

## INFLUENZA VACCINATION AND TREATMENT OVERVIEW

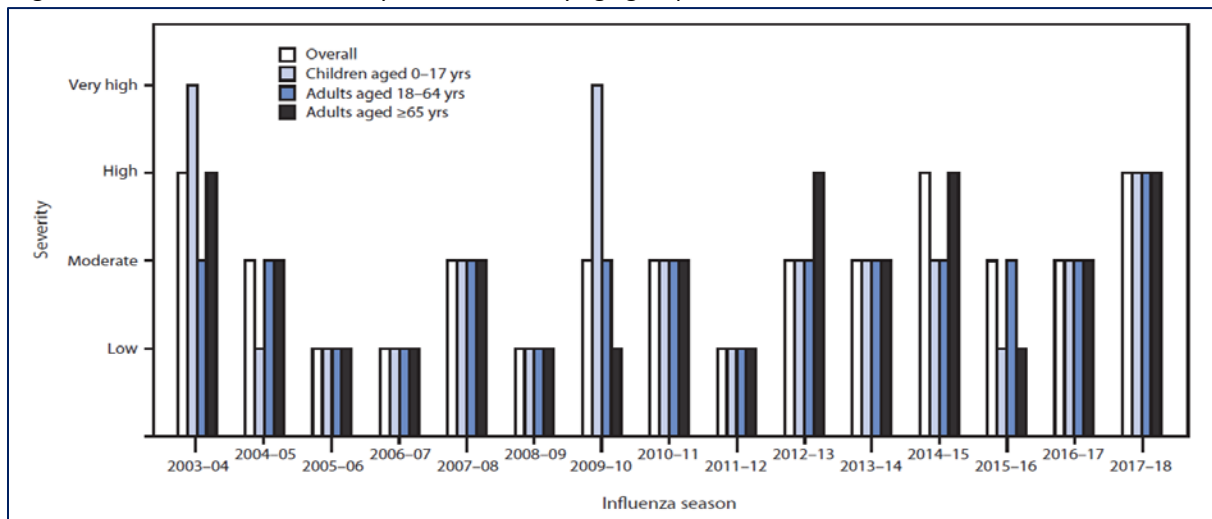
### BACKGROUND

Influenza (Flu) is a contagious respiratory illness that can cause mild to severe illness, and can even lead to death. While infection from the influenza virus can occur at any time, influenza viruses typically circulate in the United States between late fall through early spring. Although anyone is susceptible to the flu, certain individuals considered high risk of developing serious flu-related complications include individuals 65 years and older, those with certain chronic medical conditions, pregnant women, and children younger than 5 years.<sup>1</sup>

The 2017-2018 flu season was a high severity season, with peak activity during January and February 2018. Unusually high levels of outpatient influenza-like-illnesses (ILI), hospitalization rates, and influenza-associated deaths occurred.

- Influenza-like-illness peaked at 7.5%, which was the highest percentage since 2009 pandemic.
- An estimated 48.8 million illnesses, 959,000 hospitalizations and 79,400 deaths from the flu during the 2017-2018 season occurred.<sup>2</sup>
- It was the first all-age high severity season since surveillance started in 2003-2004 season. (Figure 1)

Figure 1: Influenza season severity classification, by age group and season<sup>3</sup>



<sup>1</sup>Centers for Disease Control and Prevention: Key Facts About Influenza. <https://www.cdc.gov/flu/keyfacts.htm>

