



HHS Public Access

Author manuscript

Health Econ. Author manuscript; available in PMC 2022 January 03.

Published in final edited form as:

Health Econ. 2018 February ; 27(2): 252–265. doi:10.1002/hec.3539.

Factors associated with the pricing of childhood vaccines in the U.S. public sector

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Summary

Vaccine purchase cost has grown substantially over the last few decades. A closer look at vaccine prices reveals that not all vaccines shared the same increasing pattern. Various factors, such as vaccine attributes, competition, and supply shortages, could relate to price changes. In this study, we examined whether a variety of factors influenced the prices of noninfluenza childhood vaccines purchased in the public sector from 1996 to 2014. The association differed among price-capped vaccines and combination vaccines. There was an increasing time trend in real prices for non-price-capped vaccines, which was mostly offset by the effect of market longevity. The effect of competition in lowering prices was more pronounced among non-price-capped vaccines when manufacturer and vaccine component fixed effects were excluded. Supply shortage, manufacturer name change, and number of vaccine doses in series showed no effect. The results may help policy makers better understand price behaviors and make more informed decisions in vaccine planning and financing.

Keywords

childhood vaccine prices; vaccine attributes; vaccine market; vaccine shortage

1 | INTRODUCTION

Children in the United States routinely receive vaccination to help prevent more than a dozen vaccine-preventable diseases.¹ Given the importance of childhood vaccination, U.S. federal and state governments have maintained a substantial effort to ensure the delivery of recommended vaccines to children in need. Every year, the Centers for Disease Control and Prevention (CDC) and states purchase vaccines using CDC contracts with vaccine manufacturers. In the U.S. vaccine market, the purchased doses in the public sector account for about half of total childhood vaccine purchases.² In recent years, the Vaccines for

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

¹For more information about the vaccine-preventable diseases, please see <http://www.cdc.gov/features/vfcprogram/#VFClist>.

²Based on CDC unpublished data.

Children (VFC)³ Program represents an annual spending of over 4 billion dollars.⁴ Over the last few decades, vaccine purchase cost has grown substantially. Among the publicly purchased vaccines, the average price (weighted by purchased quantity) climbed from around \$10 per dose in 1996 to over \$50 per dose in 2014 (Figure 1, in 2014 US dollars). However, when we look at prices of individual vaccines, there seem to be different patterns. Some vaccines had almost continuous increases in prices since the first year in the market, such as the 13-valent pneumococcal conjugate vaccine (PCV13) and varicella (Var) vaccine. Some vaccines had relatively stable prices, such as the hepatitis A (Hep A) vaccine, with prices within the range of \$11 to \$15 for nearly 20 years. Other vaccines exhibited decreasing trends or more transitory behavior. Figure 2 illustrates the different price trends of several selected vaccines.

The vaccine market also has several unique features in terms of its structure. There are few manufacturers, which produce and sell to both private and public buyers. About half of doses are purchased by a single buyer—CDC. CDC purchases vaccines through contracts directly with manufacturers. The production of vaccines is highly regulated by the Food and Drug Administration (FDA). The demand for vaccines is constrained by the size of birth cohorts and the number of vaccines recommended by the Advisory Committee on Immunization Practices (ACIP) (Institute of Medicine, 1993). The demand for vaccines tends to be inelastic since vaccines are recommended regardless of price changes. It is unclear what is behind vaccine price variation and how supply-side competition plays a role in the prices faced by CDC.

A literature search revealed that a limited number of studies have previously examined vaccine prices. Pauly, Sepe, Sing, and Willian (1996) provided a series of economic analyses on critical issues in vaccine supply and discussed price increases from the 1970s to the 1990s. In an empirical analysis of vaccine pricing, they used 1977 to 1992 data of three vaccines⁵ and estimated the influence on CDC purchase prices from the expected purchase doses and the number of actual and potential competitors. They found the impact of expected number of doses was positive and significantly related to price. However, estimates of the impact of competitors were unstable and sensitive to small changes in model specification. Lichtenberg (2002) had a study on vaccine prices covering a later period from 1992 to 2002. He noticed a decreasing trend in inflation-adjusted prices paid by the federal government for given vaccines. He also looked at the relationship between market concentration and prices and found a weak positive correlation. Davis, Zimmerman, Wheeler, and Freed (2002) looked at the sum of prices of recommended vaccines and found an increasing trend in the total purchase cost per child from age 0 to 6 years during 1997 to 2001. Chen, Messonnier, and Zhou (2016) updated this study using data from 1996 to 2014 for children aged 0 to 18 years. They also found an increasing trend, and the increase was largely due to vaccine recommendation updates, particularly the introduction of new vaccines. Both studies primarily focused on total purchase costs of a list of recommended

³VFC is a federally funded program that provides vaccines at no cost to children who are Medicaid-eligible, uninsured, American Indian or Alaska Native (AI/AN), or underinsured and vaccinated at Federally Qualified Health Centers or Rural Health Clinics.

⁴CDC website on budget information <http://www.cdc.gov/fmo/topic/Budget%20Information/index.html>.

⁵The three vaccines were diphtheria and tetanus toxoids and pertussis vaccine (DTP), measles–mumps–rubella (MMR) vaccine, and oral polio vaccine (OPV).

vaccines rather than cost of each specific vaccine. Some other studies examined how prices related to sellers' and buyers' behaviors, such as entry and exit of vaccine products (Danzon & Pereira, 2011) and bargaining power during vaccine purchase (Kauf, 1999). Danzon and Pereira (2011) confirmed the number of competitors was related to the increased hazard of exit from the vaccine market. Kauf (1999) and Pauly et al. (1996) used catalog prices (for private buyers) in their studies. The catalog prices, which are typically much higher than CDC purchase prices, are reported by vaccine manufacturers to CDC, and little is known about how close these reported prices are to the real transaction prices in the private sector. Freed, Cowan, Gregory, and Clark (2009) surveyed 76 private practices in five states and found that the vaccine purchase prices paid by the practices varied widely and some prices were even lower than CDC purchase prices. Thus, private sector prices are potentially varied and largely unknown, whereas CDC purchase prices, which we used here, are real transaction prices set by CDC contracts.

