RESEARCH NOTE

UPDATE Using electronic biology based platform to predict flu vaccine efficacy for 2018/2019 [version 2; referees: 2 approved, 1 approved with reservations]

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Abstract
Flu epidemics and potential pandemics pose great challenges to public health institutions, scientists and vaccine producers. Creating right vaccine composition for different parts of the world is not trivial and has been historically very problematic. This often resulted in decrease in vaccinations and reduced trust in public health officials. To improve future protection of population against flu we urgently need new methods for vaccine efficacy prediction and vaccine virus selection.

Keywords
influenza, vaccine efficacy, H3N2, electronic biology

Open Peer Review

Referee Status: ✓ ✓ ?

	Invited Referees 1	2	3
UPDATE version 2 published 29 May 2018			? report
version 1 published 08 Mar 2018	✓ report	✓ report	✗ report

1 **Daniel R. Perez**, University of Georgia, USA

2 **Abdel-Satar Arafa**, Animal Health Research Institute, Egypt

3 **Timm C. Harder**, Friedrich Loeffler Institute, Germany

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Comments (0)

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Author roles: Paessler S: Conceptualization, Investigation, Writing – Original Draft Preparation, Writing – Review & Editing; **Veljkovic V**: Conceptualization, Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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UPDATE **Updates from Version 1**

Previous version of the article is extended with an assessment of the vaccine efficacy for the 2018 flu season in Australia. These new data suggest the low effectiveness of vaccine during the flu season 2018 in Australia. The results of this new analysis is shown in Figure 2.

See referee reports

Introduction

Vaccine effectiveness (VE) against H3N2 viruses is typically lower than VE against influenza H1N1 and/or influenza B viruses. It's not uncommon to see VE of about 30 percent against H3N2 viruses. Furthermore, during the flu season 2017 in Australia, VE of the seasonal flu vaccine was around 10% resulting in record-high numbers of laboratory-confirmed influenza A infections, hospitalizations and deaths[1]. This situation raised concerns that similar could happen in the United States during the flu season 2017/2018, in which H3N2 viruses were predominant. The concerns were based on assumptions that H3N2 viruses in Australia and US were similar, as the classical phylogeny indicated, and because the vaccine composition was identical one could expect comparable levels of VE. Therefore, predicted VE of the flu vaccine in the USA at the beginning of the flu season was around 10%[2]. This prediction was justified and rationalized using the assumption that H3N2 viruses circulating in Australia in the flu season 2016–17 are similar to viruses in the Northern Hemisphere.

Comparison of Australian H3N2 viruses and viruses isolated in the USA at the beginning of the flu season 2017–18, performed using a novel functional phylogenetic tool, demonstrated significant difference between these two groups of viruses[3]. This new information led us to predict that the flu vaccine in US should work in the season 2017–18 just as well as in 2016–17[3]. Our prediction was recently confirmed in the interim CDC estimation of 2017–18 seasonal influenza VE, published and released in February 2018[1]. Moreover, the risk for a (H3N2) associated medically-attended influenza illness was reduced through vaccination by 59% among children aged 6 months through 8 years[1].

Methods

To improve VE for the flu season 2018, WHO selected in September 2017 the new vaccine virus A/Singapore/INFIMH-16-0019/2016, which is better adapted to H3N2 viruses circulating in the South Hemisphere (See WHO recommendation of vaccine compositions for the Southern Hemisphere). The WHO in February 2018 selected the same virus for the vaccine for the season 2018–19 in the North Hemisphere (See WHO recommendation of vaccine compositions for the Northern Hemisphere).

In order to assess VE against H3N2 viruses for the next flu season 2018–19 in the United States, we analyzed compatibility between new vaccine virus A/Singapore/INFIMH-16-0019/2016 and H3N2 viruses isolated in 2018 in US. This analysis was performed using the informational spectrum method (ISM) based phylogenetic algorithm, the Informational Spectrum-based Phylogenetic Analysis (ISTREE), which we previously used to assess VE for the flu season 2017–18[3]. This algorithm, which is based on the informational hallmark of proteins that determines their biological function, was previously described in more detail[4].