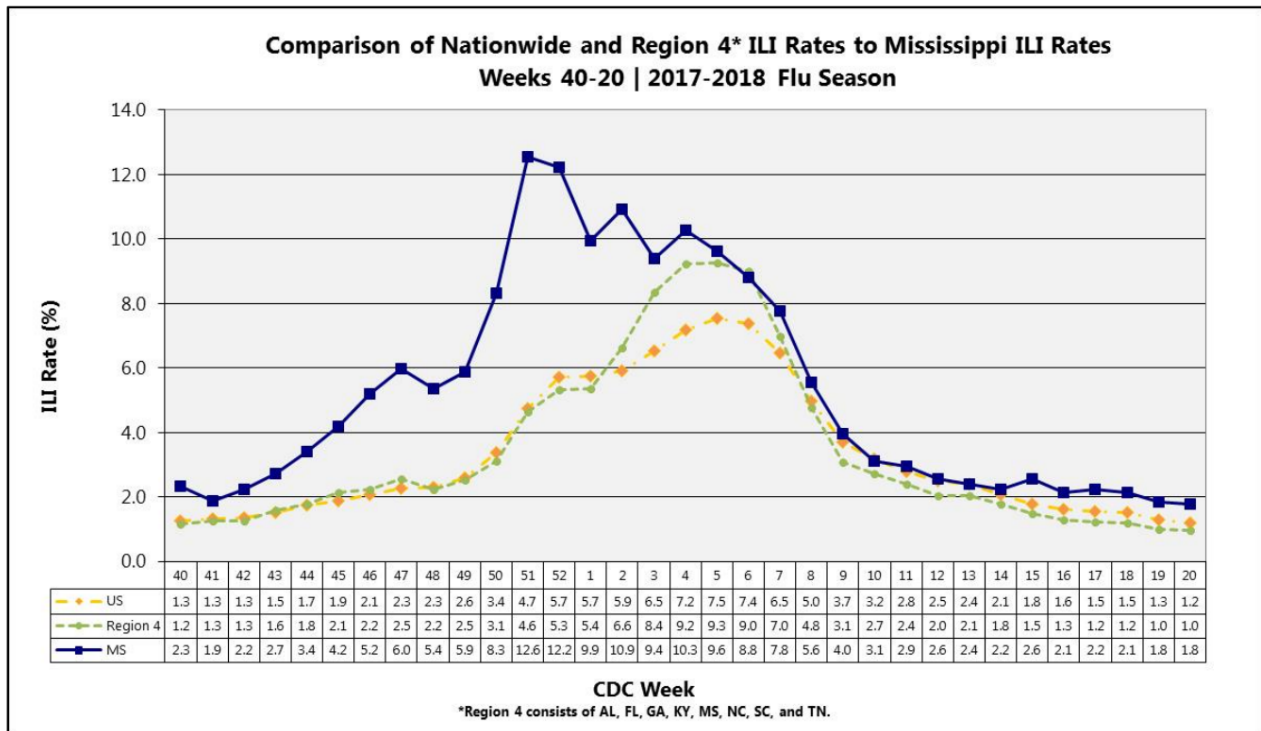
<sup>2</sup>Centers for Disease Control and Prevention: Estimated Influenza Illnesses, Medical visits, Hospitalizations, and Deaths in the United States — 2017–2018 influenza season. <https://www.cdc.gov/flu/about/burden/estimates.htm>

<sup>3</sup>Garten R, Blanton L, Elal AI, et al. Update: Influenza Activity in the United States During the 2017–18 Season and Composition of the 2018–19 Influenza Vaccine. MMWR Morb Mortal Wkly Rep 2018;67:634–642.

DOI: <http://dx.doi.org/10.15585/mmwr.mm6722a4>

Comparing the rates of ILI in Mississippi for the 2017-2018 flu season to nationwide and regional rates, Mississippi consistently had higher rates. (Figure 2)

Figure 2: Mississippi Department of Health Comparison of ILI Rates<sup>4</sup>



US and Region 4 ILI rates from the Centers for Disease Control and Prevention: <http://www.cdc.gov/flu/weekly/>.

Preventing infection is vital with flu vaccination serving as the primary source of flu prevention. Vaccination has been shown to reduce the morbidity and mortality associated with influenza. Annual vaccination is recommended by the Centers for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP) for all persons aged 6 months and older who do not have contraindications.<sup>5</sup> The flu vaccine causes antibodies to develop in the body approximately 2 weeks after vaccination. Protection from the flu vaccine is thought to persist for approximately 6 months and declines over time due to waning antibodies and changes in the circulating influenza virus from year to year. ACIP does not recommend more than one dose of

<sup>4</sup> Mississippi Department of Health: 2017-2018 Influenza Surveillance Report Week 20; May 13-19, 2018; [http://www.msdh.state.ms.us/msdhsite/\\_static/resources/7801.pdf](http://www.msdh.state.ms.us/msdhsite/_static/resources/7801.pdf)

<sup>5</sup> Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2018–19 Influenza Season. MMWR Morb Mortal Wkly Rep 2018;67(No. RR-3):1–20. DOI: <http://dx.doi.org/10.15585/mmwr.rr6703a1>

