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High-dose influenza vaccine use among patients receiving hemodialysis in the United States, 2010 – 2013

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Abstract

Background: Standard influenza vaccines may be of limited benefit to patients with end-stage renal disease (ESRD). These patients may benefit from high-dose influenza vaccine, currently indicated for patients aged ≥ 65 years. Studies in other populations have demonstrated that high-dose vaccine elicits a stronger immunological response. We compared vaccine uptake in the United States and predictors of receipt for high-dose and standard influenza vaccines.

Methods: Using data from the United States Renal Data System (2010–2013), we conducted a retrospective cohort study of 421,482 adult patients on hemodialysis. We examined temporal trends in uptake of high-dose or standard trivalent influenza vaccine each influenza season, and used multivariate logistic regression to assess the association between individual-level variables (e.g., demographics, comorbidities) and facility-level variables (e.g., facility size and type) with vaccine receipt.

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Author Contributions

LM, AB, and JBL designed the study. AB and JBL analyzed the data. All authors reviewed and interpreted the results. LM and AB drafted the manuscript. All authors participated in the revision of this article and have approved the final version prior to submission.

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Conflict of Interest

Dr. McGrath is an employee of NoviSci, LLC, a data sciences company, and previously was an employee of RTI Health Solutions. Drs. Layton and Krueger are employees of RTI International, an independent, nonprofit research organization that does work for government agencies and pharmaceutical companies. Dr. Layton was formerly an employee of UNC, where he received unrestricted salary support from the Center for Pharmacoepidemiology in the Department of Epidemiology; current member companies include GSK, Merck, and UCB. Dr. Butler has received investigator-initiated support from Amgen. Dr. Kshirsagar is an advisory board member for Akebia.

Results: The proportion of patients with ESRD who were vaccinated with any influenza vaccine increased from 68.3% in 2010 to 72.4% in 2013. High-dose vaccines were administered to 0.9% of patients during the study period, and 16.7% of high-dose vaccines were administered to patients <65 years of age. Among patients aged ≥65 years, older patients (>79 vs. 65–69 years: OR, 1.29; 95% CI, 1.19–1.41) and patients at hospital-based versus free-standing dialysis facilities (OR, 2.31; 95% CI, 2.13–2.45) were more likely to receive high-dose vaccine, while blacks (vs. whites [OR, 0.66; 95% CI, 0.61–0.71]) and patients with longer duration of ESRD (>9 vs. 0 years: OR, 0.66; 95% CI, 0.55–0.78) were less likely to receive the high-dose vaccine.

Conclusions: While the overall influenza vaccination rate has increased, use of high-dose vaccine among patients with ESRD was very low. Being an older patient, living in the Midwest, and receiving care at hospital-based facilities were the strongest predictors of receiving high-dose vaccine.

Keywords

Influenza; Influenza vaccine; High-dose; End-stage renal disease; Hemodialysis

INTRODUCTION

Prevention of influenza is important for patients with end-stage renal disease (ESRD) due to the risk of severe complications from influenza infections or influenza-related hospitalizations, mortality, and health care costs in this population. Yet, immunogenicity evidence demonstrates that patients with ESRD on chronic hemodialysis have inferior responses to the standard, seasonal trivalent influenza vaccine than the general population. Additionally, effectiveness studies suggest that the standard vaccine provides little benefit in preventing influenza-related outcomes in these patients [1–3].

High-dose inactivated influenza vaccine was licensed by the United States Food and Drug Administration in December 2009 for adults aged ≥65 years [4]; the rationale for introducing this vaccine was to induce higher antibody responses and to provide better protection than the standard vaccine among this high-risk population. The high-dose vaccine contains the same three strains as standard trivalent vaccines, but has four times as much antigen (60 vs 15 µg per strain). A postlicensure randomized controlled efficacy trial including almost 32,000 older adults showed that the high-dose vaccine was 24.2% (95% confidence interval [CI], 9.7%–36.5%) more effective overall in preventing influenza infections than the standard vaccine [5] and was 22.1% (95% CI, 3.9%–37.0%) more effective among patients with one or more high-risk comorbidity [6]. Similarly, a large, effectiveness study conducted in the general Medicare population showed that the high-dose vaccine was more effective than the standard vaccine in preventing probable influenza infection and influenza-related hospitalizations [7].

