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Research Article

USE OF COMPUTATIONAL MATRIX ADJUSTMENT TO EVALUATE THE EFFECTIVENESS OF COMMON INFLUENZA VACCINES AGAINST THE EMERGENCE OF DRIFT VARIANTS

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Abstract

Every year the FDA issues a recommendation for the composition of the year's common influenza vaccine for influenzas A and B. The FDA can consistently predict the dominance of a particular strand of influenza virus by taking into account previous years' antigenic characterization percentages. However, the sudden disappearance of dominant antigens and the sudden emergence of drift variants can disrupt this pattern, which questions the effectiveness of that year's vaccine. Basic Local Alignment Search Tool was used to compare the protein sequences for hemagglutinin and neuraminidase between the strands in the vaccine and the dominant viral strands. This study examined the effectiveness of vaccines from 2000 to 2012, focusing on the transitions between the B/Yamagata and B/Victoria lineages and A/New Caledonia and A/California lineages (H1N1). Between the years 2005 and 2006, dominance of the B/Yamagata lineage, represented by B/Shanghai/361/2002, disappeared almost entirely. For the 2005-2006 flu season, the CDC recommended a B/Shanghai/361/2002 vaccine which expressed a 98% identity to the dominant influenza B hemagglutinin sequence and a 97% identity to the dominant neuraminidase sequence. From 2007 to 2008, the A/New Caledonia virus declined to 34% of cases while the A/Solomon Islands/3/2006 virus increased to 66%. The A/New Caledonia/20/99 vaccine effectively expressed a 97% identity to the hemagglutinin sequence of A/Solomon Islands/3/2006 strand and a 98% identity to the neuraminidase sequence. This study demonstrates that from 2000 to 2012, despite drift variants in influenza viruses, the CDC-recommended vaccine effectively matches the hemagglutinin and neuraminidase protein sequences of the dominant viruses.

Key Words: neuraminidase protein sequence; hemagglutinin protein sequence; BLAST; H1N1 influenza; influenza B

Introduction

There are three prevalent types of influenza viruses: A, B, and C. Influenza A can be further characterized by the hemagglutinin (H) and neuraminidase (N) proteins on its surface. Influenza A H1N1 and influenza A H3N2 are the current influenza A viruses that can be found in humans. Hemagglutinin helps the virus bind to cells with sialic acid, which is why common influenza symptoms commonly develop in the respiratory tract (Lee, *et al.*, 2014). Neuraminidase can be located on these influenza antigens and allow the virus to enzymatically break the end of the polysaccharide chains on the cell host (Wang *et al.*, 2012; Wohlbold *et al.*, 2014). Usually, the CDC recommends a trivalent vaccine based on the common viral strands of last year's flu season. Failure to create an effective vaccine could lead to an epidemic, as a substantial population of citizens would not be immunized (Havers *et al.*, 2014; Hwisa *et al.*, 2014).

Gradual mutations in virus genes, especially the ones associated with the HA and NA proteins, are called antigenic drift. Many studies have been conducted to determine the effect of amino acid substitution in viral mutations (Koel *et al.*, 2014). Antigenic shift is the more severe case of mutation in which there is an appreciable change in the genome of the virus, a shift that creates difficulty for vaccinations (Rathore *et al.*, 2014). One particularly notable virus that mutated through antigenic shift is Norovirus (White, 2014; Rooney *et al.*, 2014). In genetic reassortment, two viruses exchange sections of their genomes to produce a significant genome change in both viruses (Steel and Lowen, 2014; Yoon *et al.*, 2014). BLAST, or Basic Local Alignment Search Tool, uses computational matrix adjustment to reposition the protein sequences in such a way that the similarities between two protein sequences can be easily compared. For this reason, it was important to use only the full hemagglutinin or neuraminidase sequence; a partial sequence would not give an accurate percent identity, as part of the sequence would be missing (Shin *et al.*, 2013).