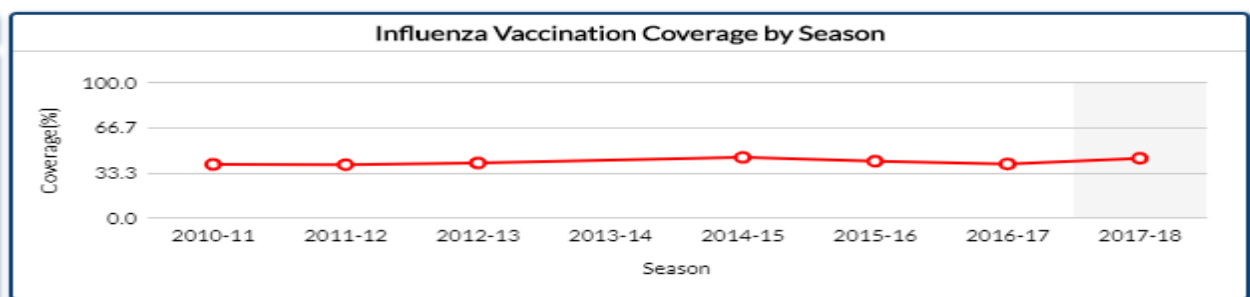
influenza vaccine each season, except for certain children age 6 months through 8 years for whom two doses are recommended.<sup>6,7</sup>

According to the CDC, vaccination coverage for the general population in the US aged 6 months or older in the 2017-2018 season was 41.7%. Mississippi was above the national average and higher than any surrounding states for flu vaccination coverage as shown below:

- Mississippi 44.3%
- Louisiana with 35.3%,
- Tennessee with 36.4%,
- Arkansas with 41.7%,
- Alabama 42.4%

The 2017-2018 vaccination coverage rates for MS was the second highest reported coverage rate for MS since the 2010-2011 season, with only the 2014-2015 season vaccination coverage rate being higher at 44.9%.<sup>8</sup> (Figure 2)

Figure 2: CDC influenza vaccination coverage by season for Mississippi



When patients with the flu are treated within 48 hours of becoming sick, antiviral drugs can reduce symptoms and duration of the illness. Antivirals have been shown to lessen symptoms and shorten illness duration by 1 to 2 days and can prevent serious flu complications such as pneumonia. Antiviral medications can be grouped into 2 classes, neuraminidase inhibitors which have activity against both influenza A and B viruses and adamantanes which are active against influenza A viruses only. In addition to only being active against influenza A viruses, high levels of resistance to adamantanes have been noted in past flu seasons and thus are not recommended for antiviral treatment or chemoprophylaxis of currently circulating influenza viruses.<sup>9</sup>

<sup>6</sup> Immunization Action Coalition. [http://www.immunize.org/askexperts/experts\\_inf.asp](http://www.immunize.org/askexperts/experts_inf.asp)

<sup>7</sup> Centers for Disease Control and Prevention: Children & Influenza. <https://www.cdc.gov/flu/protect/children.htm>

<sup>8</sup> Centers for Disease Control and Prevention: 2010-11 through 2017-18 Influenza Seasons Vaccination Coverage Trend Report. <https://www.cdc.gov/flu/fluview/reportsthtml/trends/index.html>

<sup>9</sup> Centers for Disease Control and Prevention: Influenza Antiviral Medications: Summary for Clinicians. <https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm>

At this time antiviral resistance to neuraminidase inhibitors is currently low. These agents were recommended for use in the United States during the 2017-2018 influenza season. The oral antiviral oseltamivir (Tamiflu®) is FDA indicated for the treatment of acute, uncomplicated influenza in patients 2 weeks of age and older who have been symptomatic for no more than 2 days.<sup>10</sup> Although it is also FDA indicated for prophylaxis of influenza in patients 1 year and older, the CDC and American Academy of Pediatrics (AAP) recommend prophylactic therapy in children as young as 3 months of age.<sup>11</sup> Treatment dosing is typically twice daily for 5 days, while prophylactic dosing is typically once daily for 10 days. Treatment efficacy was established in 2 placebo-controlled double-blind clinical trials containing 1355 subjects, 849 of which were determined to be influenza-infected. In both studies, there was a 1.3 day reduction in the median time to improvement in influenza-infected subjects receiving Tamiflu® compared to subjects receiving placebo. Currently in Mississippi Medicaid, beneficiaries may receive up to 2 prescriptions for oseltamivir each year.

On October 24, 2018 the FDA approved the first new antiviral for flu in nearly 20 years. Xofluza® (baloxavir marboxil) is indicated for the treatment of acute, uncomplicated influenza in patients 12 years and older who have been symptomatic for no more than 48 hours. Xofluza's mechanism of action is slightly different from previously approved anti-flu agents by working earlier in the viral replication process. Xofluza, taken as a single oral dose, should be administered within 48 hours of symptom onset and may be taken with or without food. The safety and efficacy of Xofluza was demonstrated in two randomized controlled clinical trials of 1,832 patients where participants were assigned to receive either Xofluza, a placebo, or another antiviral flu treatment within 48 hours of experiencing flu symptoms. In both trials, patients treated with Xofluza had a shorter time to alleviation of symptoms compared with patients who took the placebo. In the second trial, there was no difference in the time to alleviation of symptoms between subjects who received Xofluza and those who received the other flu treatment.<sup>12</sup>

According to published pricing information available November 2018, wholesale acquisition cost is approximately \$150 for a dose of Xofluza®.<sup>13</sup> There is currently no published information on how often Xofluza® may be taken during any given flu season.

