Vaccine 37 (2019) 5807–5811

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Short communication

Comparison of vaccine effectiveness against influenza hospitalization of cell-based and egg-based influenza vaccines, 2017–2018

Katia J. Bruxvoort [a,*], Yi Luo [a], Bradley Ackerson [a], Hilary C. Tanenbaum [a], Lina S. Sy [a], Ashesh Gandhi [b], Hung Fu Tseng [a]

[a] Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, United States
[b] Seqirus, Summit, NJ, United States

ARTICLE INFO

Article history:
Received 10 May 2019
Received in revised form 13 August 2019
Accepted 14 August 2019
Available online 22 August 2019

Keywords:
Influenza
Influenza vaccine
Vaccine effectiveness

ABSTRACT

Egg-based influenza vaccines could be less effective than cell-based vaccine due to adaptive mutations acquired for growth. We conducted a test-negative case-control study at Kaiser Permanente Southern California to assess vaccine effectiveness (VE) against hospitalization for laboratory-confirmed influenza during 2017–2018. Among the 1186 cases and 6946 controls, 74% and 59%, respectively, were ages ≥ 65 -years. For any influenza, the adjusted relative VE of cell-based vaccine versus egg-based vaccines was 43% (95% CI: −45% to 77%) for patients ages < 65 years and 6% (95% CI: −46% to 39%) for patients ages ≥ 65 -years. For influenza A(H3N2), the adjusted relative VE was 61% (95% CI: −63% to 91%) for patients ages < 65 years and −4% (95% CI: −70% to 37%) for patients ages ≥ 65 years. Statistically significant protection against influenza hospitalization of cell-based vaccine compared to egg-based vaccines was not observed, but further studies in additional influenza seasons are warranted.

1. Background

Annual influenza vaccination is the best strategy for protection against illness, hospitalization, and death from influenza, even in years when vaccines are not well matched to circulating viruses. In the 2017–2018 influenza season, United States estimates of vaccine effectiveness (VE) against laboratory-confirmed influenza associated with medically attended acute respiratory illness were 38% overall and 22% for influenza A(H3N2) [1]; estimates from Canada and Australia were even lower [2,3].

One factor that may contribute to low VE is the occurrence of genetic changes in the vaccine hemagglutinin protein during replication of the virus in eggs, which can alter antigenicity of vaccine viruses. This phenomenon, known as egg adaptation, has been especially common for recent influenza A(H3N2) viruses [4,5]. Influenza vaccine grown in mammalian cells (cell-based vaccine; Flucelvax; Seqirus Inc., Holly Springs, North Carolina) yields a vaccine strain that is more similar to seed A(H3N2) viruses and potentially more effective than egg-based vaccines.

It is unknown if VE of cell-based vaccine is better than egg-based vaccines. A study from the Centers for Medicare & Medicaid Services suggested that cell-based vaccine had 10% better effectiveness against influenza hospitalization than egg-based vaccine for individuals ages ≥ 65 years; however, virologic confirmation for influenza was not performed [6]. We conducted a test-negative case-control study to assess VE of cell-based and egg-based vaccines against hospitalization for laboratory-confirmed influenza during the 2017–2018 season.

2. Methods

Kaiser Permanente Southern California (KPSC) is an integrated health care organization serving over 4.5 million diverse members. The electronic health record (EHR) comprehensively captures health care encounters, including laboratory tests, vaccinations, and medications. As KSPC members are offered recommended vaccinations free of charge at every visit and at convenient walk-in locations, they have incentive to seek care within the organization; however, vaccinations received outside of KPSC are routinely incorporated into the EHR. Ethical approval for the study was obtained from the KPSC Institutional Review Board. All data were collected from the EHR.

* Corresponding author at: Department of Research and Evaluation, Kaiser Permanente Southern California, 100 S Los Robles Ave, Pasadena, CA 91101, United States.

