

**Antiviral Chemoprophylaxis Use during Influenza Outbreaks in Long-term Care
Facilities**

By

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Thesis

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PREFACE AND ACKNOWLEDGEMENTS

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INTRODUCTION

As many as 645,832 global seasonal influenza-associated deaths occur annually.¹ Between 70% and 85% of these deaths occur in people aged 65 years and older.² The large population of older adults who live in long term care facilities (LTCFs) are at a particularly high risk for influenza exposure and associated harms due to the close proximity of residents and thus, increased probability of transmission.³⁻⁶

Prompt use of antiviral chemoprophylaxis (e.g., oseltamivir) in LTCFs reduces the severity of influenza outbreaks by decreasing outbreak duration and the incidence of influenza among residents.⁷⁻⁹ When two or more LTCF residents are suspected to have influenza within 72 hours of one another on the same unit, and at least one has laboratory-confirmed influenza, the Centers for Disease Control and Prevention (CDC) recommends that antiviral chemoprophylaxis be initiated as soon as possible for all residents on affected wings of the facility.^{10,11} Further, the CDC recommends a 14-day duration of antiviral chemoprophylaxis and that LTCFs continue chemoprophylaxis until at least 7 days after the last resident's onset of illness. Whether or to what degree LTCFs adhere to this national CDC guideline during influenza outbreaks is unknown.

In addition to the national guidelines, LTCFs develop their own policies on antiviral chemoprophylaxis as part of facility-specific influenza outbreak control protocols. However, little data describe the existence of these policies, their alignment with national guidelines, or whether LTCFs adhere to their own self-established policies during an outbreak. Without this information, it is difficult to develop interventions to improve the use of antiviral chemoprophylaxis during influenza outbreaks. Ultimately, the lack of

data and any continued non-adherence to guidelines or policies may result in worse health outcomes for older adults in LTCFs, including functional impairment, hospitalization, and death.¹²

To fill this evidence gap, we 1) determined the proportion of LTCF influenza outbreak occurrences during which LTCFs were adherent to national guidelines, and 2) identified LTCFs that reported self-established antiviral chemoprophylaxis policies, documented variation in the policies between LTCFs, and assessed adherence to the policies during influenza outbreaks. We hypothesized that the majority of LTCFs would not adhere to national guidelines and that most would not have a local antiviral chemoprophylaxis policy, but that they would adhere to self-established policies when they did.

METHODS

Study Design and Data Source

This concurrent cohort study used respiratory outbreak surveillance data obtained through primary data collection by the Rhode Island Department of Health (RIDOH) Center for Acute Infectious Disease Epidemiology (CAIDE) for the 2017-2018 and 2018-2019 influenza seasons, defined as October 1, 2017 to May 19, 2018 and October 1, 2018 to May 18, 2019. Surveillance data was compiled by RIDOH staff from monitored respiratory outbreaks in congregate living settings.^{13,14}

Study Population

The study population consisted of RI LTCFs, including nursing homes, skilled nursing facilities, and long-term acute care hospitals that self-reported at least one influenza outbreak affecting ≥ 1 units during the 2017-2018 and 2018-2019 influenza seasons. As such, we excluded all other types of congregate living settings that were originally included in the dataset, such as assisted living facilities, prisons, and universities. We also excluded all non-influenza respiratory outbreaks.

The RIDOH defined an influenza outbreak as one case of laboratory-confirmed influenza in the residential setting or two cases of influenza-like illness (ILI) within 72 hours of each other, where ILI was defined as a fever ($\geq 100^{\circ}$ F) and cough and/or sore throat in the absence of a known cause other than influenza. That definition of an influenza outbreak deviates from some more traditional definitions but maximizes sensitivity.¹¹ We therefore further restricted our population to the CDC indication for antiviral chemoprophylaxis: two or more ill residents on the same unit with at least one case of

laboratory-confirmed influenza within 72 hours. Outbreaks are self-reported by LTCFs and RIDOH staff monitor them until 10 days have passed since the last illness onset date. LTCFs could experience multiple outbreaks during a given influenza season. We excluded LTCFs that did not provide information on antiviral use or that indicated prophylaxis was initiated but did not specify the duration.

National Guideline Adherence

Current national guidelines recommend that chemoprophylaxis should be initiated as soon as possible once an influenza outbreak is detected within a facility. CDC recommends chemoprophylaxis for a minimum of 2 weeks and continuing up to 7 days after last known influenza onset on an affected care unit. Each outbreak occurrence was assessed for adherence to this guideline by one investigator (J.S.). LTCFs were identified as non-adherent if they did not offer chemoprophylaxis, only offered it to well roommates of ill residents and not the affected unit the ill residents resided on, or offered it to the affected unit but for the incorrect duration.