While influenza vaccine is recommended for patients on dialysis, neither the Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices, nor the Kidney Disease: Improving Global Outcomes Foundation have issued a recommendation stating a preference for the type of vaccine that should be administered in this population [8]. Yet evidence demonstrates that alternative vaccination strategies can elicit an antibody

response greater than that provided by the standard vaccine [9]. Given the availability of high-dose influenza vaccine and the known poor immunogenicity of the standard dose among patients with ESRD on dialysis, we examined the national uptake of each type of influenza vaccine and quantified the association between individual- and facility-level variables and the receipt of high-dose versus standard influenza vaccine since the licensure of the high-dose vaccine in 2009 among patients receiving dialysis.

METHODS

Study population

Data for this study came from Medicare claims collected in the United States Renal Data System (USRDS) [10], which is a population-based registry of most patients with ESRD in the United States. The data included claims billed for dialysis treatment, hospitalizations, outpatient care, medication dispensings, preventive services (including vaccinations), and death.

We used USRDS data from the years 2010 through 2013. Yearly cohorts were created for each influenza vaccination season (defined as August 1 through December 31). The analysis was structured by calendar year rather than full influenza season (which typically extends into the spring of the following year), allowing for the inclusion of the 2013 vaccination season since the vast majority of vaccinations (>98%) [11] are administered in the fall of each influenza season.

We created two analysis cohorts of patients with ESRD receiving hemodialysis for this study: (1) a cohort of all adults used in the descriptive uptake analysis and (2) a cohort of older patients indicated for the high-dose vaccine used in the predictive analysis. For both cohorts, patients were required to have Medicare as a primary payer and Parts A and B coverage to ensure capture of vaccine and comorbidity information. The uptake cohort of all adults included all eligible patients aged ≥ 18 years and required patients to receive regular in-center hemodialysis treatments from May 1 through July 31 of the given year; patients could enter multiple yearly cohorts if eligible each year. The predictive cohort of older adults was restricted to patients aged ≥ 65 years (because the high-dose vaccine is indicated only for patients aged ≥ 65 years) who had at least 6 months of regular in-center hemodialysis treatments prior to August 1; baseline covariates for the predictive modeling were measured during this 6-month period.

Variables

Medicare claims were searched for Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System (HCPCS), and *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes for high-dose vaccine (CPT: 90662) and standard vaccine, which included all other non-high-dose vaccine formulations (CPT: 90654, 90656, 90658, 90660, 90661, 90672, 90673, 90688; HCPCS: G0008, G8482, Q2034, Q2035, Q2036, Q2037, Q2038, Q2039; ICD-9-CM procedure: 99.52). If a patient had more than one vaccine type in a given season, the first vaccine was used to define the patient's exposure group. Individual-level predictors included demographics, Medicaid

eligibility as an indicator of low-income status, health status variables, comorbidities (see Supplemental Table 1 of ICD-9-CM codes), medications (measured using National Drug Codes [NDC]), variables related to functional status used as frailty markers, and other preventive tests and procedures such as pneumococcal vaccination. Facility-level variables included geographic region, facility type, affiliation, profit status, and size.

Statistical Analysis

To understand overall patterns of vaccine uptake by year and vaccine type, vaccine administrations and characteristics of vaccinees in the all-adult, uptake cohort were described. We report the distributions of vaccine type and timing by influenza season, and we report frequencies of patients who received high-dose vaccine in multiple seasons.

Potential predictors of vaccine type were assessed in those aged ≥ 65 years, predictive cohort restricted to patients with 6 months of baseline in-center hemodialysis. We used multivariable logistic regression to estimate the associations between patient- and provider-level variables chosen a priori and the receipt of high-dose influenza vaccine versus standard influenza vaccine. To examine changes in predictors of high-dose vaccine receipt over time, we stratified the analysis by yearly influenza season.

Analyses were conducted with SAS, version 9.3 (SAS Institute, Cary, North Carolina) and R version 3.4.0. This study was considered exempt by the institutional review board at the University of North Carolina due to the deidentified nature of the data.