E-mail addresses: katia.bruxvoort@kp.org (K.J. Bruxvoort), Yi.X.Luo@kp.org (Y. Luo), Bradley.K.Ackerson@kp.org (B. Ackerson), Hilary.Tanenbaum@kp.org (H.C. Tanenbaum), Lina.S.Sy@kp.org (L.S. Sy), Ashesh.Gandhi@Seqirus.com (A. Gandhi), Hung-Fu.X.Tseng@kp.org (H.F. Tseng).

https://doi.org/10.1016/j.vaccine.2019.08.024
0264-410X/

The study used a test negative design [7] and included all members admitted to KPSC hospitals during October 1, 2017 to May 31, 2018 who met the following inclusion criteria: ages ≥ 4 years; 6 months of prior membership; and at least one influenza test result from a multiplex polymerase chain reaction (PCR) from a specimen taken anytime between 14 days prior to 3 days after the admission date. Patients were excluded if they were tested for influenza or diagnosed with influenza-like illness (ICD-10 codes J09-J18) prior to 14 days before the admission date; they received recombinant, high-dose, adjuvanted, or live 2017–2018 influenza vaccines prior to the admission date; or only rapid influenza tests were performed. The exposure was defined as receipt of trivalent or quadrivalent egg-based or cell-based influenza vaccine at least 21 days prior to the admission date. Test-positive cases were hospitalized patients with at least one positive influenza test result and test-negative controls were hospitalized patients with only negative test results.

VE was estimated for any influenza and by influenza type (any influenza, influenza A, influenza A(H3N2), or influenza B) for (a) cell-based vaccine compared to no influenza vaccine, (b) egg-based vaccines compared to no influenza vaccine, and (c) cell-based vaccine compared to egg-based vaccines, stratified by age. VE and 95% confidence intervals (CI) were calculated as (1- odds ratio) × 100% and were adjusted for age, sex, race/ethnicity, body

Table 1
Characteristics of patients hospitalized for influenza by influenza vaccination status, 10/01/2017–05/31/2018.

	< 65 years old							≥ 65 years old						
	Unvaccinated N = 1327		Egg-based N = 1741		Cell-based N = 75			Unvaccinated N = 1334		Egg-based N = 3498		Cell-based N = 157		
	N	%	N	%	N	%	p-value	N	%	N	%	N	%	p-value
Age at admission date							<0.01							N/A
4–18 years old	239	18.00	229	13.20	8	10.70		N/A	N/A	N/A	N/A	N/A	N/A	
19–49 years old	513	38.70	511	29.40	20	26.70		N/A	N/A	N/A	N/A	N/A	N/A	
50–64 years old	575	43.30	1001	57.50	47	62.70		N/A	N/A	N/A	N/A	N/A	N/A	
≥65 years old	N/A		N/A		N/A			1334	100.00	3498	100.00	157	100.00	
Sex							0.19							0.07
Female	670	50.50	884	50.80	46	61.30		717	53.70	1754	50.10	77	49.00	
Male	657	49.50	857	49.20	29	38.70		617	46.30	1744	49.90	80	51.00	
Race/ethnicity							<0.01							<0.01
White	433	32.60	583	33.50	22	29.30		685	51.30	1839	52.60	87	55.40	
Black	236	17.80	209	12.00	13	17.30		209	15.70	366	10.50	21	13.40	
Hispanic	507	38.20	706	40.60	30	40.00		320	24.00	901	25.80	38	24.20	
Asian/Pacific Islander	121	9.10	212	12.20	6	8.00		102	7.60	367	10.50	10	6.40	
Others/Multiple	16	1.20	16	0.90	3	4.00		10	0.70	13	0.40	1	0.60	
Native American/Alaska Native	4	0.30	7	0.40	1	1.30		2	0.10	6	0.20	0	0.00	
Unknown	10	0.80	8	0.50	0	0.00		6	0.40	6	0.20	0	0.00	
BMI classification[†]							<0.01							<0.01
Underweight	177	13.30	168	9.60	10	13.30		99	7.40	215	6.10	7	4.50	
Normal	318	24.00	408	23.40	12	16.00		436	32.70	1161	33.20	45	28.70	
Overweight	313	23.60	393	22.60	14	18.70		361	27.10	1034	29.60	48	30.60	
Obese	484	36.50	757	43.50	39	52.00		396	29.70	1063	30.40	57	36.30	
Missing	35	2.60	15	0.90	0	0.00		42	3.10	25	0.70	0	0.00	
Smoking[†]							<0.01							<0.01
No	982	74.00	1184	68.00	46	61.30		824	61.80	1939	55.40	73	46.50	
Yes	345	26.00	557	32.00	29	38.70		510	38.20	1559	44.60	84	53.50	
Number of outpatient encounters[†]							<0.01							<0.01
0	251	18.90	45	2.60	0	0.00		234	17.50	95	2.70	2	1.30	
1–4	578	43.60	520	29.90	16	21.30		522	39.10	934	26.70	25	15.90	
5–10	269	20.30	529	30.40	21	28.00		344	25.80	1227	35.10	56	35.70	
11+	229	17.30	647	37.20	38	50.70		234	17.50	1242	35.50	74	47.10	
Number of inpatient encounters[†]							<0.01							0.01
0	1101	83.00	1272	73.10	53	70.70		1060	79.50	2630	75.20	118	75.20	
1	131	9.90	257	14.80	15	20.00		172	12.90	526	15.00	29	18.50	
2+	95	7.20	212	12.20	7	9.30		102	7.60	342	9.80	10	6.40	
Number of emergency department encounters[†]							<0.01							<0.01
0	808	60.90	942	54.10	41	54.70		736	55.20	1680	48.00	75	47.80	
1	320	24.10	428	24.60	18	24.00		357	26.80	942	26.90	46	29.30	
2+	199	15.00	371	21.30	16	21.30		241	18.10	876	25.00	36	22.90	
Received influenza vaccine in 2016–2017 influenza season							<0.01							<0.01
No	862	65.00	323	18.60	7	9.30		698	52.30	255	7.30	8	5.10	
Yes	465	35.00	1418	81.40	68	90.70		636	47.70	3243	92.70	149	94.90	
Chronic Obstructive Pulmonary Disease[†]							<0.01							<0.01
No	1215	91.60	1538	88.30	63	84.00		971	72.80	2377	68.00	85	54.10	
Yes	112	8.40	203	11.70	12	16.00		363	27.20	1121	32.00	72	45.90	
Diabetes[†]							<0.01							<0.01
No	969	73.00	1029	59.10	36	48.00		712	53.40	1694	48.40	78	49.70	
Yes	358	27.00	712	40.90	39	52.00		622	46.60	1804	51.60	79	50.30	
Hypertension[†]							<0.01							<0.01
No	783	59.00	796	45.70	23	30.70		211	15.80	387	11.10	13	8.30	
Yes	544	41.00	945	54.30	52	69.30		1123	84.20	3111	88.90	144	91.70	
Congestive Heart Failure[†]							<0.01							<0.01
No	1149	86.60	1359	78.10	56	74.70		810	60.70	1959	56.00	80	51.00	
Yes	178	13.40	382	21.90	19	25.30		524	39.30	1539	44.00	77	49.00	

