System factors to explain H1N1 state vaccination rates for adults in US emergency response to pandemic

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A B S T R A C T

Introduction: During the 2009–2010 H1N1 pandemic, vaccine in short supply was allocated to states pro rata by population, yet the vaccination rates of adults differed by state. States also differed in their campaign processes and decisions. Analyzing the campaign provides an opportunity to identify specific approaches that may result in higher vaccine uptake in a future event of this nature.

Objective: To determine supply chain and system factors associated with higher state H1N1 vaccination coverage for adults in a system where vaccine was in short supply.

Methods: Regression analysis of factors predicting state-specific H1N1 vaccination coverage in adults. Independent variables included state campaign information, demographics, preventive or health-seeking behavior, preparedness funding, providers, state characteristics, and H1N1-specific state data.

Results: The best model explained the variation in state-specific adult vaccination coverage with an adjusted R-squared of 0.76. We found that higher H1N1 coverage of adults is associated with program aspects including shorter lead-times (e.g., the number of days between when doses were allocated to a state and were shipped, including the time for states to order the doses) and less vaccine directed to specialist locations. Higher vaccination coverage is also positively associated with the maximum number of ship-to locations, past seasonal influenza vaccination coverage, the percentage of women with a Pap smear, the percentage of the population that is Hispanic, and negatively associated with a long duration of the epidemic peak.

Conclusion: Long lead-times may be a function of system structure or of efficiency and may suggest monitoring or redesign of distribution processes. Sending vaccine to sites with broad access could be useful when covering a general population. Existing infrastructure may be reflected in the maximum number of ship-to locations, so strengthening routine influenza vaccination programs may help during emergency vaccinations also. Future research could continue to inform program decisions.

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1. Introduction

The novel H1N1 influenza virus was detected in the United States in April 2009. Worldwide, a pandemic was declared, and a national public health emergency was announced in the United States. In the US, plans were made for a national vaccination campaign to be rolled out in Fall 2009, when the pandemic H1N1 vaccine would be available. The campaign was implemented as a public-private partnership, with federal purchase of the vaccine. The Centers for Disease Control and Prevention (CDC) allocated vaccine pro rata to states by total population as the vaccine became available. States determined how vaccine would be allocated in their jurisdiction and either retained control of vaccine allocation to individual providers at the central level or delegated fully or partially to local jurisdictions. States or local jurisdictions invited providers to participate in the program and vaccine was shipped to designated providers through a centralized distribution process supervised by the CDC that built on an existing contract for management and distribution of vaccines in the Vaccine for Children (VFC) program. Fig. 1 shows a basic scheme of the supply chain for H1N1 vaccine from manufacturer to provider.

State decisions about where to direct vaccine were guided by recommendations of the CDC’s Advisory Committee on...
Immunization Practices (ACIP) [6], which recommended that the vaccine be initially directed to: pregnant women, persons who live with or provide care for infants aged <6 months, health-care and emergency medical services personnel who have direct contact with patients or infectious material, all people 6 months to 24 years of age, and persons aged 25 through 64 years with certain health conditions (“high-risk”). The recommendations also provided further specification of priority groups in the event of vaccine shortage and stated that decisions to broaden availability of vaccine should be made at the local level.

Overall, more than 120 million doses of vaccine were distributed to over 70 thousand locations by April 2010 [4,8,9] and 80.8 million people reported having been vaccinated [10]. The vaccine supply was insufficient to meet demand initially, and became more plentiful after Thanksgiving, a time when demand for influenza vaccination traditionally slows. Despite the pro rata allocation of H1N1 vaccine [11], state level vaccine coverage rates indicate that there were great differences in coverage across the states even when vaccine was in short supply. By the end of January 2010 [1], the coverage of adults ranged from 8.7% to 34.4% (Fig. 2).