Results and discussion

In Figure 1 the ISM-based phylogenetic tree is presented for hemagglutinin HA1 from 68 H3N2 viruses collected in the United States from January to February 2018 and stored in the publicly open database GISAID. As can be seen in this figure, the H3N2 viruses are grouped into two separate clusters and the novel vaccine virus A/Singapore/INFIMH-16-0019/2016 belongs to the small cluster encompassing only 8.8% of analyzed viruses. Previously we showed that 71% of H3N2 viruses isolated in the beginning of the US season 2017–18 were informationally compatible with vaccine virus[3]. This compatibility resulted in good protection against H3N2 viruses in this season[1]. The low informational compatibility between new vaccine virus and H3N2 viruses circulating in US suggests that VE for the next flu season in US could be very low. Of note is that H3N2 virus A/Hong Kong/4801/2014 in vaccine for the season 2017–2018 better fits US viruses than new vaccine virus A/Singapore/INFIMH-16-0019/2016. This suggests possibility that VE of the current vaccine could be even higher than that for the new vaccine.

Recently, GISAID released data for H3N2 viruses isolated in Australia in January and February, representing precursors of seasonal flu viruses in Australia in 2018 (Dataset 2. Comparison of these viruses with these collected during the flu season 2017 (Dataset 3) served as a base for prediction of VE during the next flu season in Australia. Unexpectedly, the results of this analysis showed that the predicted responsiveness to new vaccine A/Singapore/INFIMH-16-0019/2016 continuously decreases from May 2017 to February 2018 and increases for the previous vaccine A/Hong Kong/4801/2014 (Figure 2). This result suggests the low efficacy of the new vaccine against H3N2 viruses in the next flu season in Australia. Monitoring in next moths of H3N2 viruses in Australia will be necessary for confirmation of this prediction.

We propose the "ISM-based phylogenetic algorithm ISTREE analysis" for rapid and accurate analysis of different influenza A viruses that can be used for VE prediction. This is a first report VE prediction prior to flu season using computational analysis. Our prediction has been recently confirmed through laboratory reports released by CDC. Based on current data, we predict low VE for the season 2018/2019 for Australia and US due to vaccine virus selection.

Dataset 1. Human H3N2 influenza viruses collected in the United States from January to February 2018 (GISAID EpiFlu™ database, accessed February 20, 2018)

http://dx.doi.org/10.5256/f1000research.14140.d196223

Dataset 2. Human H3N2 influenza viruses collected in Australia from January to February 2018 (GISAID EpiFlu™database, accessed May 22, 2018)

http://dx.doi.org/10.5256/f1000research.14140.d204886

Figure 1. The ISM-based phylogenetic tree of HA1 from human H3N2 influenza viruses collected in the United States from January to February 2018. The vaccine viruses are marked with asterisk (green).