RESULTS

We identified 421,482 unique patients with ESRD receiving dialysis across all study years; patients could contribute to multiple vaccination seasons, resulting in 1,000,204 unique patient-seasons. Among these patient-seasons, the mean age was 62.7 years (standard deviation, 14.3), 54.4% were aged <65 years, and 55.6% were male (Supplemental Table 2). In the uptake cohort of all adults, the yearly proportion of patients who were vaccinated with any influenza vaccine increased slightly over the study period from 68.3% in 2010 to 72.4% in 2013. High-dose vaccine use increased from 0.3% to 1.3% over the four years of the study; however, almost all patients who were vaccinated received the standard seasonal vaccine (Table 1, Figure 1). Among patients aged ≥ 65 years of age, uptake of high-dose vaccine increased from 0.6% in 2010 to 2.5% in 2013. The majority of both standard vaccine and high-dose vaccine were administered in September and October; 97% of standard-dose vaccines and 93% of high-dose vaccines were administered by the end of October (Figure 1). About 81% of dialysis clinics administered only standard dose vaccine, while 18% administered both standard and high-dose. Of note, 16.7% of high-dose vaccines were administered to patients aged <65 years. About 2% of patients received multiple standard-dose vaccines within a single influenza season; receipt of multiple doses of high-dose vaccines within a single season was rare. Among patients who were eligible across two consecutive influenza seasons, 59% received repeated standard-dose vaccines and $<1\%$ received repeated high-dose vaccines.

In the predictive cohort of older adults (≥ 65 years) who received either standard or high-dose vaccine, there were 138,624 unique patients and 275,803 unique patient-seasons, after excluding 2,872 (0.7%) patients who were missing facility information. Among vaccinees in this cohort, those receiving high-dose vaccine were older than those receiving standard vaccine; 77% of high-dose patients were aged ≥ 70 years compared to 72% of patients receiving standard vaccine (Table 2). High-dose vaccine recipients were predominantly white, had a shorter duration of ESRD, and had a lower prevalence of Medicaid eligibility. These characteristics were generally similar across all influenza seasons (Supplemental Table 3).

Among patients aged ≥ 65 years, facility-level variables had the strongest associations with type of administered vaccine (Figure 2, Supplemental Table 4). Patients receiving care at hospital-based dialysis facilities were more likely to receive high-dose vaccine compared with those receiving care at free-standing clinics (odds ratio [OR], 2.31; 95% CI, 2.13–2.51); significant regional variability also was indicated: patients in the Midwest were more likely to receive the high-dose vaccine than patients in the Northeast (OR, 2.23; 95% CI, 2.02–2.45).

Some individual-level factors were also strongly associated with vaccine type. Older patients were more likely to receive high-dose vaccine (>79 vs. 65–69 years: OR, 1.29; 95% CI, 1.19–1.41), while blacks (vs. whites [OR, 0.66; 95% CI, 0.61–0.71]) and patients with longer durations of ESRD (>9 vs. 0 years: OR, 0.66; 95% CI, 0.55–0.78) were less likely to receive the high-dose vaccine (Figure 2). Receiving the high-dose vaccine was also associated with receiving additional preventive services, such as lipid testing (OR, 1.26; 95% CI, 1.19–1.33) or diabetic eye exams (OR, 1.17; 95% CI, 1.11–1.23). Patients receiving the high-dose vaccine were also less likely to have frailty markers, such as a home hospital bed (OR, 0.81; 95% CI, 0.70–0.93) or mobility aids (OR, 0.89; 95% CI, 0.82–0.97). Results were generally similar within each influenza season (Supplemental Table 4).

DISCUSSION

Although the overall vaccination rate increased slightly over the study period, more than a quarter of patients remained unvaccinated. The overall vaccination rate in 2013 for this study (72.4%) was similar to the national percentage reported for all patients with ESRD (70.7%) in the 2013–2014 season, which included hemodialysis, peritoneal dialysis, and kidney transplant patients [10]. The overall influenza vaccination rate has not changed substantially in more recent years [12]. While the proportion of patients receiving high-dose vaccine did increase marginally over the study period, the vast majority of patients with ESRD were vaccinated with the standard seasonal vaccine, which is a similar pattern to the general population [13]. Although supply of high-dose vaccine may have been limited in 2010, it was widely available in subsequent seasons, therefore vaccine supply is unlikely to explain the low uptake.