States varied in their approaches to implementing their H1N1 vaccination programs in an unprecedented situation. While the literature addressed factors related to uptake of seasonal influenza vaccine at the individual level [12,13], states and regions used their best judgment and knowledge of their jurisdictions to guide their decisions on distribution and system design, given the lack of scientific evidence in that area. The purpose of this study was to determine supply chain and system factors associated with H1N1 coverage rates at the state-wide level for adults in order to inform future events of this nature.

We hypothesized that characteristics of the vaccine supply chain in each state and decisions around targeting vaccine could predict uptake. One classic supply chain study, for example, has demonstrated that a product stocked in a large number of locations increases the probability that a particular location will be stocked out, and may also reduce the distance traveled by the final consumer [14]. Some of these characteristics of the state vaccine supply included the number of locations where vaccine was available, prioritization of the ACIP-recommended target groups, the type of providers to whom vaccine was directed, and the lead-time between vaccine allocation and availability in a state, which largely reflects differences in states’ ordering processes. Because other factors affect uptake, as evidenced by state-to-state variation in seasonal influenza coverage and individual-level studies[15–18], underlying population differences such as demographic characteristics, utilization of preventive health services, and healthcare infrastructure were also examined. It is relevant to mention that individual-level studies differ from those with a regional or ecological view. Others have used this ecological approach in the analysis of other health-related problems such as water fluoridation and tooth decay [19,20]. Data from the centralized distribution system on vaccine shipments from October 5, 2009 through December 9, 2009 were made available for analysis, thus allowing us to focus the analysis on the period during which vaccine was in short supply.

2. Methods

2.1. Design

We examined the relationship between state vaccination rates in persons 18 and over with variables covering population and health-related state characteristics and state-specific vaccination campaign information.

2.2. Data

The outcome measure is state estimates of vaccination coverage, as calculated by the CDC [1]. Participants 18 and over on the Behavioral Risk Factor Surveillance System (BRFSS) and National H1N1 Flu Survey (NHFS) were asked if they had received an H1N1 vaccine during October 2009–January 2010.

2.2.1. Population and state characteristics

From the Census, we identified population [3] characteristics including population size and density, age groups, education, race/ethnicity, income and poverty, births, and family composition [21]. We also examined measures of income inequalities [22], and segregation and disparities [23]. We extracted the geographical area, number of counties, and federal government expenditure per capita from the Census.

We estimated the total number of healthcare practitioners [24], the number of active physicians [25] per thousand population (PTP), and the percentage of the population who have not visited a doctor in the last year because of cost [2]. We determined whether states were characterized by state control, local control, or by inference, mixed control, from the 2008 National Profile of Local Health Departments [26].

To capture health-seeking behaviors and use of preventive services, we obtained state-specific influenza vaccination rates for previous seasons [7], the percent of women who had a Pap smear in the past 3 years [2], and population percentages associated with various health conditions [27].
2.2.2. State-specific vaccination programs and surveillance

We obtained information on the emergency funding provided to states for the H1N1 pandemic from CDC reports including amounts spent or obligated for assessment, planning and response [28,29].

Reports from the Outpatient Influenza-like Illness Network (ILINet) [5] obtained from the CDC, provided weekly values for the proportion of outpatient visits for influenza-like illness (ILI) at participating providers, by state, from which we calculated several measures including the percentage of weeks with \% ILI above 2.3, after week 30.

We extracted information on state processes and decisions from a survey [30] of immunization program managers conducted by the University of Michigan to provide CDC with situational awareness during the H1N1 campaign on allocation of vaccine, expansion date beyond priority groups, whether a state focused on school vaccination or not, and vaccine distribution methods.

We obtained information on the amount of vaccine allocated to each state over time, the maximum number of provider sites to which each state could have vaccine shipped through the centralized distribution system ("ship-to" sites) [8], and self-reported data from states on doses distributed to or administered in public settings [31].

Information on the date, address, and number of doses shipped to each location, from the beginning of the campaign through December 9, 2009 (which covers the major shortage period) was obtained from the centralized distribution shipping records [4]. We calculated measures such as the number of unique sites to which vaccine was shipped (ship-to sites), the average number of shipments per site, the variation in doses PTP across counties within a state, and the lead-time from allocation to shipment (i.e., the average number of days between when a state received an allocation and ordered the vaccine, plus the average number of days doses spent between order placement and shipment). Shipments during this time period were sent overnight to their destination (regardless of distance), to arrive when receiving locations within the state were open.

