

**Influenza: Current Events Call for Future Research**

*Nicole M. Bouvier, M.D.*

 Public health emergencies declared in Boston and New York State. Chicago hospitals overwhelmed, turning away ambulances carrying non-critical patients. Emergency departments filled with double the typical number of patients in Broward County, Florida. These are not scenes from the latest Hollywood disaster movie, but rather from news reports detailing a worse-than-usual influenza season across the United States1-4. According to the Centers for Disease Control and Prevention (CDC), the percentage of all health provider visits that were for influenza-like illness (ILI) rose sharply, from 2.8% to 5.6%, through the month of December 2012. By comparison, during the relatively mild 2011-2012 flu season, visits for ILI never exceeded 2.2%5.

 As of the end of December, influenza was widespread in 41 states, and 38 -- mainly in the Northeast, South, Midwest, and Mountain West -- were reporting moderate or high levels of ILI6. In New York State, more than 19,000 flu cases had been reported by mid-January, more than 4 times higher than the 4,400 cases reported during all of last winter7. Nationally, the cumulative influenza hospitalization rate has risen to 8.1 per 100,000 people, which is unusually high for this time of the year5 -- and there are still months to go before flu season officially ends.

 Why is this year’s influenza season so bad? The CDC reports that 76% of viruses tested so far have been of the influenza A(H3N2) subtype5, which has typically predominated in more severe flu seasons8, 9. Why A(H3N2) viruses seem to cause more disease and death than either influenza B or A(H1N1) strains, however, is currently unknown. We do know that the best way to prevent influenza-related morbidity and mortality is to receive the annual trivalent vaccine, comprising antigens from three recent A(H1N1), A(H3N2), and B strains. The good news is that this year’s flu vaccine is a good match for 91% of the circulating influenza viruses tested to date at the CDC5. An early estimate puts this year’s vaccine efficacy at 62%, which is comparable to prior seasons10. However, the flu vaccine offers relatively poor protection when compared to the greater than 90% efficacy of vaccines against diseases like measles, mumps, rubella, polio, diphtheria, human papilloma virus-associated cervical dysplasia, and *H. influenzae* type b meningitis11.

**Toward a Universal Influenza Vaccine**

 Developing long-lasting immunity against influenza viruses is challenging, because they continually undergo *antigenic drift* -- constantly changing their surface proteins in very subtle ways that do not affect how they infect or replicate, but do affect how the human immune system recognizes them in subsequent years. Only small parts of these surface-exposed viral proteins are so structurally or functionally critical that they cannot undergo this drift process; unfortunately, these highly conserved regions also tend to stimulate a weak immune response to virus infection and to current vaccines.

 Dr. Peter Palese, a member of the GVN Scientific Leadership Board, and his colleague, Dr. Adolfo García-Sastre, are influenza researchers at the Mount Sinai School of Medicine, a GVN Center of Excellence. Their laboratories are working to design next-generation flu vaccines that not only mimic these highly conserved regions, but also present them to the immune system in a way that provokes a more robust and durable immune response to a wide variety of influenza viruses. This sort of broadly protective “universal vaccine” would eliminate the need for annual revaccination.

 Although the annual vaccine doesn’t prevent all influenza virus infections, a well-matched vaccine can lessen the severity of those that do occur. A major problem with the flu shot is that most people don’t get it -- last year, 58% of Americans went without, even though annual influenza vaccination is recommended for everyone older than 6 months of age12.

Fortunately, circulating influenza virus strains remain sensitive to the antiviral drugs oseltamivir and zanamivir6. These medications can be given to treat or prevent influenza virus infection in anyone with severe illness or with health conditions that put them at higher risk for influenza complications, such as advancing age, pregnancy, diabetes, heart and lung disease, or immunosuppressing conditions like organ transplant or HIV/AIDS.

 Although we seem to be on track for a harsher than average influenza season, it’s important to keep things in perspective, however. In North America, influenza started circulating widely very early this year, but it may not continue to do so at such high levels for the rest of the winter. Also, the 2011-2012 season was unusually mild, so this season seems all the worse in comparison. Whether this season will eventually rank among the most severe influenza epidemics remains to be seen.

 Clearly, though, every unusually harsh influenza season should remind us that we still have a long way to go in mitigating the impact of these viruses. Lower respiratory tract infections, including influenza, remain the leading cause of death in the developing world13. We need more research to answer critical questions that will help us prevent influenza disease, many of which have been highlighted by this flu season: Why is the influenza A(H3N2) subtype associated with more morbidity and mortality? How can we improve influenza vaccines, so that they are as effective as others against many now-rare diseases? Can we boost immunization rates by making flu vaccines longer lasting, so that they better protect against constantly evolving influenza viruses -- and are thus more cost-effective for low-income countries? At my own institution, the Mount Sinai School of Medicine14, 15, as well as others16, research is underway to develop this sort of “universal vaccine” -- but more work is needed. Because influenza is a worldwide problem, international partnerships, such as those fostered by the Global Virus Network ([www.gvn.org](http://www.gvn.org)), are needed to provide lasting solutions. Only when we understand influenza viruses well enough to prevent their worst complications will we be able make flu seasons like 2012-2013 a thing of the past.