Considering price trend and competition among products in the broader pharmaceutical industry, evidence suggests a strong impact of competition on drug prices, especially after the patent expires (Dylst & Simoens, 2011; Green, 1998; Lu & Comanor, 1998). For drugs with important therapeutic gains, launch prices can be two or three times those of existing drugs used for the same purposes, and drugs that largely duplicate the actions of currently available products are typically priced at comparable levels (Lu & Comanor, 1998). When regulations restricting price increases are presented, firms would price new drugs above the expected value initially. And price decreases after drug launch are more likely when there is higher uncertainty (Shajarizadeh & Hollis, 2015). The same findings may also apply to vaccine markets. However, with fewer products and more predictable demand, the impact could be different among vaccine products.

This study aims to explain the price changes among publicly purchased childhood vaccines recommended for routine vaccination by the ACIP. A variety of potential influencing factors were considered, including vaccine attributes, competition, supply shortage, and manufacturer name changes (due to mergers or acquisitions of manufacturers). We stratified our analysis based on whether the vaccine was subject to a price-cap and whether the vaccine was a combination vaccine. Because the increasing burden of vaccine purchase cost has implications for the financing of all immunization programs, our findings may also help decision makers better understand price behavior, identify factors that contribute to lower prices, predict future price trends, and plan for future resource allocation.

The rest of the paper proceeds as follows. Section 2 elaborates the background of the vaccine market and different vaccine products. Section 3 describes the data used in the study and introduces the empirical model for the regression. Section 4 presents the results of the analysis, and Section 5 summarizes the findings and discusses the implications.

2 | BACKGROUND

2.1 | Vaccine market structure

The overall vaccine market consists of a number of smaller markets, one for each specific vaccine. Vaccines that target different diseases cannot be substituted for one another; thus,

there is no competition among them. However, substitution does exist between different brands within one vaccine type (same antigens) or between vaccines that partially overlap in providing protection against a particular disease. More generally, the vaccine market differs from markets of other commodities in several ways. The vaccine market has an inelastic demand, and the supply side is dominated by a small number of manufacturers. Given the importance and potential safety impact of vaccine products, this market is also highly regulated. A book by the Institute of Medicine (1993) described the U.S. pediatric vaccine market as “predictable, limited and stable.”

2.1.1 | Demand—In the United States, all children from birth to 18 years are recommended to follow the immunization schedules developed by the ACIP. The demand for vaccines is determined by the size of the birth cohort of each age group and vaccine take-up rate. Because population structure tends to stay stable, changes in demand are more often driven by changes in vaccine take-up rate. For newly introduced vaccines, the demand may rise gradually as vaccine uptake climbs up. Immunization campaigns are usually incorporated into the introduction process to help increase awareness and boost take-up. The demand is likely to stay stable afterward unless there are other recommendations or policy changes. Health policies, such as state vaccination requirement for daycare and school entry, Medicaid expansion, and the provision of preventive care without cost sharing under the Affordable Care Act (ACA),⁶ may also increase take-up rate.⁷ The public sector, which funds childhood vaccines through the federal VFC and Section 317 immunization funds, and other state and local immunization program funds, usually fulfills all vaccine orders and ensures vaccines are available to children in need. It, therefore, tends to be very inelastic to price changes. In the private sector, depending on the proportion of cost sharing, the demand could be more elastic than that of the public sector. However, as the preventive care has been provided without cost sharing since 2010 ACA, the demand would become less sensitive to prices in the private sector too.

2.1.2 | Supply—Because of nontrivial fixed costs and extensive production regulations, the vaccine industry is dominated by a small number of manufacturers (Coleman, Sangrue, Zhou, & Chu, 2005). Market entry is difficult and much less common than market exit (Danzon & Pereira, 2011). Some vaccines, such as the MMR and Var, rely on monopoly suppliers. Most existing vaccines are produced by no more than three manufacturers. These few manufacturers make the vaccine supply vulnerable to supply shortages (Sloan, Berman, Rosenbaum, Chal, & Giffin, 2004). Before manufacturers reach their production capacity level, the marginal cost of vaccine production would be small. Once they are close to the capacity limit, they would have little flexibility to increase production volume in a short period of time.

⁶More about Preventive Care Benefits can be found on [healthcare.gov](https://www.healthcare.gov/preventive-care-benefits/) website <https://www.healthcare.gov/preventive-care-benefits/>.

⁷School entry requirements have been demonstrated to be highly effective in increasing vaccine coverage rates (Abrevaya & Mulligan, 2011; Bugenske, Stokley, Kennedy, & Dorell, 2012; Kharbanda, Stockwell, Colgrove, Natarajan, & Rickert, 2010; Mah, Guttman, McGeer, Krahn, & Deber, 2010). Existing evidence for the effect of Medicaid expansion and ACA on vaccine take-up rate is limited and mixed. It was found that ACA provisions were associated with increases in young adult women’ human papillomavirus (HPV) vaccine initiation and completion (Lipton & Decker, 2015). For influenza vaccine coverage, there was no significant increase among young adults (Barbaresco, Courtemanche, & Qi, 2015; Lau, Adams, Park, Boscardin, & Irwin, 2014) after the 2010 ACA provisions. No evidence was found for vaccine take-up among children aged 0–18 years. It was possibly due to the existence of VFC and other vaccine programs, which had already been providing vaccines at no cost to children in need.

2.1.3 | Public and private sectors—Vaccines, as a commodity with positive externality, tend to be underconsumed. The government is actively involved in the market to promote vaccination coverage. There are two major classes of buyers in the childhood vaccine market. CDC as a major buyer in the public sector purchases about half of the vaccines in the market on behalf of the federal and state governments. The private sector consists of private health-care providers, hospitals, pharmacies, and other health care organizations. They purchase vaccines to serve the populations that do not qualify for publicly funded vaccines.

Every year, CDC announces contract opportunities for all existing pediatric vaccine products and solicits proposals from pediatric vaccine manufacturers. CDC makes multiple contract awards rather than utilizing a “winner take all” strategy to ensure sufficient supply, mitigate the possible effects of vaccine shortages and delays, and allow providers to have a full range of choices for the publicly purchased vaccines to serve their patients. With regard to vaccine pricing negotiations, CDC uses numerous price comparison sources when reviewing pricing proposals. These sources include private sector prices, prior year CDC contract prices, and prices from several other federal vaccine purchase mechanisms. Once contracts are awarded, CDC utilizes its contracts to make purchases to support a federal vaccine inventory that is used to fill orders that are shipped directly to providers administering vaccines. CDC’s immunization awardees (programs that receive CDC immunization grant funds, i.e., state health departments, certain large city immunization projects, and certain current and former U.S. territories)⁸ are also able to use their own state/local funds to place orders against the CDC contracts to purchase vaccines for their providers. Vaccines are distributed to providers at the direction of CDC’s immunization awardees. Providers, working with their state immunization program, choose vaccine products according to their preferences. Because it is CDC, but not the providers, that directly pays for the vaccines, the providers may not be sensitive to price differences (CDC, 2016).