While the use of BLAST to analyze hemagglutinin and neuraminidase protein sequence similarities is not inherently novel, this study extends the results to examine broader viral mutation patterns, in terms of percent dominance, and ultimately make a final evaluation as to

whether or not the yearly vaccination from 2000 to 2012 was indeed effective. The percent dominance is based on the antigenic characterizations released by the CDC every year based on their laboratory analysis. Unlike other studies, which made a distinction between dominant strands and other antigenically equivalent viral strands, this study characterized all antigenically equivalent viral strands as belonging to one lineage in order to more clearly examine the transition between dominant strands (Garcia-barreno *et al.*, 2014; Blitvich *et al.*, 2012; Johansson and Brett, 2008). This study ultimately proved that the vaccines recommended by the CDC between 2000 and 2012 effectively countered the rise of drift variants by closely matching the hemagglutinin and neuraminidase protein sequences.

Materials and Methods

Determining Time Periods of Dominant Viral Strands

First, a report was compiled using the US Influenza Season Summary between the years 2000 and 2012 to determine the transitions between each virus. Every year, the CDC antigenically characterizes different viruses that have been collected in US laboratories. Usually, there was one virus, such as the B/Victoria/2/87 virus in 2010 that appeared in an overwhelming majority of the collected viruses, hence it was considered the dominant strand of that particular year. The majority number ranged from 66% to 100% dominance. This study focused on the transitions between dominance of the B/Yamagata and B/Victoria lineages and A/New Caledonia/20/2009 and A/California/07/2009 lineages (H1N1). The former transition was most evident in the years 2003, 2005, 2007, and 2012. The transition between A/New Caledonia/20/2009 and A/California/07/2009 was more difficult to trace, as there were numerous intermediary viruses, such as A/Solomon Islands/3/2006, that appeared between the disappearance of the A/New Caledonia/20/2009 strand and the appearance of the A/California/07/2009 strand. According to the compilation, the A/New Caledonia/20/99 strand's dominance decreased from 90% in 2006 to 34% in 2007, following the increase of the A/Solomon Islands/3/2006 strand's dominance to 66% in 2007. Having determined the time period of these dominant viral strands, the appropriate vaccine was evaluated to determine whether or not it effectively countered the rise of drift variants such as A/Solomon Islands/3/2006.

Evaluating the Effectiveness of the Yearly Vaccine

First, the US Influenza Season Summary was used to determine all of the viral strands of Influenza A H1N1, Influenza A H2N3, and Influenza B for the years 2000 to 2012 as well as the viruses that composed each year's vaccine. The CDC has a tendency to adapt the yearly vaccine to target last year's dominant strands. Therefore, this study paid particular attention to the years in which a new dominant viral strand emerged. This study did not analyze years in which the dominant viral strand was the same as the vaccination strand, and this study did not analyze any non-dominant strands within a certain year's flu season.

The hemagglutinin and neuraminidase protein sequences for both the virus and the vaccine were compiled, using the information on the NCBI GenBank. The hemagglutinin and neuraminidase protein sequence for each virus is paired with a unique accession code, which can then be used when performing the computational matrix adjustment (Table 1). Only the complete protein sequences were used, as an incomplete or partial sequence could dramatically impact the results. First the hemagglutinin protein sequence for both the virus and the vaccination was compared using BLAST, which utilizes computational matrix adjustment to align the protein sequences with each other. An identity percentage (% identity) expresses the similarity between the two strands with the realignment taken into consideration. An Expect (E) value is also given, which expresses the significance of the match or the amount of background noise. A relatively low E value can be expected during these searches, as many of the CDC-recommended vaccinations have been carefully selected to target specific viral strands. The E value also served as a check to ascertain that the correct protein sequence was selected for BLAST, as the wrong protein sequence would inevitably result in an unusually high E value.

Table 1: A sample of viruses and vaccinations from the 2003-2004 flu season and the accession codes for their neuraminidase sequences.

A/Moscow/10/99 *	ABE73101
A/Fujian/411/2002	AFG72826
A/Panama/2007/99	CAD29965
B/Hong Kong/330/01 *	AAT69450
B/Sichuan/379/99	CAH04538

The asterisks denote the viruses present in the vaccinations. The accession codes are used to look up protein sequences.

