



RESEARCH NOTE

# Prediction of influenza vaccine effectiveness for the influenza season 2017/18 in the US [version 1; referees: 2 approved]

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**Abstract**

Vaccination against seasonal influenza viruses is the most effective way to prevent infection. A key factor in the effectiveness of the seasonal influenza vaccine is its immunological compatibility with the circulating viruses during the season. The high evolutionary rate, antigenic shift and antigenic drift of influenza viruses, represents the main obstacle for correct prediction of the vaccine effectiveness for an upcoming flu season. Conventional structural and phylogenetic approaches for assessment of vaccine effectiveness have had a limited success in prediction of vaccine efficacy in the past. Recently, a novel bioinformatics approach for assessment of effectiveness of seasonal influenza vaccine was proposed. Here, this approach was used for prediction of the vaccine effectiveness for the influenza season 2017/18 in US.

**Open Peer Review**

Referee Status:

	Invited Referees	
	1	2
<b>version 1</b> published 29 Nov 2017	 report	 report

- 1 **Richard A. Bowen**, Colorado State University, USA
- 2 **Igor S. Lukashevich**, University of Louisville, USA

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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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## Introduction

Influenza vaccine effectiveness (VE) can vary from year to year, and among different age and risk groups. An important factor determining VE is the similarity or “match” between the influenza viruses used in the vaccine production and the viruses circulating in the community during the flu season. Evolution of influenza viruses between the time of vaccine selection and the beginning of the flu season (week 40 for the Northern Hemisphere) can seriously hamper VE. For this reason, in most years, the flu vaccine is 50% to 70% effective (<http://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm>; <http://emergency.cdc.gov/HAN/han00374.asp>), and in some years VE is <10%<sup>1</sup>.

Each flu season researchers try to determine the VE adequately, but study results vary due to differences in study design, outcome(s) measured, population studied and the season in which the flu vaccine was studied. These differences make it difficult to compare the results of the several studies. However, in order to overcome these obstacles in determination of influenza VE, CDC established in 2004 the U.S. Flu Vaccine Effectiveness Network, which consists of five study sites across the United States. These study sites determine the VE by measuring the prevention of outpatient medical visits due to laboratory-confirmed influenza. The VE in the US for the period 2004–2015 determined by this Network is available.

In the 2017, flu season in Australia VE was only 10%<sup>2</sup>, which resulted in very high numbers of hospitalization and deaths among vaccinated patients. Most vulnerable was the elderly population of patients (>65 years). This low VE was ascribed to variability of the H3N2 influenza viruses that were dominant in Australia that season<sup>2</sup>.

Our previous phylogenetic analysis of H3N2 influenza viruses, based on a novel bioinformatics algorithm, demonstrated how variability of this virus could seriously affect VE of seasonal influenza vaccines<sup>3</sup>. These results pointed out that close monitoring of evolution and spread of this virus is critical for prevention of a possible pandemic<sup>3</sup>.

In this study, we compared HA1 of H3N2 viruses isolated in US and Australia in the period July/September 2017. Presented results suggest that the flu season 2017/2018 in US will be not similar to that in Australia because the VE will be likely higher. Nevertheless, this situation could be changed if the minor group of viruses, which differ from the vaccine virus, would become dominant. For this reason, close monitoring of the evolution of H3N2 viruses in US during the flu season 2017/2018 is very important.

## Methods

### Datasets

We analyzed the hemagglutinin HA1 region of 251 human H3N2 viruses collected in Australia from July to September 2017 and 113 human H3N2 viruses collected in the US in the same period (non-redundant sequences are given in [Supplementary File 1](#) and [Supplementary File 2](#)) that were stored in publicly open database GISAID (<http://platform.gisaid.org>). The vaccine virus A/Hong Kong/4801/2014 for 2017/2018 also is taken from this database.