We categorized shipments (over 75\%) by the type of provider through a series of targeted queries we generated. Thus, we calculated proportion of shipments or doses PTP to providers focused on children, primary care, county health departments, unclassified medical doctors, internists, specialists, long-term care, veterans, urgent care, hospitals, clinics, pharmacies, jails, military, government, universities, and nursing homes. The category of “specialists” includes providers that we could identify as associated with caring for the ACIP population categorized as high-risk because of health conditions such as asthma, heart disease, diabetes, etc. We also combined these in several subgroups driven by like characteristics that might explain differences in coverage: e.g., general internists and specialists combined (internists and specialists can be grouped because both serve adults; however, while internists may provide primary care, adults may be less likely to visit internists or specialists during a short campaign); targeted access (doses sent to long term care, internists, specialists, nursing homes, and children); and general access locations (primary care, MDs that could not be classified by specialization, counties, hospitals, urgent care, clinics, or pharmacies).

2.3. Analysis

Using cross-sectional data, we developed a regression model to predict vaccine coverage in adults, as of the end of January 2010, for DC and each state [1]. In a separate analysis, we constructed distinct models for children (6 m to 17 y) and high-risk adults (25–64 with a chronic condition) because we expected factors affecting coverage to differ across groups; we present those analyses in a separate paper.

We calculated simple descriptive statistics (means, standard deviations, proportions, and measures of association including Pearson’s correlation). The primary technique used for modeling was multivariate linear regression (ordinary least squares) with transformations specified when used. Data were linearly scaled to values in [0,1] before performing regressions.

Variable selection is a challenging problem [32], and our analysis poses additional difficulties because of high correlations among variables. Statistical research [33,34] sets basic principles for dealing with these problems. We performed stepwise selection of variables to better prevent introducing high correlations in the model. We explored variable inclusion both based on high association with the dependent variable and incorporating or removing one variable at a time according with their potential to improve the model (using the Akaike information criterion [35]) and their p-value, with many different combinations of starting variables explored (a deeper explanation of the variable selection.
methodology can be found in the Supplementary Methods Section file). The maximum number of dependent data points was 51 with a large number of variables to consider; however, the best models had less than ten variables each. We kept “outliers” in the analysis because we consider they speak to real extreme state cases and not to data deформities, and examined quantile–quantile (Q–Q) plots to determine whether additional transformations were needed. Models were evaluated on adjusted R-square values and the F-statistic, with an individual variable evaluated on its p-value (below 5%). The regressions were performed with R statistical software package version 2.11.1 [36]. Some descriptive statistics were calculated in Microsoft Excel versions 11 and 12.

3. Results

Seven variables including lead-time from allocation to ordering and shipment, the maximum number of ship-to sites per thousand population, past seasonal influenza coverage for non-high risk adults age 18–49, percentage of doses categorized as sent to internists and specialists, percentage of women 18 and older with a Pap smear in the last three years, percentage of weeks with ILI above 2.3 after week 30, and the percentage of residents of Hispanic or Latino origin were significant for predicting vaccination coverage in adults (Table 1). The best model found explained the variation in state-specific adult vaccination coverage with an adjusted R-squared of 0.76 and a p-value close to 0 (Table 2).

For supply decisions, a long lead-time was associated with lower coverage, and the associated coefficient has a relatively large magnitude. Additional analysis of lead-time indicated that a state’s relative lag tended to be consistent throughout the months considered. We also found that lead-time is correlated with some variables related to shipment choice (e.g., positively with use of third parties for distribution, and negatively with shipments per ship-to site). The vaccine allocated to internists and specialists as a percentage of the total shipped was negatively associated with coverage, and having a large number of maximum ship-to sites was positively associated with coverage.