2.2 | Price-capped vaccines, combination vaccines, and the rest

A few vaccines were subject to price caps established by the legislation of 1993.⁹ It directly limits the price level, so factors, such as competition, are not likely to affect the capped prices in the same way as they do for non-price-capped vaccines. For vaccines purchased under contract as of August 1993, increases in future contract prices are limited to the economy-wide price inflation. Vaccines developed subsequently are not subject to a price cap. The price cap is also removed when vaccine formulations change and the vaccine is licensed under a different FDA biologics license number (Rodewald, Orenstein, Mason, & Cochi, 2006). In 2014, there were still three vaccine brands under the price cap.¹⁰ The MMR vaccine shown in Figure 2 belongs to this group.

Another feature that may affect vaccine prices is whether the vaccine is a combination vaccine or not. In this study, a combination vaccine refers to a vaccine that satisfies the following two conditions: (a) It contains multiple antigens, and (b) through its use,

⁸From CDC Vaccine Price List website <http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/>.

⁹Omnibus Budget Reconciliation Act (OBRA) of 1993. Section 1928 of the Social Security Act. US Code. Vol. 42. p. 1396.

¹⁰They were ActHib® (Hib vaccine), IPOL® (polio vaccine), and MMR II® (MMR vaccine).

the total number of injections needed to fully immunize a child would be reduced.¹¹ Patients receiving a DTaP-Hib combination vaccine, for example, would only need one vaccination instead of two (DTaP and Hib separately). Price-capped and combination vaccines are not mutually exclusive; however, price-capped vaccines in our study were mostly noncombination vaccines.¹² The prices of combination vaccines are usually higher than the sum of the component vaccine prices (Chen, Messonnier, & Zhou, 2016). Combination vaccines also create competition among vaccines that protect against the same diseases. A few studies (Behzad, Jacobson, & Sewell, 2012; Behzad, Jacobson, Jokela, & Sewell, 2014; Robbins, Jacobson, & Sewell, 2010) compared relative prices among partially overlapping combination vaccines. Their analyses imply that competition between overlapping combination vaccines is important for vaccine pricing.

3 | DATA AND METHODS

The primary goal of this study is to analyze how various factors, such as vaccine attributes, competition, and supply shortage, are associated with prices among three groups of childhood vaccines in the public sector.

3.1 | Data

Our data include noninfluenza vaccines for children aged 0 to 18 years that were purchased by the public sector. The data cover the period from 1996, two years after the VFC program was established, to the most recent available year, 2014. We focused on routine childhood vaccines covered by the VFC program. We excluded influenza vaccines because they are influenced by seasonal factors and differ in many other important ways from other recommended vaccines. We also excluded a few less common vaccines (diphtheria and tetanus toxoids adsorbed, or DT; measles vaccine, or ME, measles–rubella vaccine, or MR; mumps vaccine, or MU; and rubella vaccine, or RU).¹³

The CDC Vaccine Price Lists provide current and archived vaccine prices on the CDC website.¹⁴ CDC costs per dose are the contract prices at which vaccines are purchased for immunization programs. Each year, one or more¹⁵ contract price lists are posted. Because the contracts are usually signed or renewed on April 1 annually, we used price lists of April 1 or the closest available ones for our analysis. The price lists also provide information on vaccine brand names, packaging types, manufacturers, federal excise tax, and whether the vaccine is thimerosal-free. Our observation unit was based on brand names. When multiple packaging types were listed under one brand name, we combined them into one

¹¹Examples include diphtheria, tetanus, acellular pertussis, and haemophilus influenzae type b vaccine (DTaP-Hib), Hep A and Hep B vaccine (Hep A-Hep B), and MMR-Var. Vaccines like MMR or DTaP that already contain multiple antigens are not considered as combination vaccines, because their corresponding single antigen vaccines are rarely used now in the United States and the use of MMR or DTaP does not result in fewer shots needed.

¹²The only price-capped combination vaccine in our study was diphtheria, tetanus, pertussis, and haemophilus influenzae type b vaccines (DTP-Hib), which were purchased during 1996 to 2000. It was included in both the price-capped and combination vaccine groups.

¹³These vaccines were only used by patients who could not take Diphtheria and Tetanus toxoids and acellular Pertussis vaccine adsorbed (DTaP) or MMR vaccine.

¹⁴<http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html>.

¹⁵The number of contracts depends on the year. In earlier years, there was only one price list for the whole year. In later years, there were usually multiple price lists.

observation using the quantity-weighted average price of all packaging types. More often than not, prices did not vary much cross packaging types. Each year, the number of vaccine brands purchased by the CDC ranged from below 20 to over 30. Totally, there were over 50 brands ever purchased in the study period (over 30 brands for non-price-capped and noncombination vaccines and about 10 brands for price-capped and combination vaccines, respectively). There have been 12 manufacturers ever involved in the contracts during the study period. Most vaccines were produced by one to three manufacturers.

For each vaccine brand, the license year and the number of approved doses were collected from ACIP vaccine recommendation documents, the FDA website,¹⁶ and the Red Book.¹⁷ Other vaccine characteristics including combination vaccine or not and antigen components (e.g., DTP-containing vaccines, Hib-containing vaccines) were collected from CDC's Pink Book (CDC, 2012). Vaccines that were subject to price caps were identified based on purchase contract of August 1993, according to the legislation of that year (see earlier discussion in Section 2.2).

There were also a few manufacturers that changed their names due to mergers or acquisitions. We identified any manufacturer name changes of the studied vaccines and confirmed that they were due to mergers based on documented merger events.¹⁸ The identified name-changing events are summarized in Table A.2.