The neuraminidase protein sequence was then analyzed for both the new dominant viral strand and the vaccination. The identity % between the two strands demonstrated the effectiveness of the vaccination against the new dominant strand. Once again, the E value was taken into account to determine the significance of the match, and by extension, this study in its entirety.

Results and Discussions

This study examined the effectiveness of vaccines from 2000 to 2012, focusing on the transitions between

dominance of the B/Yamagata and B/Victoria lineages and A/New Caledonia and A/California lineages (H1N1).

Transition between B/Yamagata and B/Victoria lineages

In 2003, the dominant viral strand changed from B/Victoria/2/87 (99% dominance) to B/Yamagata/16/88 (92% dominance) (Fig. 2). The B/Victoria/2/87 lineage was represented by the antigenically similar B/Hong Kong/330/2001 strand, and the B/Yamagata/16/88 lineage was represented by the antigenically similar B/Sichuan/379/99 strand (Socan *et al.*, 2014). In 2003, the vaccine included a B/Hong Kong/330/01 strand, which was recommended to counter the B/Victoria lineage, not the B/Yamagata lineage. However, though there was a sudden re-emergence of the B/Yamagata lineage, the recommended vaccine expressed a 90% identity to the hemagglutinin sequence of B/Yamagata and a 95% lineage to the neuraminidase sequence. The CDC reported that the mismatch during the 2003-2004 flu season led to overall decreased effectiveness.

Likewise, in 2006, dominant influenza B strand shifted from the B/Victoria lineage (77% prior to shift) to the B/Yamagata lineage (98% after shift). BLAST revealed that the yearly vaccine, B/Malaysia/2506/2004, expressed an identity of 92% to the hemagglutinin sequence of the B/Yamagata sequence and an identity of 95% to the neuraminidase sequence of the B/Yamagata sequence (Fig. 1). Overall, this vaccine, though it was not created to specifically target the B/Yamagata lineage, did align closely enough to the dominant vaccine, as evidenced by the lack of epidemics during this flu season.

Similar results were seen when analyzing similar shifts between the two lineages, in 2007 and in 2012 (Fig. 2). In 2007, the dominance shifted from the B/Victoria/02/87 lineage (77% dominance prior to shift) to the B/Yamagata lineage (98% dominance after shift). In this case, the recommended B/Malaysia vaccine expressed 94% identity to the hemagglutinin sequence of the Yamagata lineage and 95% to the neuraminidase sequence. In both sequences, there was a 0.0 E value. In 2012, dominance abruptly shifted from the B/Victoria lineage (52% dominance prior to shift) to the B/Yamagata lineage (63.8% after shift). In comparison to the previous dominance shifts, this shift was not nearly as extreme. In this case, also, the proposed vaccination strand, B/Wisconsin/1/2010, was antigenically similar to the dominant virus. The CDC uses reverse transcription polymerase chain reaction to define vaccine effectiveness (VE) and provide a confidence interval. Based on the CDC website, the acceptable VE lies between 60% to 100% effectiveness, though it is impossible to truly determine vaccine effectiveness without taking into account broader factors such as demography (Andrews *et al.*, 2014). In the scope of this study, though, because the percent similarity between viral strand and dominant viral strand was above 90%, it can be said that the vaccination is effective.