Vaccination coverage was positively associated with past influenza vaccination coverage; while we found a strong association, there were several other effects that were also large in magnitude. Coverage was also positively associated with the percentage of women with a Pap smear, and the percent of the population that is Hispanic. A long duration of ILI severity peaks (defined by the percentage of weeks in the Fall with percent ILI more than 2.3) was negatively associated with coverage. To provide more information on our modeling, Supplementary Table 2 presents examples of other variables highly correlated with those factors in our final model.

4. Discussion

In an effort to identify lessons learned for a future pandemic vaccination event, we sought to identify factors related to vaccination program decisions and processes that may have facilitated or hindered vaccine uptake. Program factors that were associated with vaccine uptake included the lead-time between allocation and ordering and shipping, and the type of providers receiving vaccine. Factors not related to program decisions such as health-seeking behaviors and population characteristics also contributed to predicting state-to-state variation, as would be expected given baseline variation in previous influenza vaccination coverage [7] and other findings [37–39].

Lead-time from allocation to ordering and shipment was negatively associated with vaccination coverage. Steps in the ordering process varied by state and could include requesting specific orders from providers (in advance of allocation or after receiving an allocation), decisions on where to distribute vaccine, and notification of decisions. States also determined the frequency of ordering, the day(s) of the week to order, the number of providers participating or receiving vaccine, and the overall process to follow, all of which could affect the lead-time. Because of the initial focus on ACIP-defined target groups, in many states adults without high risk conditions were not eligible for vaccination until demand for vaccine had already begun to wane. Delays in allocated vaccine being made available to the population could have resulted in less vaccination. On the other hand, lags in ordering could be a consequence of decreasing demand, and thus be a result of lower vaccination rates rather than a cause. The tendency for lags in ordering to be consistent for a given state throughout the time period studied, suggests the lead-time resulted from the ordering process.

We also found a relationship with the type of providers or locations to which vaccine was directed. For adults, vaccine sent to providers with specialized services or patient base was associated with lower coverage. This could be because not all adults visit internists or specialists frequently enough to be vaccinated in this time period; it could also be that those providers had less focus traditionally on vaccinating so patients looked elsewhere for vaccine. Overall, only a small proportion of vaccine was sent to internists and specialists.

One variable may be more a measure of health infrastructure than the supply chain system itself. In particular, the maximum number of sites to which vaccine could be directly shipped through the centralized distribution system was positively associated with vaccination coverage. (In contrast, another variable measured the actual ship-to sites registered or used within a state.) The maximum number of ship-to sites allowed for each state was based on a formula that included the population size as well as the number of existing VFC providers. A high number of VFC sites per capita could be a reflection of a more robust infrastructure for providing vaccine.

State factors unrelated to supply chain decisions about H1N1 vaccine were also related to coverage, specifically included usage of health services. Others have found that for an individual, past influenza vaccination is a strong predictor of annual influenza vaccination [12,17]; a relationship that may reflect both differences in infrastructure and differences in attitudes. The finding in this paper demonstrates that pandemic influenza vaccination also is associated with uptake of seasonal vaccine. The association between coverage rates and rates of receipt of Pap smear may be a reflection of utilization of preventive care, although no further analysis could be carried out to determine if this effect was present only among women.

Some characteristics of the epidemic may have also influenced coverage. For states where the epidemic lasted longer, coverage was lower. This could be because vaccine was made available to non-high risk adults later in the season, and persons may have reasoned that they had likely been exposed to the disease already and did not need vaccination. Conversely, the positive association between coverage and the percentage of Hispanics may reflect higher vaccination rates in communities with greater perceived risk [40] due to the virus emerging from Mexico. In general, Hispanic populations did not have a higher coverage than the overall average [41].