[†] Within the six months prior to admission date.

mass index, smoking, health care utilization in the 6 months prior to admission date, receipt of influenza vaccine in the 2016–2017 season, and comorbidities in the 6 months prior to admission date.

3. Results

The study included 8132 patients, who received 12,487 PCR tests. Most tests (97.6%) were conducted anytime between ≤ 6 days prior to 3 days after admission, and 81.6% were conducted on the day of or day after admission. Of patients ages < 65 years, 1327 (42.2%) were unvaccinated, 1741 (55.4%) received egg-based vaccine, and 75 (2.4%) received cell-based vaccine. Of patients ≥ 65 years, 1334 (26.7%) were unvaccinated, 3498 (70.1%) received egg-based vaccine, and 157 (3.2%) received cell-based vaccine.

Characteristics of patients varied by age and vaccine type (Table 1). Health care utilization and underlying comorbidities were less common among unvaccinated patients, but comorbidities were typically more common among recipients of cell-based vaccine than recipients of egg-based vaccines, especially among patients ages < 65 years.

The adjusted VE of egg-based vaccines against hospitalization for any influenza compared to no influenza vaccine was −11% (95% CI: −49 to 17) for patients ages < 65 years and 5% (95% CI: −16 to 22) for patients ages ≥ 65 years (Table 2). The adjusted VE against hospitalization for any influenza of cell-based vaccine compared to no influenza vaccine was 36% (95% CI: −65 to 76) for patients ages < 65 years and 10% (95% CI: −44 to 44) for patients ages ≥ 65 years. The adjusted VE of cell-based vaccine compared to egg-based vaccines against hospitalization for any influenza was 43% (95% CI: −45 to 77) for patients ages < 65 years and 6% (95% CI: −46 to 39) for patients ages ≥ 65 years.