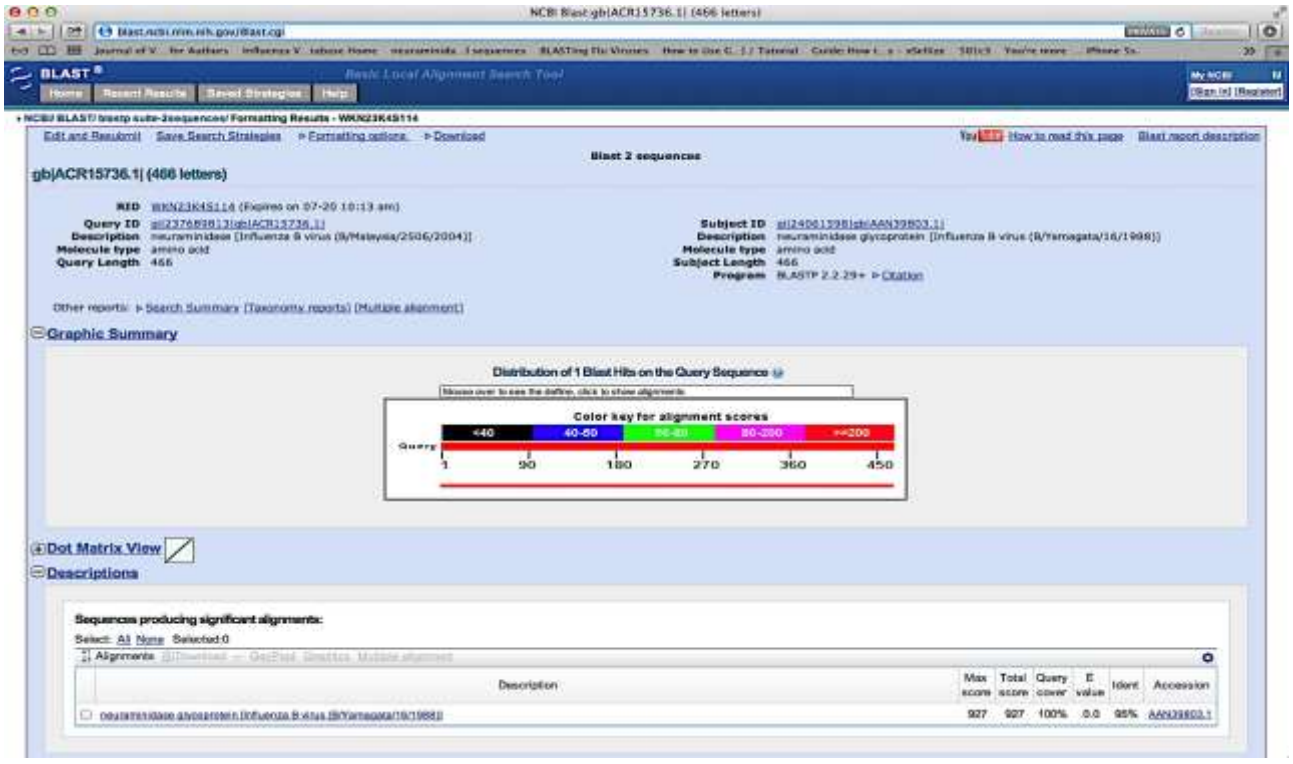

Fig. 1: The use of computational matrix adjustment to reveal the percent identity in neuraminidase protein sequences between B/Yamagata/16/88 and B/Malaysia/2506/2004. The percent identity is shown at the bottom right, next to the E value and Accession code