*Dr. Bouvier is a physician specializing in Infectious Diseases and an influenza researcher in the Department of Microbiology at the Mount Sinai School of Medicine, a Global Virus Network Center of Excellence. More information on the Global Virus Network and its Centers of Excellence can be found at* [*www.gvn.org*](file:///C%3A%5CUsers%5Cngrannell%5CAppData%5CLocal%5CMicrosoft%5CWindows%5CTemporary%20Internet%20Files%5CContent.Outlook%5C88ZI9OW2%5Cwww.gvn.org)*.*

REFERENCES

1. Surge in influenza overwhelming Chicago hospitals. United Press International. 2013 [updated January 8; cited 2013 January 9]; Available from: <http://www.upi.com/Health_News/2013/01/08/Surge-in-influenza-overwhelming-Chicago-hospitals/UPI-80491357703966/>.

2. Brochu N. H3N2 virus: Flu season hits early, influenza affecting South Florida. South Florida Sun Sentinel. 2013 [updated January 9; cited 2013 January 9]; Available from: <http://www.wptv.com/dpp/news/world/h3n2-virus-flu-season-hits-early-influenza-affecting-south-florida>.

3. O'Neill N. Flu outbreak leads NY to declare public health emergency. New York Post. 2013 [updated January 12; cited 2013 January 14]; Available from: <http://www.nypost.com/p/news/local/flu_outbreak_leads_ny_to_declare_A38EHI9GClhQ4foeF523OI>.

4. Salsberg B. Flu season has Boston declaring health emergency. Associated Press. 2013 [updated January 9; cited 2013 January 9]; Available from: <http://news.yahoo.com/flu-season-boston-declaring-health-emergency-175058891.html>.

5. Centers for Disease Control and Prevention (CDC). Flu Activity Picks Up Nationwide. 2013 [updated January 4; cited 2013 January 9]; Available from: <http://www.cdc.gov/flu/spotlights/flu-activity-picks-up.htm>.

6. Centers for Disease Control and Prevention (CDC). 2012-2013 Influenza Season Week 52 ending December 29, 2012. FluView: A Weekly Influenza Surveillance Report Prepared by the Influenza Division. 2013 [updated January 4; cited 2013 January 9]; Available from: <http://www.cdc.gov/flu/weekly/>.

7. Evans H. Flu outbreak in 2013 expected to be among the worst in decade, CDC warns. New York Daily News. New York2013 [updated January 8; cited 2013 January 9]; Available from: <http://www.nydailynews.com/life-style/health/flu-outbreak-2013-expected-worst-decade-cdc-warns-article-1.1235178>.

8. Simonsen L, Clarke MJ, Williamson GD, Stroup DF, Arden NH, Schonberger LB. The impact of influenza epidemics on mortality: introducing a severity index. Am J Public Health. 1997 Dec;87(12):1944-50.

9. Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, Fukuda K. Influenza-associated hospitalizations in the United States. JAMA. 2004 Sep 15;292(11):1333-40.

10. Centers for Disease Control and Prevention (CDC). Early Estimates of Seasonal Influenza Vaccine Effectiveness - United States, January 2013. Morbidity and Mortality Weekly Report (MMWR). 2013;62(Early Release):1-4.

11. CDC National Vaccine Program Office. The Effectiveness of Immunizations. [cited 2013 January 11]; Available from: <http://archive.hhs.gov/nvpo/concepts/intro6.htm>.

12. McIntyre AF, Gonzalez-Feliciano AG, Santibanez TA, Bryan LN, Greby SM, Biggers BB, Singleton JA. Flu Vaccination Coverage, United States, 2011-12 Influenza Season. Centers for Disease Control and Prevention (CDC). 2012 [updated October 30; cited 2013 January 14]; Available from: <http://www.cdc.gov/flu/professionals/vaccination/coverage_1112estimates.htm>.

13. World Health Organization (WHO). The top 10 causes of death, Fact sheet N°310. 2011 [updated June; cited 2013 January 14]; Available from: <http://www.who.int/mediacentre/factsheets/fs310/en/index.html>.

14. Krammer F, Pica N, Hai R, Tan GS, Palese P. Hemagglutinin Stalk-Reactive Antibodies Are Boosted following Sequential Infection with Seasonal and Pandemic H1N1 Influenza Virus in Mice. J Virol. 2012 Oct;86(19):10302-7.

15. Pica N, Hai R, Krammer F, Wang TT, Maamary J, Eggink D, Tan GS, Krause JC, Moran T, Stein CR, Banach D, Wrammert J, Belshe RB, Garcia-Sastre A, Palese P. Hemagglutinin stalk antibodies elicited by the 2009 pandemic influenza virus as a mechanism for the extinction of seasonal H1N1 viruses. Proc Natl Acad Sci U S A. 2012 Feb 14;109(7):2573-8.

16. Ekiert DC, Wilson IA. Broadly neutralizing antibodies against influenza virus and prospects for universal therapies. Curr Opin Virol. 2012 Apr;2(2):134-41.