For influenza A(H3N2), the point estimates of adjusted VE against influenza hospitalization for cell-based vaccine compared to no influenza vaccine were higher than point estimates for adjusted VE of egg-based vaccine compared to no influenza vaccine in patients ages < 65 years only (47% [95% CI: −131 to 88] and −36% [95% CI: −102 to 8], respectively). Point estimates for adjusted VE of cell-based vaccine compared to egg-based vaccine against hospitalization for influenza A(H3N2) were higher than adjusted VE estimates against any influenza in patients ages < 65 years only (61% [95% CI: −63 to 91] and 43% [95% CI: −45 to 77], respectively). Only 2 of the 75 patients ages < 65 years that received cell-based vaccine tested positive for influenza A(H3N2).

4. Discussion

The 2017–2018 influenza season was a severe, influenza A (H3N2)-predominant season in the United States, with adults hospitalized at record rates and high numbers of adult and pediatric deaths [1,8]. In our study at KPSC, the VE of both cell-based and egg-based vaccines against hospitalization for laboratory-confirmed influenza was low in the 2017–2018 season. In patients ages < 65 years, VE point estimates suggest that cell-based vaccine protection could be better than egg-based vaccines. However, statistically significant benefits were not observed. Consistent with our study, the US Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN) reported low preliminary VE against influenza hospitalization for 2017–2018 (22% (95% CI: 8 to 35) for any influenza and 16% (95% CI: −5 to 32) for influenza A(H3N2)) [9]. Despite the low VE, influenza vaccination prevented a substantial burden of influenza illness in 2017–2018 [1].

There are several possible reasons for the low VE observed among both egg-based and cell-based vaccine. Antigenic drift may have resulted in mismatch between circulating viruses and vaccines. However, genetic characterization performed by the Centers for Disease Control and Prevention indicate that most 2017–2018 circulating viruses were inhibited by antisera against cell-based vaccine reference virus, but only half were inhibited by antisera against egg-based vaccine reference virus [8], thereby suggesting that egg adaptation played a role. Although the 2017–2018 cell-based vaccine was grown in mammalian cells, only the A (H3N2) component was derived from cell-based, rather than egg-based, seed virus. For the 2018–2019 vaccine, influenza B components were also derived from cell-based seed virus, and for 2019–2020 vaccine, all components will be completely cell-derived [10]. There may be other factors that affect VE, such as the immune response to prior influenza infection/vaccination and host characteristics, that should be addressed in future vaccination strategies [11,12].

The study has several strengths and limitations. A test-negative design among hospitalized patients was used to reduce care seeking bias [13], and cases and controls were defined by laboratory results [14]. However, some hospitalized patients with influenza may have not been tested or may have only been tested with a rapid test prior to admission; these individuals would not have been included in the study. Selection bias could also occur if vaccinated patients, who had more comorbidities, were more likely to be hospitalized and tested for influenza than unvaccinated individuals. This could explain higher numbers of vaccinated than unvaccinated patients in our study. We controlled for health care utilization and differences in comorbidities in the 6 months prior to admission, but there may have been residual differences in other factors such as frailty [15]. This would underestimate VE of egg-based or cell-based vaccines compared to unvaccinated individuals but would have less of an effect on relative VE. In addition, the lag between illness onset and testing of patients in this study was unknown. Misclassification might have occurred if patients who had already cleared infection tested negative; however, most patients were tested on or close to the date of admission, when they were likely at the peak of their illness and therefore likely to be shedding influenza [16,17]. Influenza vaccination status could have also been misclassified in some patients, although this was likely infrequent due to the comprehensiveness of the EHR. Additionally, VE for non-hospitalized individuals was not determined.

In this study, VE of both cell-based vaccine and egg-based vaccine was low. Further studies with a larger number of recipients of cell-based vaccines in multiple influenza seasons are warranted in both outpatient and hospitalized settings.

Funding

This work was supported by Seqirus.

Declaration of Competing Interest

This work was funded by Seqirus. A.G. is an employee of Seqirus. K.J.B. has received unrelated research support from GlaxoSmithKline (GSK) and Dynavax. Y.L. has received unrelated research support from GSK and Novavax. B.A. has received unrelated research support from GSK, Novavax, and Dynavax. H.C.T. has received research unrelated research support from GSK. L.S.S has received unrelated research support from GSK, Novavax, and Dynavax. H.F. T. has received unrelated research support from GSK and Novavax.