### Informational Spectrum Method (ISM)

The ISM is a virtual spectroscopy method for the study of the informational content of the protein primary structure. This method, which is described in detail elsewhere<sup>4</sup>, consists of two basic steps:

- (i) Representation of amino acids in the protein primary structure with their electron-ion interaction potential (EIIP)
- (ii) Conversion of the obtained numerical sequence into informational spectrum (IS) by Fourier transformation.

Frequencies in IS represent information, which is encoded by the protein primary structure, and which determines its interaction with other proteins, DNA/RNA and small molecules.

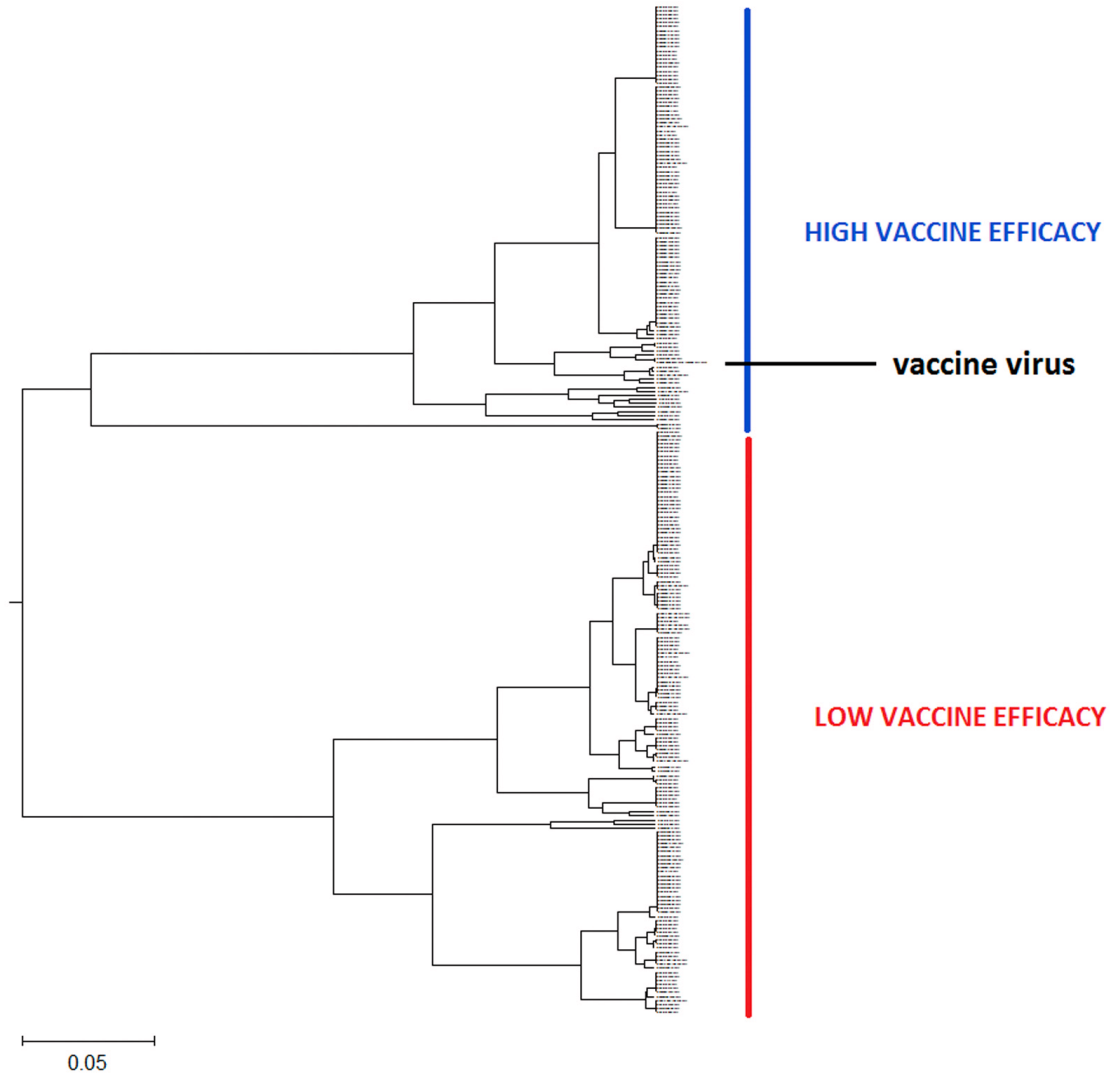
### Phylogenetic analysis

The phylogenetic tree of the HA1 influenza proteins is generated with the ISM-based phylogenetic algorithm ISTREE. This algorithm was previously described in detail<sup>5</sup> (for access to ISTREE we refer the reader to <http://istree.bioprotection.org>). Here, we used the ISM distance measure  $d$  defined on the specific frequency  $F = 0.299$ . This frequency was extracted by ISM as the common frequency component for HA1 of H3N2 influenza viruses<sup>3</sup>. The schematic presentations of calculated phylogenetic trees are given in [Figure 1](#) and [Figure 2](#). These trees in high resolution are given in [Figure S1](#) and [Figure S2](#).