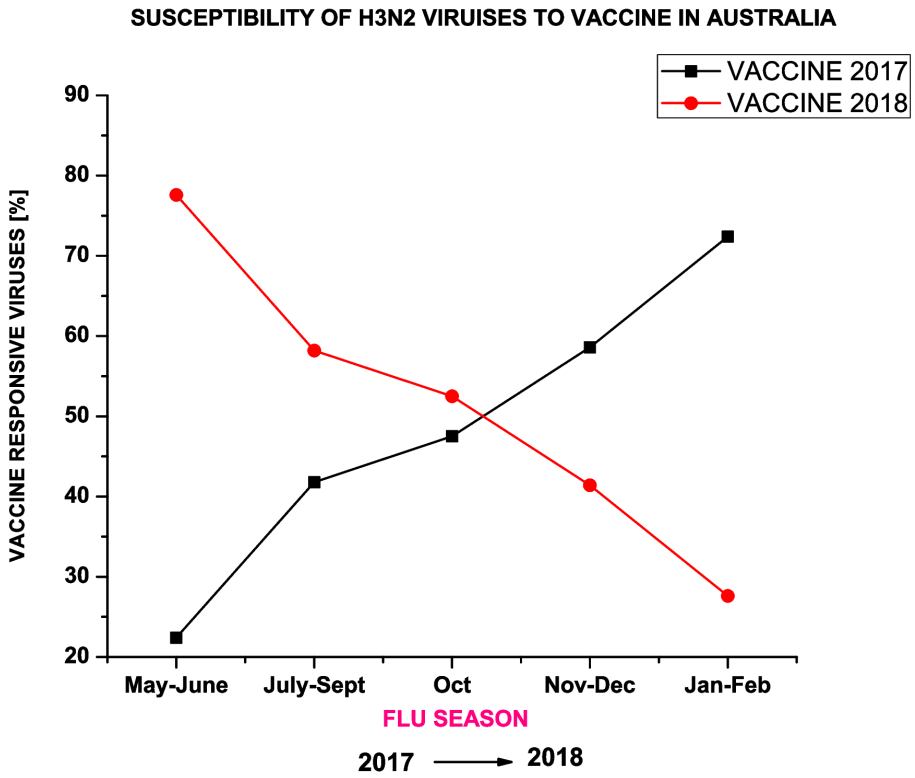

Figure 2. Assessment of the responsiveness to flu vaccines A/Hong Kong/4801/2014 and A/Singapore/INFIMH-16-0019/2016 of H3N2 viruses collected in Australia between May 2017 and February 2018.

Dataset 3. Human H3N2 influenza viruses collected in Australia from May 2017 to December 20178 (GISAID EpiFlu™database, accessed May 22, 2018)

http://dx.doi.org/10.5256/f1000research.14140.d204887

Data availability

Sequence data of the viruses were obtained from the GISAID EpiFlu™ Database. To access the database each individual user should complete the "Registration Form For Individual Users". This form, together with detailed instructions, are available on the website. After submission of the Registration form, the user will receive a password. There are no any other restrictions for the access to GISAID. Conditions of access to, and use of, the GISAID EpiFlu™ Database and Data are defined by the Terms of Use.

Dataset 1: Human H3N2 influenza viruses collected in the United States from January to February 2018 (GISAID EpiFlu™ database, accessed February 20, 2018). 10.5256/f1000research.14140.d196223[5]

Dataset 2: Human H3N2 influenza viruses collected in Australia from January to February 2018 (GISAID EpiFlu™ database, accessed May 22, 2018). 10.5256/f1000research.14140.d204886[6]

Dataset 3: Human H3N2 influenza viruses collected in Australia from May 2017 to December 20178 (GISAID EpiFlu™ database, accessed May 22, 2018). 10.5256/f1000research.14140.d204887[7]

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References

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PubMed Abstract | Publisher Full Text | Free Full Text

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PubMed Abstract | Publisher Full Text

3. Paessler S, Veljkovic V: **Prediction of influenza vaccine effectiveness for**

the influenza season 2017/18 in the US [version 1; referees: 2 approved]. *F1000Res.* 2017; **6**: 2067.
PubMed Abstract | Publisher Full Text | Free Full Text

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Publisher Full Text

5. Paessler S, Veljkovic V: **Dataset 1 in: Using electronic biology based platform to predict flu vaccine efficacy for 2018/2019.** *F1000Research.* 2018.
Data Source

6. Paessler S, Veljkovic V: **Dataset 2 in: Using electronic biology based platform to predict flu vaccine efficacy for 2018/2019.** *F1000Research.* 2018.
Data Source

7. Paessler S, Veljkovic V: **Dataset 3 in: Using electronic biology based platform to predict flu vaccine efficacy for 2018/2019.** *F1000Research.* 2018.
Data Source

Open Peer Review

Current Referee Status: ✔ ✔ ?

Version 2

Referee Report 30 May 2018

doi:10.5256/f1000research.16453.r34493

? **Timm C. Harder**
Federal Research Institute for Animal Health, Friedrich Loeffler Institute, Greifswald, Germany

In their response the authors obviously accepted the necessity of an independent backup of their data. They even mentioned published work that corroborates their previous predictions. It would be much appreciated if they include this link to CDC data in their paper.