Acknowledgements

Potential conflicts of interest. A.G. is an employee of Seqirus. K.J.B. has received unrelated research support from GlaxoSmithKline

Table 2
Vaccine effectiveness against hospitalization for influenza of cell-based and egg-based influenza vaccines, 10/01/2017–05/31/2018.

Influenza type	Age at index date < 65 years old				Age at index date ≥ 65 years old				Total			
	Test positive (N)	Test negative (N)	Vaccine Effectiveness (%) (95% CI)	Adjusted* Vaccine Effectiveness (%) (95% CI)	Test positive (N)	Test negative (N)	Vaccine Effectiveness (%) (95% CI)	Adjusted* Vaccine Effectiveness (%) (95% CI)	Test positive (N)	Test negative (N)	Vaccine Effectiveness (%) (95% CI)	Adjusted† Vaccine Effectiveness (%) (95% CI)
Any influenza												
Unvaccinated	122	1205	–	–	242	1092	–	–	364	2297	–	–
Egg-based vs. unvaccinated	180	1561	−14 (−45 to 11)	−11 (−49 to 17)	612	2886	4 (−13 to 19)	5 (−16 to 22)	792	4447	−12 (−28 to 2)	−2 (−20 to 14)
Cell-based vs. unvaccinated	5	70	29 (−78 to 72)	36 (−65 to 76)	25	132	15 (−34 to 45)	10 (−44 to 44)	30	202	6 (−40 to 37)	14 (−31 to 43)
Cell-based vs. egg-based	N/A	N/A	38 (−55 to 75)	43 (−45 to 77)	N/A	N/A	11 (−38 to 42)	6 (−46 to 39)	N/A	N/A	17 (–23 to 44)	15 (−26 to 43)
Influenza A												
Unvaccinated	85	1205	–	–	188	1092	–	–	273	2297	–	–
Egg-based vs. unvaccinated	132	1561	−20 (−59 to 10)	−12 (−58 to 20)	474	2886	5 (−15 to 21)	8 (−15 to 26)	606	4447	−15 (–33 to 1)	−1 (−21 to 16)
Cell-based vs. unvaccinated	3	70	39 (−97 to 81)	46 (−81 to 84)	19	132	16 (−39 to 50)	14 (−46 to 49)	22	202	8 (−45 to 42)	18 (–32 to 49)
Influenza A (H3N2)												
Unvaccinated	60	1205	–	–	167	1092	–	–	227	2297	–	–
Egg-based vs. unvaccinated	112	1561	−44 (−99 to −4)	−36 (−102 to 8)	435	2886	1 (−19 to 19)	5 (−19 to 24)	547	4447	−24 (−46 to −6)	−7 (−30 to 12)
Cell-based vs. unvaccinated	2	70	43 (−140 to 86)	47 (−131 to 88)	19	132	6 (−56 to 43)	2 (−67 to 42)	21	202	−5 (−68 to 34)	6 (−54 to 42)
Cell-based vs. egg-based	N/A	N/A	60 (−65 to 90)	61 (−63 to 91)	N/A	N/A	4 (−56 to 42)	−4 (−70 to 37)	N/A	N/A	15 (−34 to 47)	12 (−40 to 45)
Influenza B												
Unvaccinated	37	1205	–	–	54	1092	–	–	91	2297	–	–
Egg-based vs. unvaccinated	48	1561	0 (−55 to 35)	−7 (−81 to 37)	138	2886	3 (–33 to 30)	−8 (−61 to 27)	186	4447	−6 (−36 to 18)	−4 (−42 to 24)
Cell-based vs. unvaccinated	2	70	7 (−294 to 78)	16 (−277 to 81)	6	132	8 (−118 to 61)	−6 (−163 to 57)	8	202	0 (−109 to 52)	1 (−113 to 54)

Note: For each influenza type, the number of test positives and number of test negatives are displayed for the unvaccinated patients in the first row, egg-based vaccine recipients in the second row, and cell-based vaccine recipients in the third row.

* Adjusted for age at admission date (continuous), sex, race/ethnicity, BMI, smoking status, health care utilization, influenza vaccination status in the previous season, and comorbidities.