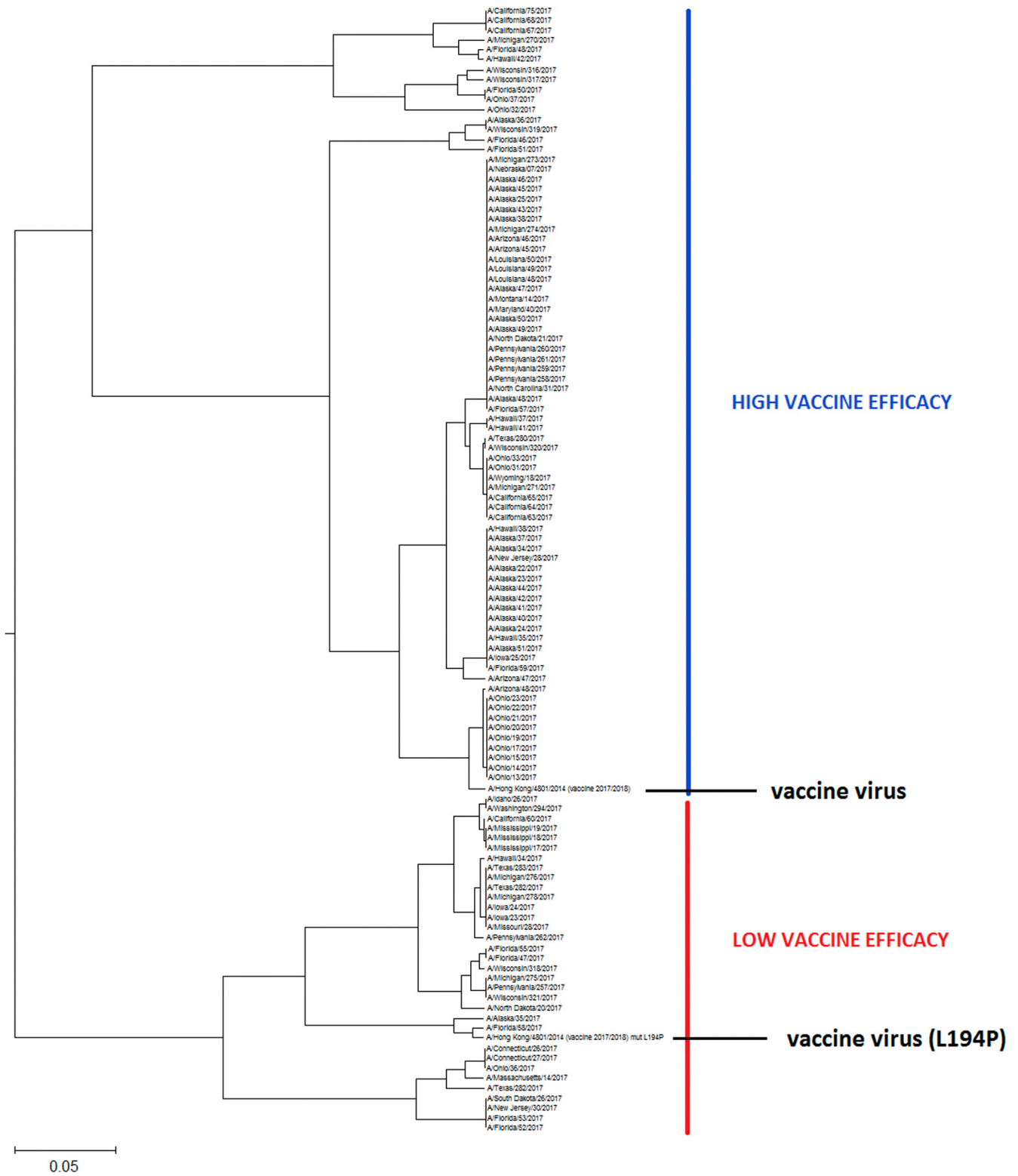
## Results

Previously, it was shown that the IS frequency component  $F(0.299)$  is the informational hallmark of H3N2 viruses, which determines biological properties of HA1 of these influenza viruses<sup>3</sup>. We also showed that informational complementarity represented with  $F(0.299)$  between circulating influenza viruses and the vaccine virus correlate with VE of seasonal flu vaccine<sup>3</sup>.

In [Figure 1](#) and [Figure S1](#), the ISM-based phylogenetic tree is presented for HA1 from H3N2 viruses collected in Australia from July to September 2017 ([Supplementary File 1](#)). We constructed this tree using the amplitude on the frequency  $F(0.299)$  as a distance matrix of the HA1 sequences. In [Figure 2](#) and [Figure S2](#),



**Figure 1.** The schematic presentation of the ISM-based phylogenetic tree of HA1 from human H3N2 influenza viruses collected in Australia from July to September 2017. This tree in high resolution is given in [Figure S1](#).



**Figure 2.** The schematic presentation of the ISM-based phylogenetic tree of the HA1 from human H3N2 influenza viruses collected in US from July to September 2017. This tree in high resolution is given in Figure S2.

we present the phylogenetic tree calculated for HA1 of 113 H3N2 viruses isolated in the US between July and September 2017.

In these phylogenetic trees, we included HA1 from the vaccine virus A/Hong Kong/4801/2014.

