



MEDICAL AND RESEARCH ADVISORY COMMITTEE

(MARAC)

MARAC Statement on Influenza, National Shortage of Oseltamivir (Tamiflu) and the Influenza Vaccine

December 6, 2022 — The Sickle Cell Disease Association of America (SCDAA) Medical and Research Advisory Committee (MARAC) shares the following:

For individuals with sickle cell disease and their caregivers

What is influenza, and why should I worry about it?

Influenza (“flu”) is a contagious viral infection that can cause severe medical problems in anyone. It is worse than a common cold. The problems are potentially bigger for individuals with sickle cell disease. Influenza can trigger sickle cell vaso-occlusive pain or acute chest syndrome. This means that influenza has a high chance of sending you to the hospital and possibly to the intensive care unit with severe breathing problems. If you already have lung problems from asthma or from repeated acute chest syndrome, then influenza is even more likely to cause you to be severely ill.

What can I do?

Prevention Tip #1: MARAC strongly encourages all individuals with sickle cell disease (and their families) to get their flu shot every year. Although the shot might cause symptoms for a day or two (sore injection site, muscle aches and mild fever), these problems are small compared to the potential problems of influenza infection. To find a flu shot near you, visit [vaccines.gov](https://www.vaccines.gov).

Prevention Tip #2: Wash your hands. Stay away from people who are coughing or sneezing or wear a mask around them.

Prevention Tip #3: During flu season, it is very important for individuals with sickle cell disease to take all their medications as prescribed. Hydroxyurea can protect against sickle cell pain or acute chest syndrome. Penicillin can protect against bacterial infection when a person is already weakened by influenza. Asthma medications can keep lungs functioning better.

If you think you have the flu, see your health care team early. If you can be diagnosed with influenza in the first 48 hours of the illness, you will probably be eligible to start a prescription treatment for influenza called oseltamivir (Tamiflu). Oseltamivir can shorten the course of influenza and reduce the risk of severe problems.

For health care providers and policymakers

Sickle cell disease has a high risk for complications and high morbidity from influenza (references 1-6 below). Sickle cell disease has both altered immune response and vulnerability to lung inflammation, triggering hospitalizations for acute chest syndrome, pain or other sickle cell complications. Health care providers should monitor sickle cell patients with influenza for possible acute chest syndrome. Acute chest syndrome is greatly



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feared because it is the leading cause of death in sickle cell disease in the United States. Much of the clinical experience regarding sickle cell and the flu was gained from the 2009 H1N1 influenza but some is more recent, including a CDC report from 2021 (ref 2).

SCDAA MARAC notes that there is a national shortage of the treatment for influenza called oseltamivir (Tamiflu) and stewardship of its use is important. Oseltamivir reduces complications in influenza (Lee 2020, Wiemken 2021). MARAC recommends that sickle cell disease should be included in the list of conditions to prioritize for oseltamivir. Sickle cell disease is a rare disease nationally and might be overlooked in national policy because of its rarity. However, the special needs of sickle cell disease should be acknowledged.

References and highlight points

1. Morrison C, Maurtua-Neumann P, Myint MT, Drury SS, Bégué RE. Pandemic (H1N1) 2009 outbreak at camp for children with hematologic and oncologic conditions. *Emerg Infect Dis.* 2011 Jan;17(1):87-9. doi: 10.3201/eid1701.091499. PMID: 21192861; PMCID: PMC3204616.

An outbreak of influenza A pandemic (H1N1) 2009 occurred among campers and staff at a summer camp attended by children with hematologic and oncologic conditions. **The overall attack rate was 36% and was highest among children and adolescents (43%), persons with cancer (48%), and persons with sickle cell disease (82%).**

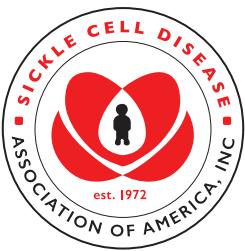
2. Payne AB(1), Adamkiewicz TV(2), Grosse SD(1), Steffens A(3), Shay DK(3), Reed C(3), Schieve LA(1). Influenza vaccination rates and hospitalizations among Medicaid enrollees with and without sickle cell disease, 2009-2015. *Pediatr Blood Cancer.* 2021 Dec;68(12):e29351. doi: 10.1002/pbc.29351.

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BACKGROUND: Persons with sickle cell disease (SCD) face increased risks for pulmonary and infection-related complications. This study examines influenza vaccination coverage and estimates influenza-related morbidity among Medicaid enrollees with and without SCD.