Facility Policy Adherence

LTCFs that had at least one influenza outbreak were contacted to report on their own written antiviral chemoprophylaxis policies. Staff responsible for infection control were interviewed by one investigator (J.S.). Both the presence of a written protocol and duration of chemoprophylaxis use during an outbreak were ascertained to assess LTCF policy adherence.

LTCF Characteristics

LTCF characteristics like the number of residents were measured by LTCF staff at the time an influenza outbreak occurred. Staff-reported vaccination rates were measured using local Minimum Data Set (MDS) assessments.

Statistical Analyses

Descriptive statistics, specifically crude proportions and percentages, were used to evaluate adherence to national guidelines and LTCF-specific policies both overall and stratified by the duration of antiviral chemoprophylaxis documented in LTCF-specific policies.

Data were analyzed using R 3.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study cohort

Our initial cohort consisted of 53 LTCFs that reported 74 outbreaks with complete data. The average number of residents in each LTCF was 99 (SD 46). The average vaccination rate of residents was 89% (SD 9%). Staff from 52 LTCFs were contacted and interviewed for LTCF-specific policies.

National Guideline Adherence

A total of 90 influenza outbreaks were reported to RIDOH and met criteria for initiating antiviral chemoprophylaxis; 74 had complete data (Figure 1). Of the 74 outbreaks, 50 (68%) involved chemoprophylaxis use that did not adhere to national guidelines. Non-adherence was consistent across influenza seasons (Supplementary Figure S1). LTCFs that reported self-established policies that aligned with national guidelines were more adherent (Table 1).

LTCF Policy Adherence

Thirty-seven percent (n=19) of LTCFs reported no written policy on chemoprophylaxis and 44% (n=23) reported a policy that did not align with national guidelines (Figure 2). For outbreaks that occurred in LTCFs that reported policies with specified durations (n=42), 50% (n=21) were non-adherent to their own policy. Of those occurrences where the facility deviated from the local policy, 57% (n=12) offered chemoprophylaxis for less than the duration stated by the local policy while 43% (n=9) exceeded the duration of the local policy.

DISCUSSION

In this cohort study, we observed that deviations from national antiviral chemoprophylaxis guidelines were common among LTCFs. Many facilities also had no self-established policies or had policies that did not align with national guidelines. When influenza outbreaks occurred, LTCFs did not provide antiviral chemoprophylaxis in a way that was consistent with their own local policies. These results suggest that qualitative research may be necessary to better understand why facilities are non-adherent to national guidelines and local policies, and once the reasons are understood, interventions might be required to improve guideline and policy adherence.

Prior studies have focused on the effects of chemoprophylaxis in LTCFs.^{7,9,15-19} Our study meaningfully contributes to the existing literature by documenting modern LTCF antiviral chemoprophylaxis use; describing variation in LTCF self-established antiviral chemoprophylaxis policies; and assessing adherence to both national influenza control guidelines and self-established policies. Few data are available on variation in LTCF adherence to national guidelines or local policies. A prior review noted that evidence did not support a single approach to antiviral use in LTCFs and instead advocated for using clinical judgement.¹⁷ While LTCF provider and staff beliefs akin to the perspective described in the review may explain, in part, the observed rates of non-adherence, other factors are likely also involved and remain to be elucidated.

Of particular note, over one third of facilities employed a self-established chemoprophylaxis policy of 10 days and facilities with this policy that experienced an outbreak were the most likely to adhere to it compared to others. days and the drug

packaging of oseltamivir, the most commonly used antiviral drug within LTCFs, typically provides a 10-day supply.^{10,20} Thus, the policies that do not coincide with national guidelines may originate from community guidance and drug packaging. Proper education of LTCF staff about LTCF-specific national guidelines and changing oseltamivir packaging (or doing some repackaging) may be easy interventions to increase chemoprophylaxis adherence. Further study is warranted to document the consequences of non-adherence to national antiviral chemoprophylaxis guidelines in LTCFs and assess the comparative effectiveness of 10-day versus 14-day prophylaxis regimens.

Limitations

The findings of this study must be interpreted in light of several limitations.

First, both influenza outbreaks and policies were self-reported by LTCF staff. If reporting was biased, outbreaks may have been under ascertained and policy information may have been inaccurate. Missing data arose from instances where LTCF staff neglected to provide documentation of antiviral use. It is possible that those who did not provide documentation were more likely to have guideline deviations, resulting in underestimation of non-adherence.