Limited supply or supply shortages were identified according to the CDC's website of Current Vaccine Shortages & Delays¹⁹ and several other references (see Table A.3 for details). We recorded the time of shortage and affected vaccine brands. Shortages started before April of a particular year were counted as shortages in that year. There were a few shortages that started after April and ended later than April the next year, we counted them as shortages in the next year. Such shortage events are summarized in Table A.3

3.2 | Variables and empirical model

We used a multivariate regression model to examine the relationship between variables of interest and vaccine prices. The analysis was conducted separately for price-capped vaccines, combination vaccines, and the rest because (a) some variables are not defined or have little variation for some groups (more details in the following paragraphs); (b) price-capped vaccines had less variation in prices and would weaken the relationship tested in this study; (c) combination vaccines compete with both component vaccines and overlapping combination vaccines, the effects would be better detected when examined separately from noncombination vaccines. The general form of our estimation equations is as below

$$\ln P_{ijkt} = \alpha + X_{ijkt}\beta + M_{ijkt}\gamma + \varepsilon_{ijkt}. \quad (1)$$

¹⁶<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/default.htm> (retrieved in Sep 2013).

¹⁷RED BOOK Online® developed by Truven Health Analytics Inc.

¹⁸Table 12.4 from "Markets for Pharmaceutical Products" by Fiona Scoot Morton and Margaret Kyle (2012), Chapter 12 in M.V.

Pauly, T.G. McGuire, and P.O. Barros, editors, Handbook of Health Economics Volume 2 (Elsevier), pp. 763–823.

¹⁹<http://www.cdc.gov/VACCINES/vac-gen/shortages/default.htm> (retrieved in Sep 2013).

Dependent variable $\ln P_{ijkt}$ stands for the natural logarithm of adjusted pretax price (in 2014 US dollars)²⁰ for brand i of vaccine type j produced by manufacturer k in year t . In our baseline model, the explanatory variables are represented by X_{ijkt} , a vector of basic vaccine attributes and a linear time trend. We then extended the model by including a vector of additional variables, M_{ijkt} , covering competition, manufacturer name changes, and supply shortages. In additional specifications, we also included manufacturer fixed effects (for any unobserved time-invariant differences across manufacturers) and vaccine antigen component fixed effects²¹ (for unobserved time-invariant differences due to antigen component). Difference in production costs across manufacturers, as an important but unobserved factor, is likely to be captured by the manufacturer fixed effects. Variation in vaccine effectiveness across antigen types is likely to be captured by the antigen component fixed effects. The error term is represented by ε_{ijkt} .

A complete variable list with detailed information on variable definition and data sources is presented in Table A.1. The standard errors in all regressions were clustered by vaccine types. All regressions were performed in Stata 14 (College Station, TX).

Among the basic vaccine attributes in X_{ijkt} , there was an “age” measure, defined as the number of years since the product license was approved, to capture the effect of being “young” or “old” vaccines in the market. It is observed that more recently introduced vaccines have higher prices, primarily due to the use of new and better technologies in vaccine development and production. And, as manufacturers recoup the fixed cost of producing the vaccines, their prices are likely to go down over time because the marginal production cost would be small. We included the number of doses approved for use for each product (except combination vaccine products) to distinguish multiple doses versus single dose. For combination vaccines, the approved dose is harder to define, because it usually depends on individual vaccination history. We, therefore, excluded this variable from the regression for combination vaccines and replaced it by another measure—*Components*—that counts the number of components a combination vaccine has.²² The more components a combination vaccine contains (i.e., the more diseases it can prevent), the more expensive it could be. Another vaccine attribute included is whether a vaccine product contains thimerosal, a mercury-based preservative used in multidose vials of vaccines. Thimerosal was eliminated in most vaccine products since 2000 as a precautionary measure.²³ The variable is likely to reflect the effect of removing thimerosal on vaccine production cost and then vaccine prices.

²⁰Excluding the federal excise tax from vaccine prices. Natural logarithm of price was used because the adjusted pretax prices were skewed (skewness = 1.46 compared to 0 in normal distribution). The prices were deflated using the Consumer Price Index, or CPI (2014 = 100). The general CPI, rather than CPI on medical care, was used to adjust for general economy-wide inflation and reflect the real value of a dollar in 1 year versus another. GDP deflator could also be a good or even better index to adjust for trends in expenditures (see http://meps.ahrq.gov/about_meps/Price_Index.shtml for more details). We still used CPI in order to be consistent and comparable with previous literature. Moreover, our experiments with different deflators showed that it had little impact on our findings.

²¹Examples include diphtheria, tetanus and pertussis (DTP)-containing vaccines, and Hep A-containing vaccines. A full list of antigen components included can be found in Table A.1.

²²For example, *Components* equals to 2 for Hep B-Hib vaccine (which has two components—Hep B and Hib) and 3 for diphtheria, tetanus, acellular pertussis, polio inactivated, and hepatitis B vaccine, DTaP-IPV-Hep B (which has three components—DTaP, IPV, and Hep B).

²³For more information about thimerosal in vaccines, see <http://www.cdc.gov/vaccinesafety/concerns/thimerosal/>.

Additional variables of interest are represented by M_{ijkt} . We first included three competition variables—two measure direct competition and one indicates indirect competition. Direct competition refers to competition among vaccines of the same type (same antigens). They provide immunization against the same disease(s) and only differ in brand names; thus, they are usually close substitutes and compete directly with each other.²⁴ We counted the number of brands for each vaccine type and created indicators for (a) direct competition with one other brand (being one of the two brands of a vaccine type), denoted as *DirectCompete1*, and (b) direct competition with two or more other brands (being one of three or more brands of a vaccine type),²⁵ denoted as *DirectCompete2*. The underlying default case is no direct competition (being the only brand of a vaccine type). In fact, the default case corresponds to the case of a monopoly supplier, whereas *DirectCompete1* and *DirectCompete2* are linked to duopoly and oligopoly suppliers, respectively. The competition level increases from 0 in the default case to the maximal in *DirectCompete2*. Another indirect competition measure, *IndirCompete*, is introduced to capture the competition between noncombination and combination vaccines, which partially share common vaccine antigens. These products do not belong to the same vaccine types (i.e., they are not perfect, or close, substitutes) but partially overlap in providing immunization against certain diseases.²⁶ The dummy variable *IndirCompete* is created with 1 indicating the existence of partial substitutes. The values of competition variables varied across vaccines. For a particular vaccine, the values of competition variables could vary from year to year if there were changes in the numbers of directly competing and indirectly competing products. Thus, the competition variables are identified based on variation over time and across vaccines.