PROCEDURE: Influenza vaccination coverage and hospitalizations related to influenza and pneumonia/acute chest syndrome (ACS) during each influenza season from 2009-2010 to 2014-2015 were assessed among enrollees in the IBM MarketScan® Multi-State Medicaid Database. Enrollees with SCD were identified as enrollees with greater than or equal to three claims listing SCD within a 5-year period during 2003-2017. Vaccinations were identified in outpatient claims. Hospitalizations associated with influenza or pneumonia/ACS were identified using inpatient claims. This study includes a series of cross-sectional assessments by season.



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RESULTS: From 2009-2010 through 2014-2015 seasons, the SCD sample ranged from 5044 to 8651 enrollees; the non-SCD sample ranged from 1,841,756 to 3,796,337 enrollees. Influenza vaccination coverage was higher among enrollees with SCD compared with enrollees without SCD for all seasons (24.5%-33.6% and 18.2%-22.0%, respectively). **Age-standardized rates of influenza-related hospitalizations were 20-42 times higher among SCD enrollees compared with non-SCD enrollees, and ACS/pneumonia hospitalizations were 18-29 times higher. Among enrollees with SCD, influenza-related hospitalization rates were highest among children aged 0-9 years.** Among enrollees without SCD, influenza-related hospitalization rates were highest among adults aged 40-64 years.

CONCLUSIONS: Although vaccine coverage was higher in persons with versus without SCD, efforts to increase influenza coverage further are warranted for this high-risk group, who experienced markedly higher rates of influenza and ACS/pneumonia hospitalizations during each season.

3. Bundy DG(1), Strouse JJ, Casella JF, Miller MR. Burden of influenza-related hospitalizations among children with sickle cell disease. *Pediatrics*. 2010 Feb;125(2):234-43. doi: 10.1542/peds.2009-1465. Epub 2010 Jan 25. Erratum in *Pediatrics*. 2011 May;127(5):1007-9. DOI: 10.1542/peds.2009-1465. PMCID: PMC3283164 PMID: 20100764 [Indexed for MEDLINE]

OBJECTIVE: Children with sickle cell disease (SCD) are considered to be at high risk for complications from influenza infection despite minimal published data that characterize the burden of influenza in this population. Our objectives were to (1) estimate the rate of influenza-related hospitalizations (IRHs) among children with SCD, (2) compare this rate with rates of children with cystic fibrosis (CF) and children with neither SCD nor CF, and (3) explore mechanisms that underlie these potentially preventable hospitalizations.

METHODS: We analyzed hospitalizations from 4 states (California, Florida, Maryland, and New York) across 2 influenza seasons (2003-2004 and 2004-2005) from the Healthcare Cost and Utilization Project State Inpatient Databases. We included hospitalizations with a discharge diagnosis code for influenza in a child <18 years of age. We used census data and disease prevalence estimates to calculate denominators and compare rates of IRH among children with SCD, CF, and neither disease.

RESULTS: There were 7896 pediatric IRHs during the 2 influenza seasons. Of these, 159 (2.0%) included a co-occurring diagnosis of SCD. Annual rates of IRHs were 112 and 2.0 per 10 000 children with and without SCD, respectively, across both seasons. **Children with SCD were hospitalized with influenza at 56 times (95% confidence interval: 48-65) the rate of children without SCD. Children with SCD had approximately double the risk of IRH compared with children with CF (risk ratio: 2.1 [95% confidence interval: 1.5-2.9]).** IRHs among children with SCD were not longer, more costly, or more severe than IRHs among children without SCD; they were also rarely nosocomial and **co-occurred with a diagnosis of asthma in 14% of cases.**

CONCLUSIONS: IRHs are substantially more common among children with SCD than among those without the disease, which supports the potential importance of vigorous influenza vaccination efforts that target children with SCD.



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4. George A(1), Benton J, Pratt J, Kim MO, Kalinyak KA, Kalfa TA, Joiner CH. The impact of the 2009 H1N1 influenza pandemic on pediatric patients with sickle cell disease. *Pediatr Blood Cancer*. 2011 Oct;57(4):648-53. doi: 10.1002/pbc.23030.

BACKGROUND: Respiratory infections are associated with clinically significant illness in patients with sickle cell disease (SCD). The 2009 H1N1 pandemic was perceived as a significant threat to this population.

METHODS: We undertook a chart review of all patients with SCD followed at our institution to identify those with confirmed H1N1 infection. Further chart and laboratory data was collected on affected patients to analyze clinical courses and the factors that correlated with disease severity.

RESULTS: Approximately half of the patients with confirmed H1N1 infection were managed successfully on an outpatient basis with oseltamivir therapy. Among the patients admitted, the most common diagnosis was acute chest syndrome (ACS). Most admitted patients had uncomplicated clinical courses, with a median length of admission of 3 days and no mortality or requirement for mechanical ventilation. **A past history of ACS or reactive airway disease correlated with a higher rate of admission and of ACS incidence during the acute illness.** Chronic transfusion therapy or hydroxyurea therapy with high hemoglobin F levels had a strong inverse correlation with incidence of ACS.