We found that facility-level factors, including receipt of care at hospital-based dialysis clinics and geographic region, were the strongest predictors of receiving a high-dose influenza vaccine. Although high-dose vaccine is available at other locations such as some

pharmacies, it is likely that most patients on hemodialysis receive vaccination at their primary dialysis clinic. Many dialysis clinics make decisions regarding what vaccines they will or will not offer based on a variety of factors, including cost, availability, effectiveness, and safety. The types of vaccines available to patients are then limited by the formulary decisions made by each dialysis clinic. During the study period, it is likely that many private dialysis facilities did not include the high-dose influenza vaccine on their formulary; we saw that only 18% of dialysis clinics administered high-dose vaccine. One reason may be cost and the risk of over-stocking the more expensive high-dose vaccine; in 2013, Medicare's reimbursement for the high-dose vaccine (\$31.82) was higher than the standard injectable vaccine (\$6.02), although other types of standard vaccine, such as the recombinant vaccine, were more expensive than the high-dose [14]. From 2013 to 2016, which was after the study period, reimbursement increased for both the high-dose vaccine (\$42.72) and the standard injectable vaccine (\$9.40) [15].

It may also be difficult for providers to provide high-dose vaccine given limited information on effectiveness and safety in the dialysis population. Several studies have shown that the standard trivalent vaccine has limited effectiveness in preventing influenza-related morbidity and mortality among immunocompromised patients, including those on hemodialysis [1], or the elderly [16]. While limited evidence shows that the high-dose vaccine is more effective than the standard vaccine among the general elderly population [7, 17, 18] and nursing home patients [19], with estimates ranging from 13% to 24% more effective, no studies have assessed the comparative effectiveness among patients on chronic hemodialysis. Similarly, there is a lack of data on the safety of this vaccine in the dialysis population; while one would expect similar rates of mild adverse events as seen in the general older population [20], there have been no large-scale safety studies in the dialysis population. It is important to note that while influenza vaccine is recommended for patients on dialysis, a preference for type of influenza vaccine has not been stated in national guidelines.

Several patient-level factors also were associated with high-dose influenza vaccine receipt. Older patients were more likely to receive the high-dose vaccine, a finding similar to the results of a study in the general Medicare population [11]. Providers may be more likely to administer this vaccine to older populations in response to immune senescence, as the higher antigen content provides a better immune response. Although most patients with ESRD have some level of immune impairment, providers may still associate the benefit of a higher antigen vaccine with the lowest immune system function. Also, black patients were much less likely to receive the high-dose vaccine than white patients. Racial differences in receipt of influenza vaccination have been previously documented, with higher uptake among whites compared to other racial and ethnic groups [21, 22]. Finally, an evident dose-response trend was shown for the number of years patients had ESRD. The high-dose vaccine was given most often to patients newly initiating dialysis, followed by a steady decline in high-dose receipt as the number of years with ESRD increased. This finding could reflect patients recently transitioning from pre-ESRD to ESRD, who may have been more likely to have been monitored closely in the primary care setting.

There are several limitations to consider when evaluating the results of this study. First, because we limited the vaccine period from August through December of each season, some

vaccinations may have been missed if they were administered early in the subsequent year. However, this likely represents only a small percentage of vaccines. One study of Medicare patients in 2010–2011 showed that >98% of influenza vaccines were administered prior to December 31 in each influenza season [11]. This restriction allowed us to include vaccinations administered in 2013, as we did not have access to 2014 USRDS data. Second, vaccines were assessed using administrative claims data collected for insurance reimbursement purposes. Therefore, it is possible that some vaccinations were missed if a patient paid for the vaccine out of pocket. Because patients on chronic hemodialysis are seen in the dialysis clinic between 2 and 3 times per week, and influenza vaccines are fully covered by Medicare Part B for this population, it is unlikely that many patients would pay for the vaccine themselves. Additionally, we assessed vaccinations using CPT and HCPCS codes. It is possible that some vaccines could have been billed using NDC codes if a patient received the vaccine at a pharmacy. We expect this to be a small fraction of claims, and to have limited impact on results. Third, there was a limited number of patients receiving high-dose vaccine during the study period and it is possible that variables associated with receiving high-dose vaccine could change over time. The data that were available allowed for a review of uptake nationally. However; it will be important to monitor trends in uptake as more data become available. Finally, we had a limited set of facility-level variables, and several of these variables were the strongest predictors of vaccination. In some instances, large dialysis providers may stock only one type of vaccine, thus limiting patient choice. Provider-wide formulary decisions and internal vaccine dispensing policies may explain some of the role of the facility type in vaccine administrations.