## Discussion

Low VE of influenza vaccine in Australia prompts the US and the European health authorities to prepare for the severe influenza season 2017/2018 with suboptimal VE on the Northern hemisphere<sup>2</sup>. On the other hand, there are no data or reported analysis of H3N2 viruses circulating in US in 2017 that would allow to predict the VE for the next flu season. Therefore, we performed the ISM-based phylogenetic analysis of H3N2 viruses representing precursors of seasonal flu viruses in the US. Result of this analysis served as the base for prediction of VE during the flu season 2017/2018 in the US.

As presented in [Figure 1](#) and [Figure 1S](#), all analyzes of Australian viruses generate two clusters and place the vaccine virus into the smaller group. This result suggests that vaccine would not be efficient against majority of Australian H3N2 viruses in the flu season 2017. This conclusion is in accord with reported low VE of influenza vaccine in Australia in 2017 flu season<sup>2</sup>.

As can be seen in [Figure 2](#) and [Figure 2S](#), the US H3N2 viruses also are grouped into two separate clusters, however, in contrast to Australian viruses, the vaccine virus A/Hong Kong/4801/2014 belongs to the largest cluster encompassing 71% of analyzed viruses. This result suggests that VE, at least in the beginning of this flu season will not be suboptimal in the US<sup>2</sup>. As for the prediction of VE in Australia, this could change during the flu season if some of the viruses from the small cluster would emerge. For this reason, continual monitoring of the evolution of H3N2 viruses is necessary.