Second, we only had data on two influenza seasons and only for Rhode Island, limiting generalizability to other older seasons and other geographic locations that have markedly different characteristics that could influence the results. Third, it was not possible to ascertain other attributes of LTCF self-established policies aside from the duration of chemoprophylaxis use, though this would be a worthwhile focus of future research.

Finally, health outcomes between residents during outbreak occurrences were not compared due to the nature of our data. Further study is warranted to document the consequences of non-adherence to national antiviral chemoprophylaxis guidelines in LTCFs.

Conclusions and Implications

In conclusion, we found that LTCFs often deviated from national guidelines and their own local policies regarding use of antiviral chemoprophylaxis during influenza outbreaks. Adoption of antiviral chemoprophylaxis policies and harmonizing existing policies to national guidelines could reduce non-adherence to guideline-recommended practices for effectively controlling influenza outbreaks.

CONFLICT OF INTEREST

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REFERENCES

1. Iuliano AD, Roguski KM, Chang HH, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet (London, England)*. 2018;391(10127):1285-1300.
2. Kostova D, Reed C, Finelli L, et al. Influenza Illness and Hospitalizations Averted by Influenza Vaccination in the United States, 2005-2011. *PloS one*. 2013;8(6):e66312.
3. Harris-Kojetin L, Sengupta M, Park-Lee E, et al. Long-Term Care Providers and services users in the United States: data from the National Study of Long-Term Care Providers, 2013-2014. *Vital & health statistics Series 3, Analytical and epidemiological studies*. 2016(38):x-xii; 1-105.
4. Bosco E, Zullo AR, McConeghy KW, et al. Long-term Care Facility Variation in the Incidence of Pneumonia and Influenza. *Open forum infectious diseases*. 2019;6(6):ofz230.
5. Dickinson DT, He J, Gussin G, Gravenstein S, Dembry LM, Huang SS. Quantifying influenza exposure within California hospitals and nursing homes using administrative data. *American journal of infection control*. 2019.
6. McConeghy KW, Huang SS, Miller LG, et al. Hospital Influenza Admissions as a Harbinger for Nursing Home Influenza Cases. *Journal of the American Medical Directors Association*. 2019.
7. Drinka PJ, Gravenstein S, Schilling M, Krause P, Miller BA, Shult P. Duration of antiviral prophylaxis during nursing home outbreaks of influenza A: a comparison of 2 protocols. *Archives of internal medicine*. 1998;158(19):2155-2159.

8. Gravenstein S, Drinka P, Osterweil D, et al. Inhaled zanamivir versus rimantadine for the control of influenza in a highly vaccinated long-term care population. *Journal of the American Medical Directors Association*. 2005;6(6):359-366.
9. Ye M, Jacobs A, Khan MN, et al. Evaluation of the use of oseltamivir prophylaxis in the control of influenza outbreaks in long-term care facilities in Alberta, Canada: a retrospective provincial database analysis. *BMJ open*. 2016;6(7):e011686.
10. Interim Guidance for Influenza Outbreak Management in Long-Term Care and Post-Acute Care Facilities. 2019;
<https://www.cdc.gov/flu/professionals/infectioncontrol/ltc-facility-guidance.htm>. Accessed November 5th, 2019.
11. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2019;68(6):e1-e47.
12. Gozalo PL, Pop-Vicas A, Feng Z, Gravenstein S, Mor V. Effect of Influenza on Functional Decline. *Journal of the American Geriatrics Society*. 2012;60(7):1260-1267.
13. *Rhode Island Department of Health 2017-2018 Influenza Epidemiology and Surveillance Report*. Rhode Island Department of Health;2018.