For regressions among combination vaccines, different competition variables are needed. It is because competition measures defined above have little or no variation among combination vaccines.²⁷ We introduced two new measures that better capture the competition among combination vaccines—*ShareComp1* and *ShareComp2*. Depending on how similar one combination vaccine is compared to the others, we count the number of components in common with other combination vaccines. If there is one and only one component in common, *ShareComp1* equals to 1 (0 otherwise). If there are two or more components in common, *ShareComp2* equals to 1 (0 otherwise).²⁸

²⁴For example, Tripedia® and Infanrix® are two brand names of DTaP vaccines and they belong to the same vaccine type (DTaP), so there is direct competition between the two. Another example is HPV vaccine, which has two brands—Gardasil® and Cervarix®. Although they are not exact substitutes for each other (Cervarix protects against HPV types 16 and 18 and Gardasil protects against HPV types 6, 11, 16, and 18. Gardasil also protects against genital warts and cancers of the anus, vagina, and vulva in addition to cervical cancers, and it was the only HPV vaccine available for males before the new 9-valent HPV vaccine Gardasil 9® was introduced in 2015), they are still close enough (in protecting against cervical cancers in women) and are thus considered as of the same vaccine type (HPV).

²⁵The definition actually requires the other brands to be produced by different manufacturers. It is true in most cases. In very rare cases that another brand (of the same vaccine type) is produced by the same manufacturer, we do not consider it as a totally different brand.

²⁶For example, measles, mumps, rubella, and varicella (MMR-V) vaccine and MMR vaccine (two different vaccine types) overlap in protecting against MMR. These products can serve as partial substitutes and thus compete indirectly with each other.

²⁷In fact, all combination vaccines had *IndirCompete* equal to 1 because they all at least indirectly competed with their component vaccines in providing protection against certain diseases. They also had much less direct competition, because few of them had more than one brand.

²⁸For example, Hep-Hib vaccine in 2014 has *ShareComp1* equals to 1 (there were combination vaccine products that contained either Hep B or Hib in 2014) and *ShareComp2* equals to 0 (no other combination vaccine product that contained both Hep and Hib in 2014).

Market events such as name changes due to mergers and acquisitions may also affect product prices. We captured such events by a name-change indicator. For manufacturers that were merged or acquired by other firms and changed their names, we assigned 1 for their products and 0 for all other products in the event year. We also included a 1-year lag term for any delayed effects of a name-change event. The name-change events that affected vaccines in our study are summarized in Table A.2. It turned out that all the observed name-changing mergers in our study were between manufacturers that did not produce the same vaccines. Therefore, the mergers in our case did not reduce the number of competing products (thus did not reduce competition). To distinguish from mergers that commonly result in reduced competition, we refer to the mergers in our study as name-changing events. Thus, the model would indicate whether a name change due to a merger that did not reduce the number of competing products was still associated with any price change.

Many vaccines experienced shortages or limited supply during the study period. We introduced several shortage indicators and tested whether reduced supply raised prices as suggested by economic theory. Because one product in shortage may not only affect itself but also affect its directly or indirectly competing products, we created two groups of shortage indicators—shortage in own products and shortage in competing products, each with 1-year lag effects. We also summarized reasons of the shortages in Table A.3. Although a couple of shortages had no clearly identified reasons, many others were related to problems during the manufacturing process, which tended to be exogenous.²⁹

For the stratified regressions, we did not include fixed effects in the regressions for price-capped vaccines and combination vaccines, because these two groups had fewer observations. We also excluded *age* from the regression for price-capped vaccines, because price-capped vaccines were older and ages of these vaccines were highly correlated with the time trend. For combination vaccines, we did not specify the approved doses, because it usually depends on individual vaccination history. Instead, we provided the component counts for each combination vaccine. We also excluded indirect competition variables and replaced the direct competition variables by *ShareComp1* and *ShareComp2* for combination vaccines.

4 | RESULTS

Table 1 presents summary statistics for this data set. Among the three groups of vaccines, the non-price-capped and noncombination vaccines had the most observations (300 observations). The mean vaccine price during 1996 to 2014 was about \$11 for price-capped vaccines and \$41 for combination vaccines (in 2014 \$, excluding federal excise tax). The mean price of non-price-capped and noncombination vaccines fell between the two. Among non-price-capped and noncombination vaccines, the majority of the observations had one directly competing products and about 10% of the observations had two or more. Over half of the observations had indirectly competing products. Among price-capped vaccines, the proportion of observations that had indirect competing products was as high as 78%. Among

²⁹We also conducted a robustness check in which we only included shortages that were clearly due to problems during the manufacturing process. The results were discussed in the Results section.

combination vaccines, more than half of the observations had shared one component with at least another combination vaccine, and about one third of the observations had shared two or more components with at least another combination vaccine. There were only a small number of products that ever experienced manufacturer name changes or shortage events. The average age of vaccine observations was about 16 and 6 years for price-capped vaccines and combination vaccines, respectively. The average age of the other vaccines was between the two. The average approved doses in a vaccine series were about 3 doses for noncombination vaccines. And the average number of components in combination vaccines was over 2. The majority of our vaccine observations were thimerosal-free due to the fact that thimerosal was eliminated in most vaccine products since 2000. Among vaccine antigen components, many non-price-capped and noncombination vaccine observations contained DTP. Hib-containing was common among price-capped vaccines. And combination vaccines had many DTP-, Hib-, and Hep B-containing products.

Table 2 presents regression results for seven models among three groups of vaccines. Models A through E are for non-price-capped and noncombination vaccines. Models F and G are for price-capped vaccines and combination vaccines, respectively. In each model, the dependent variable is the natural logarithm of inflation-adjusted pretax vaccine prices. Models A to G show whether the associations persist as more controls are added and whether the pattern is the same across price-capped vaccines, combination vaccines, and the rest.