This is the first study characterizing the uptake of high-dose influenza vaccine in patients with ESRD. Use of high-dose vaccine is extremely limited in the dialysis population and is likely associated with decisions made at the level of the dialysis facility. Further research on the comparative effectiveness and safety of this vaccine is needed to assist providers, patients, and the Centers for Disease Control and Prevention in deciding if a preferential recommendation is warranted to provide the most protection to this vulnerable population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Cumulative percent of adult (≥ 18 years) patients with end-stage renal disease receiving dialysis immunized with influenza vaccine, by year

Figure 2.
Individual and facility-level predictors of high-dose versus standard dose influenza vaccination among patients aged ≥ 65 years with end-stage renal disease receiving dialysis, 2010–2013

Table 1.

Number and Proportion of Patients With End-stage Renal Disease Receiving Dialysis Vaccinated With Influenza Vaccine in August-December in the United States Renal Data System, by Vaccine Type and Year

Cohort	Type of Vaccine	2010	2011	2012	2013
Uptake cohort of all adults (18 years)		N=241,115	N=248,364	N=253,796	N=256,929
	High-dose vaccine	776 (0.3)	2,188 (0.9)	2,674 (1.1)	3,319 (1.3)
	Standard vaccine	162,663 (67.5)	165,419 (66.6)	174,920 (68.9)	175,690 (68.4)
	Unknown vaccine	1166 (0.5)	5592 (2.3)	3944 (1.6)	6888 (2.7)
	No vaccine	76,510 (31.7)	75,165 (30.3)	72,258 (28.5)	71,032 (27.7)
Predictor cohort of older adults (aged 65 years)		N=110,530	N=113,116	N=115,321	N=117,016
	High-dose vaccine	667 (0.6)	1,681 (1.5)	2,220 (1.9)	2,890 (2.5)
	Standard vaccine	75,475 (68.3)	75,677 (66.9)	79,678 (69.1)	79,546 (68.0)
	Unknown vaccine	618 (0.6)	2,616 (2.3)	1,839 (1.6)	3,281 (2.8)
	No vaccine	33,770 (30.6)	33,142 (29.3)	31,584 (27.4)	31,299 (26.8)

Note: Data presented as n (%). Analysis restricted to first influenza vaccine per influenza season.

Table 2.

Characteristics Measured During the 6-month Baseline for Patients With End-stage Renal Disease (ESRD) Aged 65 Years Receiving Dialysis and Influenza Vaccination by Influenza Vaccine Type, 2010–2013

Characteristic	High-dose Vaccine (N =5,725 patient-seasons)		Standard Vaccine (N =270,078 patient-seasons)		Standardized Mean Difference ^a
	N	%	N	%	
Age (years)					0.14 ^b
65–69	1,298	22.7	76,214	28.2	
70–74	1,404	24.5	67,174	24.9	
75–79	1,315	23.0	56,046	20.8	
>79	1,708	29.8	70,644	26.2	
Race					0.27 ^b
White	4,321	75.5	170,937	63.3	
Black	1,116	19.5	82,425	30.5	
Other	288	5.0	16,716	6.2	
Male	2,982	52.1	135,933	50.3	0.04
Medicaid eligibility	1,397	24.4	94,778	35.1	0.24 ^b
Cause of ESRD					0.09
Diabetes	2,534	44.3	129,321	47.9	
Hypertension	1,855	32.4	86,924	32.1	
Glomerulonephritis	453	7.9	17,949	6.7	
Other	883	15.4	35,884	13.3	
Years with ESRD					0.21 ^b
0	405	7.1	13,592	5.0	
1–2	2,479	43.3	96,313	35.7	
3–4	1,355	23.7	67,918	25.2	
5–9	1,169	20.4	71,236	26.4	
10	317	5.5	21,019	7.8	
Hospital days in last month					0.03
0	5,066	88.5	239,026	88.5	
1–6	446	7.8	19,617	7.3	
7	213	3.7	11,435	4.2	
Skilled nursing facility days in last month					0.04
0	5,489	95.9	256,889	95.1	
1–27	146	2.6	7,997	3.0	
28	90	1.6	5,192	1.9	
Comorbidities					