The Division of Medicaid (DOM) requested MS-DUR conduct an analysis of oseltamivir claims during the 2017-2018 flu season. As DOM's electronic edit currently limits beneficiaries to two oseltamivir prescriptions per year, MS-DUR analyzed claims to determine if beneficiaries were

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<sup>10</sup> Tamiflu®{package insert}. California: Genentech, Inc. 2012; [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/021087s062lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021087s062lbl.pdf) (Accessed November 2018).

<sup>11</sup> American Academy of Pediatrics Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children, 2011-2012. *Pediatrics* 2011; 128:813-25; PMID:21890834; <http://dx.doi.org.umiss.idm.oclc.org/10.1542/peds.2011-2295>

<sup>12</sup>Xofluza®{package insert}. California: Genentech, Inc. 2018; [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/210854s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210854s000lbl.pdf) (Accessed November 2018).

<sup>13</sup> Forbes. <https://www.forbes.com/sites/joshuacohen/2018/11/01/the-new-anti-flu-drug-xofluzas-value-proposition/#7305d2c5e999>

obtaining more than two prescriptions during a flu season. Additionally MS-DUR evaluated the concomitant utilization of antibiotics and oseltamivir during the 2017-2018 flu season.

## **METHODS**

Pharmacy claims for oseltamivir were extracted for the period January 1, 2017 to June 30, 2018. The analysis included prescriptions from DOM's three pharmacy programs, both Coordinated Care Organizations and Fee-For-Service. The number of beneficiaries taking oseltamivir and the number of prescriptions filled were determined for calendar year 2017 (January – December 2017) and for the state fiscal year 2018 (July 2017 – June 2018).

## **RESULTS**

Table 1 shows the number of beneficiaries taking oseltamivir and the number of prescriptions filled during each time period. During CY 2017 a small percentage of children in all three programs received more than two prescriptions for oseltamivir. This is not unusual in that the early, periodic, screening, diagnostic and treatment (EPSDT) guidelines allow children to exceed most prescription limits. When using the SFY 2018, the number of children obtaining more than two prescriptions for oseltamivir actually decreased slightly in all three programs.

Utilization of oseltamivir among adults indicates that a small number of beneficiaries are receiving more than two prescriptions per flu season due to the current edit.

<b>TABLE 1: Number of Claims for Tamiflu (Oseltamivir) Per Year by Calendar Year and State Fiscal Year</b>						
	<b>Plan</b>	<b>Number of Tamiflu Claims</b>	<b>Number of Beneficiaries CY 2017 (January - December 2017)</b>		<b>Number of Beneficiaries FY 2018 (July 2017 - June 2018)</b>	
<b>Children (<math>&lt; 21</math> years old)</b>	<b>FFS</b>	<b>1</b>	10,005	93.9%	14,637	95.2%
		<b>2</b>	612	5.7%	697	4.5%
		<b>3 or more</b>	40	0.4%	35	0.2%
	<b>UHC</b>	<b>1</b>	24,225	92.5%	25,727	93.2%
		<b>2</b>	1,860	7.1%	1,790	6.5%
		<b>3 or more</b>	100	0.4%	76	0.3%
	<b>MAG</b>	<b>1</b>	24,722	94.1%	26,797	97.5%
		<b>2</b>	1,524	5.8%	679	2.5%
		<b>3 or more</b>	34	0.1%	17	0.1%
<b>Adults (<math>\geq 21</math> years old)</b>	<b>FFS</b>	<b>1</b>	965	92.9%	2,369	95.6%
		<b>2</b>	73	7.0%	97	3.9%
		<b>3 or more</b>	1	0.1%	12	0.5%
	<b>UHC</b>	<b>1</b>	2,579	96.9%	2,556	97.3%
		<b>2</b>	81	3.0%	69	2.6%
		<b>3 or more</b>	1	0.0%	3	0.1%
	<b>MAG</b>	<b>1</b>	3,050	97.7%	3,279	99.6%
		<b>2</b>	70	2.2%	12	0.4%
		<b>3 or more</b>	1	0.0%	0	0.0%

Table 2 illustrates the number of prescriptions filled for oseltamivir and the amount paid to pharmacies during SFY 2018 (July 1, 2017 – June 30, 2018). During the 2017-2018 flu season, there were a total of 82,491 prescriptions filled for oseltamivir with DOM paying almost \$12 million dollars for treatment.