The model in column A is the baseline specification with four independent variables—age (years in the market since licensure), approved doses, thimerosal-free indicator, and time trend. The estimation results indicate that older vaccines were associated with lower prices. This tends to agree with our prior expectation. Meanwhile, the linear time trend of vaccine prices is significantly positive, suggesting climbing prices over time (after inflation adjustment). Taking new vaccines as an example, the estimate implies that a vaccine introduced in the current year (with age = 0) would have a higher launch price than 1 year ago, independent of inflation. Approved doses are not significant, which implies, for example, that a vaccine with 3-dose series might not be more expensive per dose than a vaccine with 4-dose series, keeping everything else equal. The indicator for the removal of thimerosal suggests thimerosal-free vaccines were not priced significantly different from vaccines with thimerosal.

The model in column B (model A+ competition and shortage variables) explores the impact of competition, manufacturer name changes, and shortages on vaccine prices. Three variables that measure direct and indirect competition show significantly negative effects on vaccine prices. The magnitudes of the three variables are large compared to the other estimated coefficients. Manufacturer name change and its lag term do not show a significant association with prices, which might relate to the fact that the name-changing mergers observed in this study did not result in a reduction in the number of competing products. We indicated shortages in own product as well as in competing (both directly and indirectly) products. None of the four shortage indicators is significant.³⁰ The insignificance may

³⁰We also ran regressions including only shortages due to problems during manufacturing process as a robustness check, the results were similar. All of the four shortage indicators remained insignificant.

relate to CDC's responses to reported shortages. Temporary changes in immunization recommendations are usually made during shortages, including deferring selected doses, prioritizing vaccine administration for high-risk groups, or using alternative products. CDC may also activate vaccine stockpile to enhance the availability of the vaccine in shortage (Rodewald et al., 2006; Santoli, Klein, Peter, & Orenstein, 2004; Shrestha, Wallace, & Meltzer, 2010). All these strategies help mitigate the impact of supply disruption and could also make the effect of shortage insignificant in the empirical model. Overall, the inclusion of the additional variables shows a substantial increase in the explanatory power, mainly due to the competition variables, with the adjusted R^2 doubled in model B compared to model A.

The models in columns C (model B + manufacturer fixed effects), D (model B + component fixed effects), and E (model B + manufacturer and component fixed effects) introduced manufacturer fixed effects and vaccine antigen component fixed effects to the model. The adjusted R^2 increases from 0.74 in model C to 0.86 in model E. When comparing models C and D to model B, it suggests antigen component fixed effects explain more of the variation in the model than the manufacturer fixed effects do. In terms of competition measures, their effects are diluted and become statistically insignificant in model E. When the fixed effects are included to capture the unobserved time-invariant effects across manufacturers and across antigen components, they may also partially pick up the effects of competition. It is because competition variables could have little variation over time if, for example, there was no product entry or exit for a few years, though they still had cross-product variation. Manufacturer name-change indicators and shortage indicators remain insignificant in models C to E.

Among models A to E, there are a few results that worth noticing. First, the variables age and time trend are consistently significant. However, joint significance tests suggest the effects offset each other (except in models B and C). Nevertheless, the two variables are not highly correlated,³¹ and each reveals a significant association through a different channel. When a new vaccine enters the market, it is the time trend, rather than age, that affects the level of launch price in a particular year. It helps explain why new vaccines were getting more and more expensive. Meanwhile, the offset effect of age and time trend may help explain why existing vaccines had more stable prices. Second, different from age and time trend variables, manufacturer name-change or shortage variables are not significant in any models. For manufacturer name changes, the insignificance may largely relate to the fact that no one name-changing merger observed in the study was between two manufacturers that directly competing in producing the products. Thus, the level of competition was not affected by the event. For shortages, the insignificance is possibly due to CDC's responses to supply disruptions. As strategies that mitigated the effects of shortages were used, the empirical association between shortage and prices would also be weakened. Third, competition is likely to play a role in reducing prices, though the effects are diluted when fixed effects are introduced.

The model in column F is for price-capped vaccines. This group has fewer observations (88 observations) because some price-capped vaccines exited the market and vaccines developed

³¹The correlation coefficient of age and time trend is 0.33 in models A to E and 0.48 in model G.

subsequently were not subject to price caps. The model excluded age and all fixed effects (reasons discussed in Section 3.2.). We found no significant association in the model. The insignificant time trend tends to agree with the fact that they were price capped. Little of the price variation is explained by the factors in the model for price-capped vaccines, and the adjusted R^2 is low (0.06).

The model in column G is for combination vaccines. Because there were no more than ten combination vaccines, we had only 90 observations during the study period. We excluded fixed effects (reasons explained in Section 3.2.) and replaced approved dose by component counts and redefined competition variables faced by combination vaccines. Although we included fewer variables in the model, the explanatory power of the model is high (adjusted $R^2 = 0.90$). Similar to models A to E, the opposite effects of time trend and age offset each other (jointly insignificant). The number of components a combination vaccine has is positively and significantly associated with prices. The association between competition variables and prices is strong. Greater competition (caused by sharing components among combination vaccines) placed downward pressure on prices.

5 | CONCLUSION AND DISCUSSION

In this study, we investigated historical prices of noninfluenza childhood vaccines purchased in the public sector over the years 1996 to 2014. We used a stratified multivariate analysis to examine the heterogeneous effects of various factors that may relate to price changes among price-capped vaccines, combination vaccines, and the rest. We found an increasing time trend in launch prices among all but price-capped vaccines. And the effect of time trend was offset by the effect of staying longer in the market in most models. Although approved dose and thimerosal indicator were not significant in predicting prices, the number of components contained in a combination vaccine is positively related to its prices. As expected, the more components a combination vaccine has the more expensive it is. Our results also provide evidence for competition in the supply side of the vaccine market, though the effects were diluted when antigen component and manufacturer fixed effects were included. Both direct and indirect competition was likely to be negatively associated with prices. For combination vaccines, the competition was measured by how much overlap it has with other combination vaccines and this type of competition was found to reduce the prices. Manufacturer name-change indicators or supply shortage indicators did not help explain the price variation. For name-changing mergers observed in this study, the events did not result in reduced competition because the numbers of competing products were unaffected. For shortages, it may relate to CDC's responses that mitigated the effect of supply disruptions. Overall, only age and time trend appeared to be consistently significant in all models, and their net effects were mostly insignificant, which reflected the "predictable, limited, and stable" nature of the pediatric vaccine market.