† Adjusted for age at admission date (dichotomous at age 65), sex, race/ethnicity, BMI, smoking status, health care utilization, influenza vaccination status in the previous season, and comorbidities.

(GSK) and Dynavax. Y.L. has received unrelated research support from GSK and Novavax. B.A. has received unrelated research support from GSK, Novavax, and Dynavax. H.C.T. has received research unrelated research support from GSK. L.S.S has received unrelated research support from GSK, Novavax, and Dynavax. H.F.T. has received unrelated research support from GSK and Novavax.

References

[1] Rolfes MA, Flannery B, Chung J, O'Halloran A, Garg S, Belongia EA, et al. Effects of Influenza Vaccination in the United States during the 2017–2018 Influenza Season. Clin Infect Dis 2019.

[2] Sullivan SG, Chilver MB, Carville KS, Deng YM, Grant KA, Higgins G, et al. Low interim influenza vaccine effectiveness, Australia, 1 May to 24 September 2017. Euro Surveill 2017;22.

[3] Skowronski DM, Chambers C, De Serres G, Dickinson JA, Winter AL, Hickman R, et al. Early season co-circulation of influenza A(H3N2) and B(Yamagata): interim estimates of 2017/18 vaccine effectiveness, Canada, January 2018. Euro Surveill 2018;23.

[4] Zost SJ, Parkhouse K, Gumina ME, Kim K, Diaz Perez S, Wilson PC, et al. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. Proc Natl Acad Sci USA 2017;114:12578–83.

[5] Wu NC, Zost SJ, Thompson AJ, Oyen D, Nycholat CM, McBride R, et al. A structural explanation for the low effectiveness of the seasonal influenza H3N2 vaccine. PLoS Pathog 2017;13:e1006682.

[6] Izurieta HS, Chillarige Y, Kelman J, Wei Y, Lu Y, Xu W, et al. Relative effectiveness of cell-cultured and egg-based influenza vaccines among the U.S. elderly, 2017–18. J Infect Dis 2018.

[7] Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. Vaccine 2013;31:2165–8.

[8] Garten R, Blanton L, Elal AIA, Alabi N, Barnes J, Biggerstaff M, 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;67:634–42.

[9] Flannery B, Chung JR, Ferdinands JM. Preliminary estimates of 2017-18 seasonal influenza vaccine effectiveness against laboratory-confirmed influenza from the US Flu VE and HAIVEN Networks. Meeting of the Advisory Committee on Immunization Practices. Atlanta 2018.

[10] Flannery B, Fry AM. Comparing influenza vaccine types: the path towards improved influenza vaccine strategies. J Infect Dis 2018.

[11] Belongia EA, Skowronski DM, McLean HQ, Chambers C, Sundaram ME, De Serres G. Repeated annual influenza vaccination and vaccine effectiveness: review of evidence. Expert Rev Vaccines 2017;16:1–14.

[12] Xie H, Li L, Ye Z, Li X, Plant EP, Zoueva O, et al. Differential effects of prior influenza exposures on H_3N_2 cross-reactivity of human postvaccination sera. Clin Infect Dis 2017;65:259–67.

[13] Fukushima W, Hirota Y. Basic principles of test-negative design in evaluating influenza vaccine effectiveness. Vaccine 2017;35:4796–800.

[14] McElhaney JE, McNeil SA. Test-negative design: The importance of laboratory-confirmed illness in estimating the effectiveness of influenza vaccine in older adults. J Infect Dis 2017;216:399–401.

[15] Andrew MK, Shinde V, Ye L, Hatchette T, Haguinet F, Dos Santos G, et al. The importance of frailty in the assessment of influenza vaccine effectiveness against influenza-related hospitalization in elderly people. J Infect Dis 2017;216:405–14.

[16] Leekha S, Zitterkopf NL, Espy MJ, Smith TF, Thompson RL, Sampathkumar P. Duration of influenza A virus shedding in hospitalized patients and implications for infection control. Infect Control Hosp Epidemiol 2007;28:1071–6.

[17] Ip DKM, Lau LLH, Chan KH, Fang VJ, Leung GM, Peiris MJS, et al. The dynamic relationship between clinical symptomatology and viral shedding in naturally acquired seasonal and pandemic influenza virus infections. Clin Infect Dis 2016;62:431–7.