Competing Interests: No competing interests were disclosed.

Referee Expertise: Virology, diagnostics, and epidemiology of influenza A

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Version 1

Referee Report 27 March 2018

doi:10.5256/f1000research.15380.r31708

✘ **Timm C. Harder**
Federal Research Institute for Animal Health, Friedrich Loeffler Institute, Greifswald, Germany

The authors provide an analysis of HA sequences of recent H3N2 influenza viruses from the ongoing season using the protein sequence-based clustering algorithm ISTREE. This method has been developed and published by one of the authors several years ago. ISTREE seeks to combine molecular data and provide a clustering with respect to antigenic relatedness of the influenza virus HA. Previous publications provided a retrospective analysis of genetic and antigenic data. Basically, ISTREE is advertised as an alternative to antigenic cartography of influenza viruses using serologic data based on hemagglutination inhibition (HI).

In fact, such algorithms would be of great interest and value in terms of vaccine selection. The prospective statements re appropriate vaccine strains for a future influenza season made by the authors here are quite clear but they are solely based on ISTREE assessments. No flanking/supporting data based on

standard HI assays is provided. Assessing the validity of the ISTREE data therefore is not possible. The data may well turn out to be useful but, as it currently stands, they may be totally misleading as well.

Solid antigenic data will be required to validate the potentially useful ISTREE algorithm.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Referee Expertise: Virology, diagnostics, and epidemiology of influenza A

I have read this submission. I believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 04 Apr 2018

Veljko Veljkovic, Biomed Protection, Galveston, USA, USA

The major Referee's criticism concerning our study is the lack of serology/virology data to support our approach for making valid predictions. This criticism misses the major point of the study, which is to rapidly release predictions based on in silico screening to allow other scientists to look at it as early as possible and to test it through the flu season. However, as we have mentioned in our paper we used this method previously and if the reviewer would have read the paper carefully, he would have realized that our prediction for the flu season 2017/18 was confirmed several months later by CDC using various serological assays. These data can be found in CDC laboratory reports (see the latest CDC report: https://www.cdc.gov/flu/weekly/index.htm) and present a totally independent validation of our approach.

Competing Interests: No competing interest

Referee Report 22 March 2018

doi:10.5256/f1000research.15380.r31709

Abdel-Satar Arafa
National Laboratory for Veterinary Quality Control on Poultry Production, Animal Health Research Institute, Giza, Egypt

The article “Using electronic biology based platform to predict flu vaccine efficacy for 2018/2019” is clearly presented and technically sound enough for publication in F1000Research online. It is well-written and supported by computational well-developed bioinformatics analysis.

I just suggest one observations that should be clarified to enhance the work:
- Fig 1 The ISM tree based analysis is not supported by a tool to predict grouping like bootstrapping method to confirm accurate grouping

Finally, the article is recommended for publication in its present format.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Virology, avian influenza, genetic analysis

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 22 March 2018

doi:10.5256/f1000research.15380.r31711

Daniel R. Perez
Department of Population Health, Poultry Diagnostic and Research Center (PDRC), University of Georgia, Athens, GA, USA

This is a provocative research article based on the authors' previous development of the informational spectrum method that takes into account how virus/receptor interactions modulate the antigenic cross-reactive phenotype of the HA protein of influenza A viruses. Using this method, the authors were able to shed light on the lack of efficacy of the vaccine against the H3 subtype during the 2014/15. They were also able to predict that in the US, the vaccine against the H3 subtype was going to be more efficacious than previously anticipated by the CDC. Later in the 2017/18 season, the CDC confirmed the authors' prediction. In this latest article, the authors predict that the selection of the vaccine candidate for the 2018/19 is less than ideal and suggest that vaccine efficacy against the H3 subtype will be lower than in this past season. This type of work is fascinating and necessary and hopefully it becomes part of the toolkit for the selection of vaccine candidates against influenza.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.