CONCLUSIONS: Our results indicate that in general the impact of the H1N1 influenza pandemic on patients with SCD was mild, but that past clinical history correlated with the severity of illness.

Additionally, effective hydroxyurea therapy and chronic transfusion therapy appeared to be protective against the incidence of ACS. Our results suggest guidelines for the management of patients with SCD during future influenza pandemics as well as during seasonal influenza epidemics.

5. Inusa B, Zuckerman M, Gadong N, Afif M, Arnott S, Heath P, Marais G, Robertson P, Payne H, Wilkey O, Rees DC. Pandemic influenza A (H1N1) virus infections in children with sickle cell disease. *Blood*. 2010 Mar 18;115(11):2329-30. doi: 10.1182/blood-2009-12-260836.

Hospitals in London were contacted to ask for details of children with SCD and confirmed pandemic influenza A (H1N1) presenting between April and August 2009. Eight of 12 hospitals responded, reporting 21 cases among approximately 2200 children with SCD seen in those centers. All had sickle cell anemia (HbSS); H1 and N1 viral RNA was detected in combined nose and throat swab samples from all 21 children. All patients showed a fall in platelet count, with 3 showing trough levels of less than $100 \times 10^9/L$. There was also a highly significant fall in hemoglobin, with a smaller and less significant fall in reticulocyte count; 10 patients had acute chest syndrome (ACS). All 21 children were prescribed oseltamivir, with a median delay from the onset of symptoms of 3.2 days (range, 0-6 days). Seventeen were given broad spectrum antibacterial, and 18 intravenous fluids. Eleven children received blood transfusions, due to the combination of falling hemoglobin and ACS, including both those on regular blood transfusions. Nineteen were admitted to hospital, for a median of 3 days (range, 0-27 days). Four were admitted to high-dependency units and one to pediatric intensive care; one required mechanical ventilation. All patients recovered from the acute illness. Few oseltamivir side effects were reported, with 2 children developing diarrhea and nausea. Based on weekly estimates by the United Kingdom Health Protection Agency, it was calculated that there should have been approximately 40 cases of pandemic influenza A (H1N1) among the 2200 children with SCD in this survey, suggesting that



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50% presented to hospital and 25% developed ACS. This is a high complication rate compared with the estimated hospitalization rate of 7% for the general population.

6. Cohen AL(1), McMorrow M(2), Walaza S(3), Cohen C(3), Tempia S(4), Alexander-Scott M(5), Widdowson MA(6). Potential Impact of Co-Infections and Co-Morbidities Prevalent in Africa on Influenza Severity and Frequency: A Systematic Review. PLoS One. 2015 Jun 11;10(6):e0128580. doi: 10.1371/journal.pone.0128580.

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Infectious diseases and underlying medical conditions common to Africa may affect influenza frequency and severity. We conducted a systematic review of published studies on influenza and the following co-infections or co-morbidities that are prevalent in Africa: dengue, malaria, measles, meningococcus, *Pneumocystis jirovecii* pneumonia (PCP), hemoglobinopathies, and malnutrition. Articles were identified except for influenza and PCP. Very few studies were from Africa. Sickle cell disease, dengue, and measles co-infection were found to increase the severity of influenza disease, though this is based on few studies of dengue and measles and the measles study was of low quality. **The frequency of influenza was increased among patients with sickle cell disease. Influenza infection increased the frequency of meningococcal disease.** Studies on malaria and malnutrition found mixed results. Age-adjusted morbidity and mortality from influenza may be more common in Africa because infections and diseases common in the region lead to more severe outcomes and increase the influenza burden. However, gaps exist in our knowledge about these interactions.

7. Lee JJ, Smith M, Bankhead C, et al. Oseltamivir and influenza-related complications in children: a retrospective cohort in primary care. Eur Respir J 2020; 56: 1902246 [<https://doi.org/10.1183/13993003.02246-2019>]. → **this analysis examined all children with influenza, not limited to sickle cell disease.**

BACKGROUND: Influenza and influenza-like illness (ILI) place considerable burden on healthcare systems, especially during influenza epidemics and pandemics. During the 2009/10 H1N1 influenza pandemic, UK national guidelines recommended antiviral medications for patients presenting within 72 h of ILI onset. However, it is not clear whether antiviral treatment was associated with reductions in influenza-related complications.

METHODS: Our study population consisted of a retrospective cohort of children aged <17 years who presented with influenza/ILI at UK primary care practices contributing to the Clinical Practice Research Datalink during the 2009/10 pandemic. We used doubly robust inverse-probability weighted propensity scores and physician prior prescribing instrumental variable methods to estimate the causal effect of oseltamivir prescribing on influenza-related complications. Secondary outcomes were complications requiring intervention, pneumonia, pneumonia or hospitalisation, influenza-related hospitalisation and all cause hospitalisation.