Characteristic	High-dose Vaccine (N =5,725 patient-seasons)		Standard Vaccine (N =270,078 patient-seasons)		Standardized Mean Difference ^a
	N	%	N	%	
Cancer	961	16.8	36,482	13.5	0.09
Ischemic heart disease	3,969	69.3	174,745	64.7	0.10 ^b
Diabetes	3,735	65.2	180,380	66.8	0.03
Vascular infection	206	3.6	9,278	3.4	<0.01
Coagulopathy	441	7.7	16,825	6.2	0.06
Chronic obstructive pulmonary disease	1,393	24.3	57,310	21.2	0.07
Transfusion	643	11.2	25,992	9.6	0.05
Substance abuse	230	4.0	9,327	3.5	0.03
Lipid abnormality	2,918	51.0	119,909	44.4	0.13 ^b
Liver disease	542	9.5	16,183	6.0	0.13 ^b
Dementia	449	7.8	25,041	9.3	0.05
Anemia	5,686	99.3	269,498	99.8	0.07
Hypertension	4,201	73.4	191,753	71.0	0.05
Frailty Indicators					
Home hospital bed	186	3.3	12,594	4.7	0.07
Mobility aids ^c	633	11.1	34,795	12.9	0.06
Diabetes mellitus complications	2,381	41.6	121,076	44.8	0.07
Ambulance/life support	1,865	32.6	95,141	35.2	0.06
Weakness	854	14.9	45,672	16.9	0.05
Use of oxygen	978	17.1	39,925	14.8	0.06
Skin ulcer (decubitus)	708	12.4	31,205	11.6	0.03
Difficulty walking	874	15.3	44,996	16.7	0.04
Screening tests/prevention ^d					
Pneumonia vaccine receipt	555	9.7	27,027	10.0	0.01
Hepatitis B vaccine receipt	1,493	26.1	66,406	24.6	0.03
Cancer screening	1,134	19.8	45,421	16.8	0.08
Diabetic eye exam	2,432	42.5	100,353	37.2	0.11 ^b
Lipid test	2,404	42.0	94,309	34.9	0.15 ^b
Facility profit status					0.50 ^b
For profit	3,788	66.2	227,051	84.1	
Nonprofit	1,937	33.8	43,027	15.9	
Facility type					0.50 ^b
Free-standing	4,002	69.9	241,555	89.4	
Hospital-based	1,723	30.1	28,523	10.6	

Characteristic	High-dose Vaccine (N =5,725 patient-seasons)		Standard Vaccine (N =270,078 patient-seasons)		Standardized Mean Difference ^a
	N	%	N	%	
Facility size (number of dialysis stations)					0.16 ^b
<20	3,066	53.6	123,946	45.9	
20–29	1,887	33.0	106,531	39.4	
30–80	772	13.5	39,601	14.7	
Region					0.37 ^b
Northeast	861	15.0	47,744	17.7	
South	1,915	33.5	115,554	42.8	
West	787	13.8	47,796	17.7	
Midwest	2,159	37.7	57,671	21.4	
Other	...	...	1,313	0.5	

^aCalculated as the difference in means or proportions of a variable divided by the pooled SD of the variable. A standardized mean difference of 0.1 or greater would suggest a substantial difference in means or proportions between groups.

^bSubstantial difference in mean or proportion between groups.

^cDefined as use of walker, wheelchair, or modified bathroom equipment.

^dDefined during baseline period until date of influenza vaccine.

Symbol: ... = Cell size too small to display.