14. Berns Abby TB. *Influenza Surveillance Report 2018-2019 Season Summary October 1, 2018-May 18, 2019 Rhode Island*. Rhode Island Department of Health;2019.
15. Singh D, Jiang D, Van Caesele P, Loeppky C. The effect of timing of oseltamivir chemoprophylaxis in controlling influenza A H3N2 outbreaks in long-term care facilities in Manitoba, Canada, 2014-2015: a retrospective cohort study. *Infection Control & Hospital Epidemiology*. 2018;39(8):955-960.
16. Rainwater-Lovett K, Chun K, Lessler J. Influenza outbreak control practices and the effectiveness of interventions in long-term care facilities: a systematic review. *Influenza Other Respir Viruses*. 2014;8(1):74-82.
17. Lansbury LE, Brown CS, Nguyen-Van-Tam JS. Influenza in long-term care facilities. *Influenza and Other Respiratory Viruses*. 2017;11(5):356-366.
18. Ambrozaitis A, Gravenstein S, van Essen GA, et al. Inhaled zanamivir versus placebo for the prevention of influenza outbreaks in an unvaccinated long-term care population. *Journal of the American Medical Directors Association*. 2005;6(6):367-374.
19. Rubin MS, Nivin B, Ackelsberg J. Effect of timing of amantadine chemoprophylaxis on severity of outbreaks of influenza a in adult long-term care facilities. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2008;47(1):47-52.
20. Inc H-LR. TAMIFLU - oseltamivir phosphate capsule Revised 08/2009; <https://www.fda.gov/media/77829/download>.

Table 1. Adherence by long-term care facilities to national antiviral chemoprophylaxis guidelines for influenza outbreak occurrences stratified by local policy-specific duration antiviral use (N=74)

National guideline adherence	LTCF Policy Reported						Missing [†] (n=1)	Overall (n=74)
	All LTCF policies (n=47)	≥7 days (n=9)	10 days (n=17)	14 days (n=17)	Not specified* (n=4)	No LTCF policy (n=26)		
Adherent	14 (29.8%)	1 (11.1%)	4 (23.5%)	7 (41.2%)	2 (50.0%)	10 (38.5%)	0 (0%)	24 (32.4%)
Non-adherent	33 (70.2%)	8 (88.9%)	13 (76.5%)	10 (58.8%)	2 (50.0%)	16 (61.5%)	1 (100%)	50 (67.6%)

Abbreviations: LTCF, long-term care facility.

*LTCF reported presence of chemoprophylaxis policy that did not include a specified duration.

[†]LTCF was considered non-adherent. Chemoprophylaxis was offered to well roommates but not affected unit. Duration of antiviral use was not documented.

Figure 1. Flow diagram of study population and distribution of adherence to national antiviral chemoprophylaxis guidelines for long-term care facility influenza outbreak occurrences (N=74)