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RESULTS: We included 16162 children, of whom 4028 (24.9%) were prescribed oseltamivir, and 753 (4.7%) had recorded complications. **Under propensity score analyses oseltamivir prescriptions were associated with reduced influenza-related complications (risk difference (RD) -0.015, 95% CI -0.022--0.008), complications requiring further intervention, pneumonia, pneumonia or hospitalisation and influenza-related hospitalisation**, but not all-cause hospitalisation. Adjusted instrumental variable analyses estimated reduced influenza-related complications (RD -0.032, 95% CI -0.051--0.013), pneumonia or hospitalisation, all-cause and influenza related hospitalisations.

CONCLUSIONS: Based on causal inference analyses of observational data, oseltamivir treatment in children with influenza/ILI was associated with a small but statistically significant reduction in influenza-related complications during an influenza pandemic.

8. Influenza Antiviral Medications: Summary for Clinicians. Information for the 2022-2023 influenza season. Centers for Disease Control and Prevention. <https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm> accessed December 3, 2022.

Priority Groups for Antiviral Treatment of Influenza

Antiviral treatment is recommended as soon as possible for any patient with suspected or confirmed influenza who:

- is hospitalized;
- has severe, complicated, or progressive illness; or
- **is at higher risk for influenza complications.**

Decisions about starting antiviral treatment for patients with suspected influenza should not wait for laboratory confirmation of influenza virus infection. Empiric antiviral treatment should be started as soon as possible in the above priority groups.

Clinicians can consider early empiric antiviral treatment of non-high-risk outpatients with suspected influenza [e.g., influenza-like illness (fever with either cough or sore throat)] based upon clinical judgement, if treatment can be initiated within 48 hours of illness onset.

Antiviral Drug Options

- **For hospitalized patients with suspected or confirmed influenza, initiation of antiviral treatment with oral or enterically-administered oseltamivir is recommended as soon as possible.**
- For outpatients with complications or progressive disease and suspected or confirmed influenza (e.g., pneumonia, or exacerbation of **underlying chronic medical conditions**), initiation of antiviral treatment with oral oseltamivir is recommended as soon as possible.
- For outpatients with suspected or confirmed uncomplicated influenza, oral oseltamivir, inhaled zanamivir, intravenous peramivir, or oral baloxavir may be used for treatment, depending upon approved age groups and contraindications. In one randomized controlled trial, baloxavir had greater efficacy than oseltamivir in adolescents and adults with influenza B virus infection (Ison, 2020).



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9. Wiemken, T. L., Furmanek, S. P., Carrico, R. M., Peyrani, P., Hoft, D., Fry, A. M., & Ramirez, J. A. (2021). Effectiveness of oseltamivir treatment on clinical failure in hospitalized patients with lower respiratory tract infection. *BMC Infectious Diseases*, 21(1), 1-7.

BACKGROUND: Influenza is associated with excess morbidity and mortality of individuals each year. Few therapies exist for treatment of influenza infection, and each require initiation as early as possible in the course of infection, making efficacy difficult to estimate in the hospitalized patient with lower respiratory tract infection. Using causal machine learning methods, we re-analyze data from a randomized trial of oseltamivir versus standard of care aimed at reducing clinical failure in hospitalized patients with lower respiratory tract infection during the influenza season.

METHODS: This was a secondary analysis of the Rapid Empiric Treatment with Oseltamivir Study (RETOs). Conditional average treatment effects (CATE) and 95% confidence intervals were computed from causal forest including 85 clinical and demographic variables. RETOS was a multicenter, randomized, unblinded, trial of adult patients hospitalized with lower respiratory tract infections in Kentucky from 2009 through 2012. Adult hospitalized patients with lower respiratory tract infection were randomized to standard of care or standard of care plus oseltamivir as early as possible after hospital admission but within 24 h of enrollment. After randomization, oseltamivir was initiated in the treatment arm per package insert. The primary outcome was clinical failure, a composite measure including failure to reach clinical improvement within 7 days, transfer to intensive care 24 h after admission, or rehospitalization or death within 30 days.

RESULTS: A total of 691 hospitalized patients with lower respiratory tract infections were included in the study. The only subgroup of patients with a statistically significant CATE was those with laboratory-confirmed influenza infection with a **26% lower risk of clinical failure when treated with oseltamivir (95% CI 3.2–48.0%).**

CONCLUSIONS: This study suggests that addition of oseltamivir to standard of care may decrease clinical failure in hospitalized patients with influenza-associated lower respiratory tract infection versus standard of care alone. These results are supportive of current recommendations to initiate antiviral treatment in hospitalized patients with confirmed or suspected influenza as soon as possible after admission.