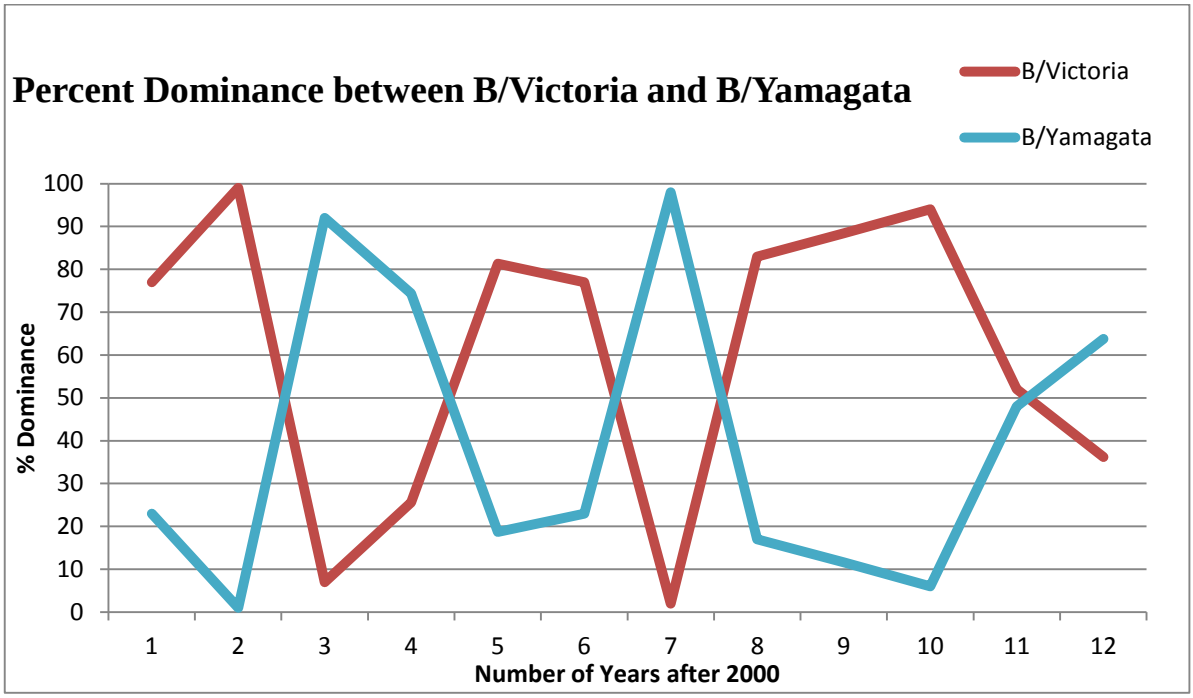

Fig. 2: Percent dominance B/Victoria and B/Yamagata strands. Data shown is rounded to two decimal points.

Transition between A/New Caledonia and A/California lineages (H1N1)

In 2006, the A/New Caledonia/20/99 strand was 90% dominant, but by 2009, it had been replaced by the A/California/7/2009 strand, which was 99.8% dominant. Between these three years, two other deviant strands emerged as well: A/Solomon Islands/3/2006 and A/Brisbane/59/2007, but these strands disappeared or considerably mutated within one flu season cycle. For example, during the 2008 flu season, A/Brisbane/59/2007 exhibited a 100% dominance, but the recommended yearly vaccine actually had a A/Brisbane/59/2007 strand. The next year, 2009, the same strand of A/Brisbane was recommended in the yearly influenza vaccination though the A/California/7/2009 exhibited 99.5% dominance. The Brisbane and California lineages were poorly matched; they expressed 80% identity in terms of hemagglutinin sequence and 81% identity in terms of neuraminidase sequence. This relatively low identity match may have at least partially contributed to the 2009 pandemic in which there were 274,304 hospitalizations and 12,469 deaths in the United States (Kang *et al.*, 2014; Rajao *et al.*, 2014). If the vaccine hemagglutinin and neuraminidase protein sequences do not adequately match the hemagglutinin and neuraminidase sequences of the dominant viral strand, then the vaccine is not considered a "good match" (Skowronski *et al.*, 2014). More research is necessary, however, to determine the impact of broader socio economic patterns on the 2009 pandemic (Kahn *et al.*, 2014).

Evaluation of Yearly Vaccinations between Years 2000 to 2012

In conclusion, this research proved that the yearly vaccinations from 2000 to 2012 effectively counter the emergence of drift variants of common influenza A (H1N1) and B because the vaccine and the dominant viral strands' hemagglutinin and neuraminidase protein sequences are closely aligned. The only exception occurred in the year 2009, in which the vaccination's protein sequence was radically different from the dominant viral strand's protein sequence (Nelson et al., 2014; Wen et al., 2014). Further research would be advised to examine whether matching with neuraminidase or matching with hemagglutinin is more important in regards to vaccination effectiveness; with only a few exceptions, the data demonstrates that a greater degree of matching with neuraminidase protein sequence occurred more frequently than matching with hemagglutinin protein sequence.

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