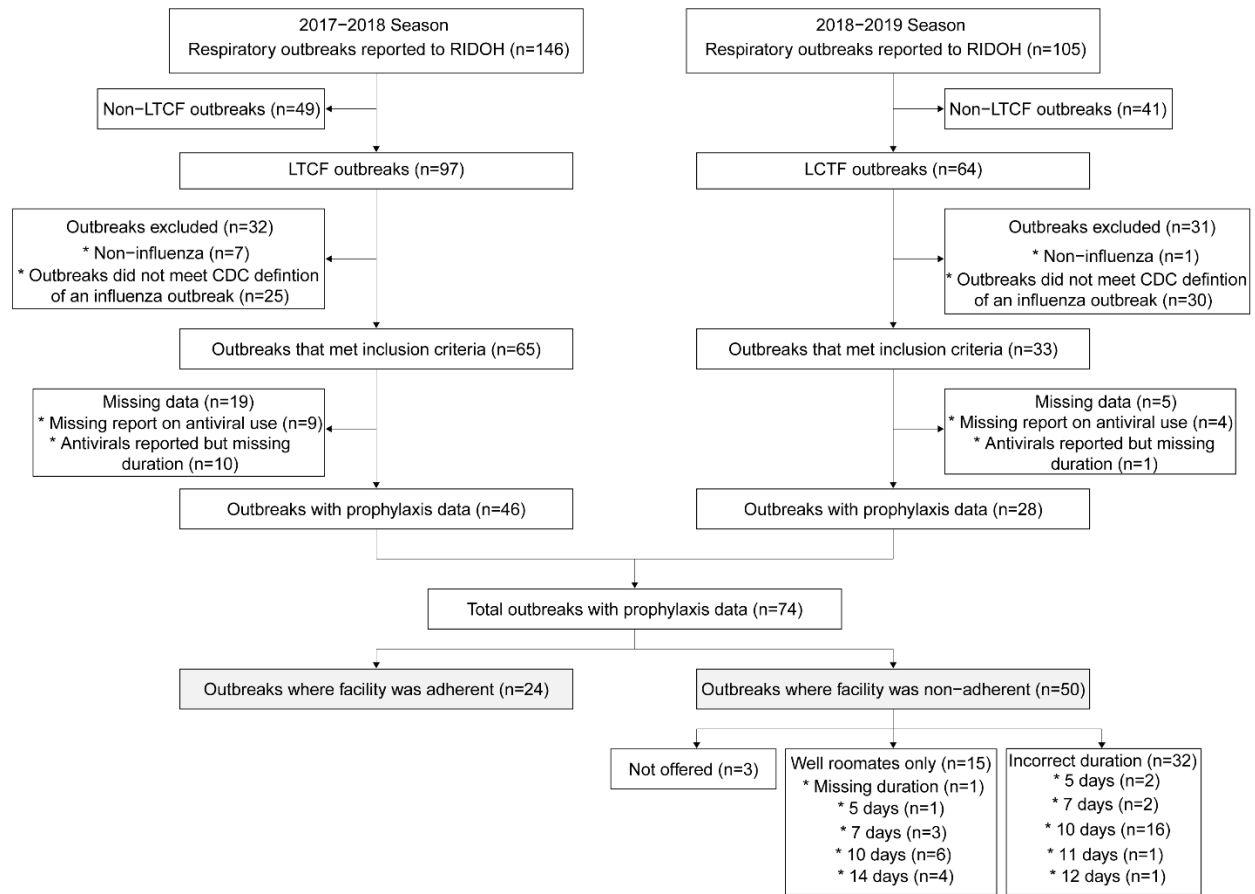


Figure 1A. Flow diagram of study population and distribution of adherence to national antiviral chemoprophylaxis guidelines for long-term care facility influenza outbreak occurrences stratified by influenza season (N=74)

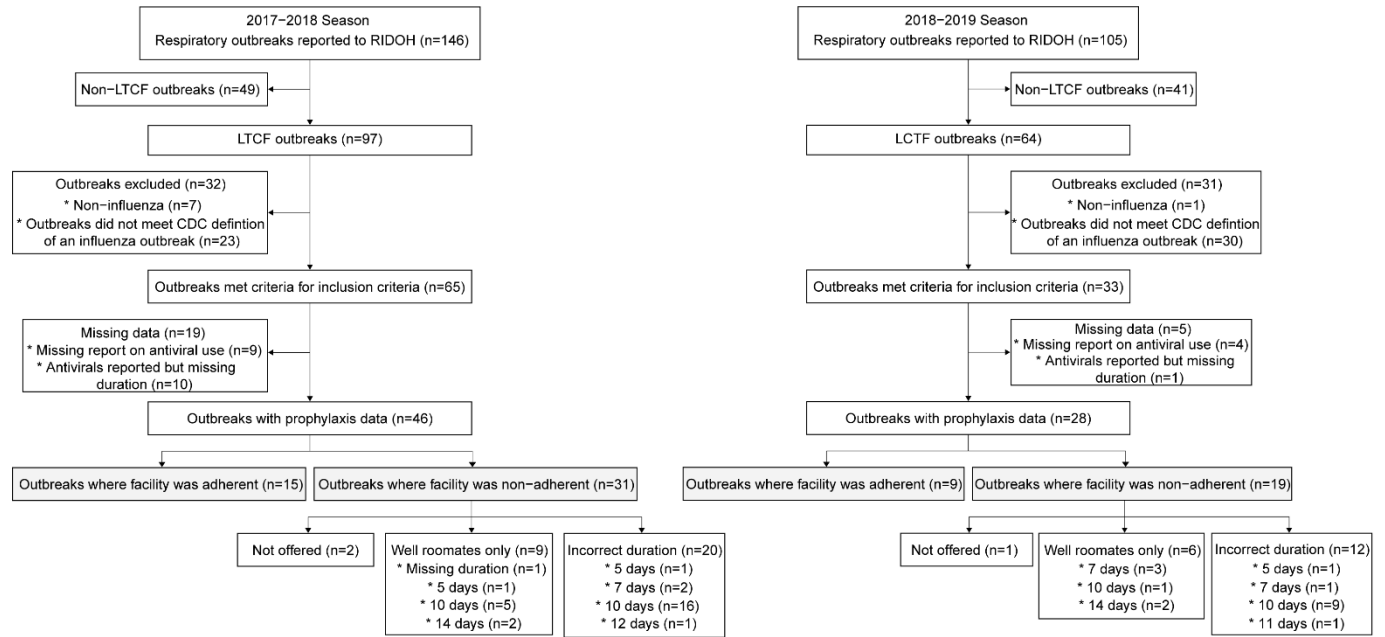


Figure 2. Existence of long-term care facility-established antiviral chemoprophylaxis policies and policy-specified durations among facilities that reported at least one influenza outbreak (N=52)