<b>TABLE 2: Number of Tamiflu (Oseltamivir) Prescriptions Filled and Amount Paid July 1, 2017 - June 30, 2018</b>		
<b>Plan</b>	<b>Number of Prescriptions Filled</b>	<b>Amount Paid</b>
FFS	18,740	\$2,590,453
UHC	32,242	\$4,798,877
MAG	31,509	\$4,572,832
<b>TOTAL</b>	<b>82,491</b>	<b>\$11,962,162</b>

*NOTE: Paid amounts represent amount reported on claims as paid to the pharmacy. These amounts do not reflect final actual costs after rebates, etc.*

Tables 3 and 4 display concomitant use of oseltamivir and antibiotics during the 2017-2018 flu season. Antibiotic claims were considered to be concomitant if there were any days of overlap with oseltamivir and the days supply for the antibiotic was < 30 days. Overall concomitant antibiotic use (predominately azithromycin and amoxicillin) occurred with approximately 28.3% of oseltamivir claims with any overlap. When the antibiotic claim was within 2 days of the oseltamivir claim, concomitant use was approximately 22%.

<b>Table 3: Number of Tamiflu (Oseltamivir) Prescription Claims and Concomitant Claims for Antibiotics</b>						
<i>July 1, 2017 - June 30, 2018</i>						
Plan	Age Group	Number of Oseltamivir Claims	Oseltamivir Claims With Overlapping Antibiotic Claims			
			Any Overlap days supply < 30 days		Dispensed within 2 days of Oseltamivir Claim	
FFS	Children	15,369	3404	22.1%	2653	17.3%
	Adult	2,478	373	15.1%	230	9.3%
UHC	Children	27,593	8090	29.3%	6361	23.1%
	Adult	2,628	1045	39.8%	749	28.5%
MAG	Children	27,493	8188	29.8%	6437	23.4%
	Adult	3,291	1223	37.2%	919	27.9%

\* Children are Medicaid beneficiaries below the age of 21 at fill

**Table 4: Antibiotics Prescribed Concomitantly With Tamiflu (Oseltamivir)***July 1, 2017 - June 30, 2018*

Antibiotic	Number of Concomitant Claims	% of All Concomitant Claims	Antibiotic	Number of Concomitant Claims	% of All Concomitant Claims
Azithromycin	9232	41.36%	Ertapenem	5	0.02%
Amoxicillin	8526	38.19%	Methenamine	5	0.02%
Amoxicillin-Clavulanate	2452	10.98%	Atovaquone	3	0.01%
Sulfamethoxazole-Trimethoprim	547	2.45%	Ivermectin	3	0.01%
Clarithromycin	249	1.12%	Tobramycin	3	0.01%
Clindamycin	249	1.12%	Demeclocycline	2	0.01%
Doxycycline	215	0.96%	Linezolid	2	0.01%
Penicillin V Potassium	211	0.95%	Moxifloxacin	2	0.01%
Nitrofurantoin	157	0.70%	Tinidazole	2	0.01%
Levofloxacin	140	0.63%	Trimethoprim	2	0.01%
Ciprofloxacin	117	0.52%	Aztreonam	1	0.00%
Metronidazole	114	0.51%	Colistimethate	1	0.00%
Minocycline	48	0.22%	Dapsone	1	0.00%
Erythromycin	10	0.04%	Gentamicin	1	0.00%
Pyrantel	8	0.04%	Neomycin	1	0.00%
Ampicillin	6	0.03%	Piperacillin-Tazobactam	1	0.00%
Rifaximin	6	0.03%	Vancomycin	1	0.00%

**CONCLUSIONS AND RECOMMENDATIONS**

During the 2017-2018 flu season, there were a total of 82,491 prescriptions filled for oseltamivir with DOM paying almost \$12 million dollars for treatment. Only a small number of adult beneficiaries are receiving more than two oseltamivir prescriptions during a single flu season due to the current edits. There did appear to be significant concomitant use of antibiotics along with oseltamivir during the 2017-2018 flu season. Concomitant antibiotic use with antiviral drugs used to treat influenza may be an area to consider for further analysis and a potential DUR educational initiative for providers.

This report was prepared to provide an update to the DUR Board on the 2017-2018 flu season and current treatment options. Feedback from the Board is appreciated as no specific recommendations are currently proposed.