Recently, lack in effectiveness of influenza vaccine against H3N2 viruses has been attributed to mutation L194P in HA1, which is generated during the egg-based vaccine production process<sup>6</sup>. To test the effect of this mutation on the informational properties of HA1, we included this mutant of the vaccine virus in our analysis. As presented in [Figure 2](#) and [Figure 2S](#), this particular mutation is shifting the vaccine virus from the larger to the small cluster. This suggests that the vaccine carrying this mutation may protect only against smaller fraction of viruses during the flu season 2017/2018 and therefore result in low VE.

In summary, the presented results suggest that (i) the influenza vaccine will be effective against H3N2 viruses in the beginning of the flu season 2017/2018 in the US; (ii) it will be necessary to continue monitoring of evolution of H3N2 viruses during the flu season; and (iii) the vaccine with mutation L194P may have lower VE.

## 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 Terms of Use.

## Competing interests

No competing interests were disclosed.

## Grant information

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

## Supplementary material

**Supplementary File 1:** The names of the human H3N2 influenza viruses collected in Australia from July to September 2017, taken from GISAID (<http://platform.gisaid.org>).

[Click here to access the data.](#)

**Supplementary File 2:** The names of the human H3N2 influenza viruses collected in US from July to September 2017, taken from GISAID (<http://platform.gisaid.org>).

[Click here to access the data.](#)

**Figure S1:** The ISM-based phylogenetic tree of HA1 from human H3N2 influenza viruses collected in Australia from July to September 2017.

[Click here to access the data.](#)

**Figure S2:** The ISM-based phylogenetic tree of the HA1 from human H3N2 influenza viruses collected in US from July to September 2017.

[Click here to access the data.](#)

## References

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# Open Peer Review

Current Referee Status:  

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Version 1

Referee Report 01 February 2018

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**Igor S. Lukashevich**

School of Medicine, Department of Pharmacology and Toxicology, University of Louisville, Louisville, KY, USA

This is very timing report addressing the most important public health issue, prediction of influenza vaccine efficacy. While we certainly are better prepared to flu epidemics in 2018 than in 1918, low efficiency of vaccination in recent flu season in Australia and currently ongoing flu in the US with increasing numbers of severe cases among children and elderly patients raised reasonable questions regarding prediction of correct vaccine formulations. Influenza viruses are moving targets and we have to do better job to predict and manufacture effective vaccines in timing manner. The authors applied innovative Informative Spectrum Method and analysed an extensive collection of influenza isolates from Australia and the US during July – September 2017. Based on this analysis they have predicted sub optional vaccine effectiveness for ongoing flu season in the US. The manuscript is well-written, results are solid and supported by well-developed bioinformatics tools. Discussion is appropriate. The manuscript is recommended for accelerated publication.

**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?**

Yes

**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:** Medical virology, vaccine R&D

**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 18 December 2017

doi:[10.5256/f1000research.14319.r28515](https://doi.org/10.5256/f1000research.14319.r28515)



**Richard A. Bowen**

Department of Biomedical Sciences, Colorado State University, Fort Collins, CO, USA

This is a very interesting report describing a technique for computational assessment of potential vaccine efficacy of H3N2 influenza viruses. It is clear that improved techniques for predicting seasonal influenza virus vaccine efficacy are needed and this could become one of a group of evaluations that yield more precise predictions.

I am not competent to evaluate the mathematical underpinnings of these analyses, but it would seem like some statistical analyses should be invoked; I leave it to the other reviewer(s) and editors to indicate if that is the case. The other comment I would make is that it seems as if a more historical set of evaluations would be valuable - the 2017 season is not yet over and, as the authors repeatedly indicate, things make change in terms of the viruses that come to predominate, especially in the U.S.

Overall, I think this is a valuable contribution to forecasting for influenza virus efficacy and encourage the authors to use additional historical datasets for further evaluate the utility of the technique.

Minor comments:

In the 2017, flu season in Australia VE was only 10% -> In the 2017 flu season in Australia, VE was ..

In this study, we compared HA1 of H3N2: you haven't defined HA1 yet - might say the sequence of hemagglutinin HA1

**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?**

Partly

**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 (including influenza) and animal models

**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.**

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