If covariates have strong effects, adjustment for them will reduce residual variance and therefore Treatment effect uncertainty
- Less focus on a single pre-specified model for safety analyses than for efficacy analyses

Main Rationale—Treatment by Covariate Interactions

- Estimating Treatment x Covariate interactions in a safety analysis is equivalent to searching for vulnerable subgroups
- MBLR– cross every Covariate with the Treatment effect

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Rationale for EB Model Across End Points

Coping with Fine Granularity of Adverse Event Data or Several Efficacy Measures

- Compare T vs. C on K potential AEs or Efficacy measures that are similar in meaning
- Approach 1—separate analyses of all K measures
  - Small counts lead to non significant comparisons
  - Adjustment for multiple comparisons further reduces sensitivity
- Approach 2—define a single measure as the union or mean of the K measures
  - Significant T vs C difference may be washed out by the pooling
  - Even if significant, little information about the original K measures

Compromise Approach—EB Hierarchical Model

- K individual estimates that "borrow strength" from each other
- Estimate separate vector of coefficients for each response measure
  - But a prior distribution shrinks corresponding coefficients across responses toward each other
  - The amount of shrinkage is controlled by certain prior variances that are also estimated from the data
  - Treatment-Covariate interaction effects, which are *apriori* less likely, are also shrunk toward the null hypothesis value of 0

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Bayesian Shrinkage Models

Statistical Validity of Searching for Extreme Differences

- Most significant adverse event or patient subgroup

Classical Approach to Post-Hoc Interval Estimates

- Maintain centers of CI at observed differences
- Expand widths of every CI
- Expansion is greater the more differences you look at
  - If you look at too many, the CI's are too wide to be useful

Bayesian Approach

- Requires a prior distribution for differences
  - Can estimate it from the multiple observed differences available
- Centers of CI's are "shrunk" toward average or null difference
  - High-variance differences shrink the most
- Widths of CI's usually shrink a little too
  - The more you look at, the better you can model the prior dist.

Safety Study Difficulties

Analysis of safety data versus studies of efficacy

1. Prespecification of end points is rarely possible for safety analyses
2. Sample sizes are typically inadequate for many safety issues
3. The optimal granularity of adverse event definitions is often uncertain
4. Subset analyses across subpopulations can rarely be prespecified
5. Pooled analyses of many studies are necessary to compare product safety profiles
6. Combining safety information from clinical trials and observational data may be necessary

All of the above issues can be thought of as variations on problems of multiple comparisons

Hierarchical Bayesian analysis methods analyze commonalities among the diverse effects Shrinkage techniques help the estimates "borrow strength" from each other

W DuMouchel, "Multivariate Bayesian Logistic Regression for Analysis of Clinical Study Safety Issues", *Statistical Science*, 2012, vol. 27, no. 3, 319-349). The cited pages include three invited discussions of the methodology.

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Robustness to Post-Hoc Selection

Simulation Study of Bayesian Estimation from Article Cited on last Slide

- Draw "true parameters" from the prior distributions 1000 times
- Estimate main and interaction effects each time
  - Get both MBLR and Standard "unshrunk" estimates

Focus on Estimating the "Most Significant" Interaction (Subset Difference)

- 80 Interactions (8 covariates x 10 response events)
- For each simulation, select β_{gk} that has *largest* b_{gk}/se_{gk}
- Compare accuracy of estimates and confidence limits

Note that Bayesian Shrinkage Eliminates Selection Bias!

	SIM.COEF	SD.SIMC	BIAS	RMSE	Z.SCORE	CI.05	CI.95
MBLR	1.7651	0.6094	0.0005	0.2923	-0.0052	0.067	0.056
Stnd	1.7445	0.5981	0.2184	0.4330	0.5794	0.008	0.135

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Proposal for Enhancement of the Current MBLR Method

Use Network Meta-Analysis to Compare Multiple Interventions Across Studies

Add Estimation of a Study-Level Variance Component (Shrinkage Parameter)

- Allow Study-Level Variables such as *Prospective* vs *Observational*
- Incorporate Extra Uncertainty for Observational Studies

Allow Borrowing Strength Across Multiple Efficacy Endpoints

- Example: Multiple Values of Duration Since Vaccination

Explore Markov Chain Monte Carlo Computational Approach

Recommended Aspects of Analysis Methodology

Graphical Representation of Comparisons with Confidence Intervals

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