Comparing to previous research, our study had similar as well as different findings. Both Pauly et al. (1996) and Lichtenberg (2002) found an unstable or weak association between competition and prices. In our study, the effect of competition was more apparent among non-price-capped vaccines. For combination vaccines, the effect of competitive pressure is consistent with previous studies on the pricing of overlapping combination vaccines (Behzad

et al., 2012; Behzad et al., 2014; Robbins et al., 2010). The stratified analysis demonstrates the heterogeneous effects among different groups of vaccines. We also re-examined the positive relationship between vaccine doses and prices found in Pauly et al. (1996); our more recent data did not show any significant association in the models. Our study included thimerosal indicator, which was not studied before, and we found no significant association.

Another factor that is influential to vaccine pricing, but not included in the analysis, is the therapeutic gain or value added by the vaccine product. The so-called “value-based pricing” has been used for pricing innovative medicines, including vaccines (Lee & McGlone, 2010; Garattini, Van de Vooren, & Freemantle, 2014). We did not incorporate this information due to the lack of measures that systematically quantify the value added by each available vaccine product. However, this limitation is addressed to some extent by using the antigen component fixed effects in the model. The value added by each vaccine is usually specific to antigen component types; the variation is thus likely to be captured by the antigen component fixed effects.

Our results suggest few of the factors included in the model explain the price variation. The high adjust R^2 in some models implies more were explained by manufacturer and component fixed effects than by the other variables. These fixed effects could capture important but unobserved time-invariant differences in manufacturer production cost, value added by antigen component, and so on. Nevertheless, for the budgeting and planning purposes, the findings suggest that (a) shortages and manufacturer name changes similar to what were observed in the study are not likely to affect prices. There would be little impact on budgets when such shortages or name changes occur; (b) new vaccines tend to be more expensive than similar vaccines launched before, the increase in prices should be considered to ensure enough budgets for new vaccines; (c) in terms of reducing vaccine prices or controlling prices from increasing, competition may still be more influential than other factors; (d) due to the significance of manufacturer and component fixed effects, it could be more rewarding to focus on vaccine-specific trends. When predicting price changes of a particular vaccine, the history prices of that vaccine may tell a lot as manufacturer and component fixed effects are embedded in its history prices.

We believe this paper contributes to the literature by providing the most up-to-date evidence on the association of various factors, especially competition, supply shortage, and vaccine attributes, with prices of publicly purchased vaccines. This paper also represents the first effort to address the heterogeneous effects of those variables among different vaccines. The findings may help decision makers understand vaccine price behavior better, establish expectations of future price trends, and inform decisions in vaccine planning and financing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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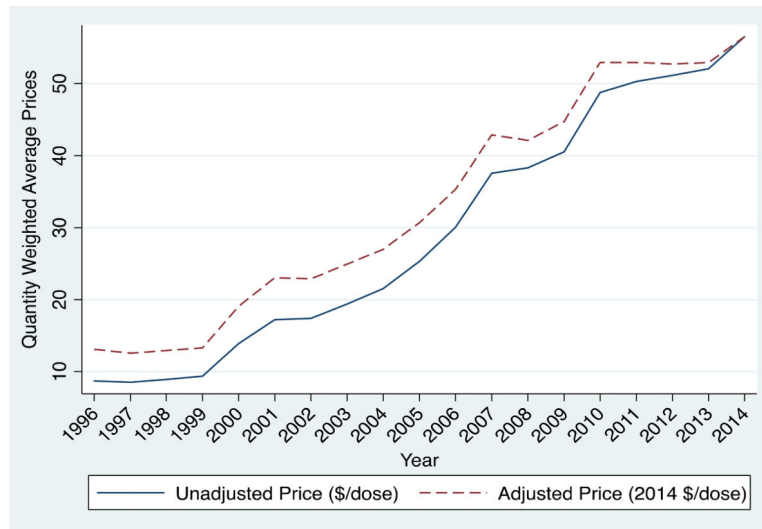


FIGURE 1. Quantity weighted average prices of all noninfluenza pediatric vaccines purchased in the public sector, 1996–2014. Adjusted prices are prices (including excise tax) deflated by consumer price index (in 2014 \$)

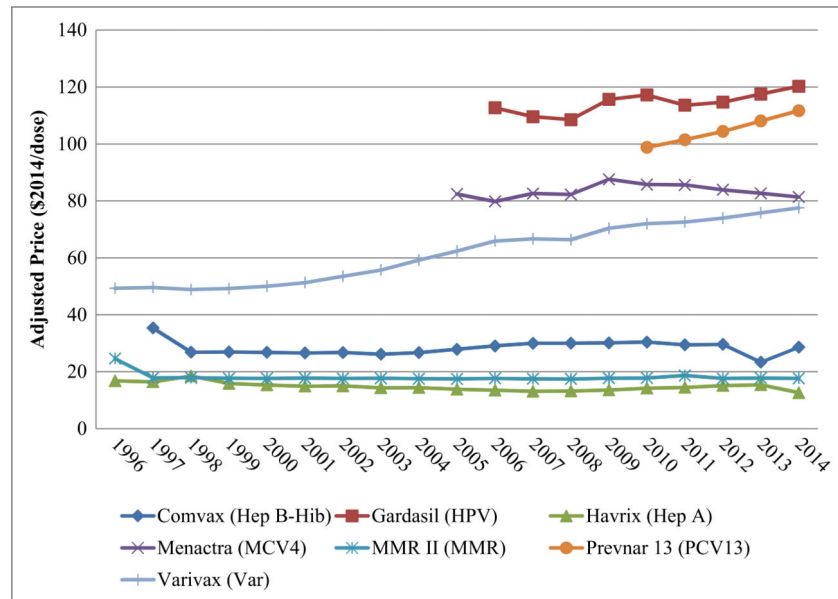


FIGURE 2.

Adjusted pretax prices of selected vaccine brands in the public sector, 1996–2014. Prices are excluding excise tax and adjusted using the consumer price index (in 2014 \$). Vaccine types are indicated in the parenthesis after each brand name. Hep A = hepatitis A vaccine; Hep B-Hib = hepatitis B and haemophilus influenza type b vaccine; HPV = human papillomavirus vaccine; MCV4 = meningococcal conjugate vaccine; MMR = measles–mumps–rubella vaccine; PCV13 = 13-valent pneumococcal conjugate vaccines; Var = varicella vaccine

TABLE 1

Descriptive statistics of vaccine prices, competition, and vaccine attributes among non-price-capped and noncombination vaccines, price-capped vaccines, and combination vaccines, United States, 1996–2014

Variable	Non-price-capped and noncombination vaccines (<i>n</i> = 300)		Price-capped vaccines (<i>n</i> = 88)		Combination vaccines (<i>n</i> = 90)		
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	
Price	32.260	31.346	10.888	4.940	40.618	20.600	
DirCompete1	0.680	0.467	0.261	0.442	ShareComp1	0.556	0.500
DirCompete2	0.100	0.301	0.205	0.406	ShareComp2	0.333	0.474
IndirCompete	0.513	0.501	0.784	0.414			
Manufacturer name change	0.017	0.128	0.068	0.254		0.033	0.181
Name change t-1	0.017	0.128	0.057	0.233		0.022	0.148
Shortage	0.050	0.218	0.034	0.183		0.133	0.342
Shortage t-1	0.043	0.204	0.023	0.150		0.111	0.316
Shortage_oth	0.117	0.322	0.193	0.397		0.344	0.478
Shortage_oth t-1	0.103	0.305	0.159	0.368		0.311	0.466
Age	8.550	6.729	15.693	11.298		6.300	4.172
Aprvd doses	2.593	1.391	3.136	1.085	Components	2.211	0.410
Thimerosal-free	0.840	0.367	0.534	0.502		0.822	0.384
DTP-containing (ref.)	0.320	0.467	0.182	0.388		0.544	0.501
Hib-containing	0.087	0.282	0.330	0.473		0.533	0.502
Hep A-containing	0.123	0.329	0.000	0.000		0.144	0.354
Hep B-containing	0.147	0.354	0.034	0.183		0.478	0.502
HPV-containing	0.047	0.211	0.000	0.000		0.000	0.000
Men-containing	0.050	0.218	0.000	0.000		0.000	0.000
MMR-containing	0.000	0.000	0.216	0.414		0.111	0.316
Pneumo-containing	0.110	0.313	0.034	0.183		0.000	0.000
Polio-containing	0.000	0.000	0.261	0.442		0.289	0.456
Rota-containing	0.053	0.225	0.000	0.000		0.000	0.000
Var-containing	0.063	0.244	0.000	0.000		0.111	0.316

Note. Definitions of each variable are provided in Table A.1. DTP-containing = diphtheria, tetanus and pertussis containing vaccines; Hep A-containing = hepatitis A containing vaccines; Hep B-containing = hepatitis B containing vaccine; Hib-containing = haemophilus influenza type b containing vaccines; HPV-containing = human papillomavirus containing vaccines; Men-containing = meningococcal containing vaccines; MMR-containing = measles–mumps–rubella containing vaccines; Pneumo-containing = pneumococcal containing vaccines; Rota-containing = rotavirus containing vaccines; Var-containing = varicella containing vaccines.

TABLE 2
Impacts of vaccine attributes, competition, and shortages on prices of publicly purchased childhood vaccines, 1996–2014

	Non-price-capped and noncombination vaccines (<i>n</i> = 300)					Price-capped vaccines (<i>n</i> = 88)		Combination vaccines (<i>n</i> = 90)
	A	B	C	D	E	F	G	
Age	-0.058** (0.023)	-0.056*** (0.013)	-0.072*** (0.010)	-0.043*** (0.008)	-0.058*** (0.016)			-0.045** (0.015)
Aprvd doses	-0.101 (0.119)	0.056 (0.067)	0.078 (0.065)	0.054 (0.040)	0.073 (0.078)	0.188 (0.222)	Components	0.314** (0.099)
Thimerosal-free	0.176 (0.269)	-0.041 (0.154)	-0.008 (0.212)	-0.037 (0.104)	0.017 (0.133)	0.571 (0.391)		-0.014 (0.058)
T	0.076** (0.026)	0.089*** (0.018)	0.105*** (0.016)	0.063*** (0.015)	0.073*** (0.018)	0.010 (0.019)		0.060*** (0.012)
Competition variables								
DirCompete1		-0.981*** (0.259)	-1.020*** (0.252)	-0.181 (0.138)	-0.079 (0.112)	-0.096 (0.382)	ShareComp1	-0.699*** (0.143)
DirCompete2		-1.032*** (0.330)	-1.010*** (0.273)	-0.336** (0.138)	-0.242 (0.221)	-0.161 (0.339)	ShareComp2	-1.054*** (0.111)
IndirCompete		-0.569** (0.215)	-0.483** (0.192)	-0.310 (0.206)	-0.276 (0.185)	0.121 (0.409)		
Manufacturer name change		-0.063 (0.084)	0.048 (0.082)	0.016 (0.110)	-0.002 (0.071)	-0.217 (0.185)		-0.259 (0.213)
Name change t-1		-0.087 (0.078)	0.025 (0.081)	0.011 (0.103)	0.002 (0.070)	-0.409 (0.260)		-0.105 (0.057)
Shortage variables								
Shortage		-0.051 (0.082)	0.032 (0.085)	0.018 (0.061)	0.012 (0.035)	0.018 (0.243)		-0.041 (0.030)
Shortage t-1		0.010 (0.149)	0.085 (0.111)	0.094 (0.098)	0.094 (0.101)	0.041 (0.281)		-0.047 (0.037)
Shortage_oth		-0.098 (0.130)	-0.133 (0.151)	-0.060 (0.069)	-0.069 (0.054)	-0.197 (0.151)		0.021 (0.048)
Shortage_oth t-1		0.028 (0.199)	-0.053 (0.159)	-0.088 (0.098)	-0.108 (0.112)	0.041 (0.112)		0.042 (0.023)
Manufacturer fixed effects			Yes		Yes			
Component fixed effects				Yes	Yes			
Adj R ²	0.313	0.687	0.735	0.844	0.857	0.063		0.897

Note. In all the models, the dependent variable is the natural logarithm of pretax price in 2014 US dollars. Models A through G vary by the independent variables included. Variables with blank spaces indicate that these variables were excluded from the model. Definitions of each variable are provided in Table A.1. Standard errors (in the parenthesis) were clustered by vaccine types.

* Significance level at $p < .10$.

** Significance level at $p < .05$.

*** Significance level at $p < .01$.