This study had several limitations. First, cross sectional studies and regressions are useful for identifying associations, but they have a number of intrinsic limitations, for example, we cannot determine causality, and for complex cases like the one analyzed other good regression models may also exist for the same set of variables. Supplementary Table 2 presents a summary of variables highly correlated with those in the model. Secondly, the ecological
Table 1
List of variables in the best model, including the dependent variable at the top. Table shows the variable's name, description (with reference for the data), average value, standard deviation, and maximum and minimum values.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Reference</th>
<th>Average</th>
<th>Std. Dev.</th>
<th>Maximum</th>
<th>Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent</td>
<td>Coverage on persons aged ≥ 18 yrs</td>
<td>MMWR [1]</td>
<td>19.9</td>
<td>5.3</td>
<td>34.4</td>
<td>8.7</td>
</tr>
<tr>
<td>Indep1</td>
<td>Percent of women age 18 and older who report having had a Pap smear within the last three years, 2008</td>
<td>State health facts [2]</td>
<td>82.7</td>
<td>2.9</td>
<td>88.9</td>
<td>74.1</td>
</tr>
<tr>
<td>Indep2</td>
<td>Resident population: Hispanic or Latino Origin, percent (July 1 2009 – estimate)</td>
<td>Census [3]</td>
<td>9.8</td>
<td>9.6</td>
<td>44.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Indep3</td>
<td>Average days from allocation to shipment of vaccine</td>
<td>CDC shipments report (calculation) [4]</td>
<td>6.3</td>
<td>2.3</td>
<td>12.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Indep4</td>
<td>Percentage of weeks with % ILI above 2.3, after week 30</td>
<td>Report CDC [5]</td>
<td>42</td>
<td>24.4</td>
<td>97.4</td>
<td>10.3</td>
</tr>
<tr>
<td>Indep5</td>
<td>Seasonal influenza coverage for non-high risk adults 18–49 yrs on the 2007–2008 season</td>
<td>CDC influenza vaccination coverage [7]</td>
<td>22.6</td>
<td>5.1</td>
<td>37.8</td>
<td>11.9</td>
</tr>
<tr>
<td>Indep6</td>
<td>Maximum number of ship-to sites per state per thousand population</td>
<td>Report CDC (calculation) [8]</td>
<td>0.5</td>
<td>0.1</td>
<td>0.74</td>
<td>0.00</td>
</tr>
<tr>
<td>Indep7</td>
<td>Percentage of doses categorized as sent to internists or specialistsb</td>
<td>Report CDC (calculation) [4]</td>
<td>1.17</td>
<td>1.08</td>
<td>6.07</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* Value for Alaska where all vaccine was shipped to a single warehouse then distributed to providers by the state.
* Overall, approximately 75% of shipments were categorized by type of provider.

approach followed does not point to individual characteristics of the population but to state-level conditions, and does not analyze potential variations within states. Third, the data from the centralized distribution system covers shipments through December 9, 2009, and the outcome measure is vaccination coverage as of the end of January 2010. The gap may not be as large as it seems, since coverage for adults increased from 17.3% (adults ≥ 19 [42]) at the end of December 2009 to around 18.2% (adults ≥ 18, derived from state-specific rates [1] and adult populations [3]) at the end of January 2010. Additionally, the number of people vaccinated by the end of January (74M) is approximately the same as the total vaccines shipped by December 9 (72M) though this comparison does not take into account receipt of second doses by children. Fourth, the vaccine shipment data represented shipment location, which is not necessarily the same as the final place of administration of vaccine (e.g., vaccine may have been distributed from a third party distributors or local health department to providers). As a result, the number of locations of administration may be underestimated, or the provider type may be misclassified. Fifth, some shipping data were missing or potentially inaccurate. Provider type could not be determined for 25% of shipments, the information on state and local decisions and processes was not always complete, and databases could have errors. Finally, the number of dependent variable observations is fairly small (51), and many factors may potentially be associated with H1N1 coverage.

The distribution and administration of the H1N1 vaccine was a test of the health emergency response systems, and it is an opportunity to identify specific approaches that may result in higher vaccine uptake in a future event of this nature. Several of the findings warrant further consideration. The findings suggest that continued efforts to increase uptake of influenza vaccination may result in increased uptake in an emergency response. The negative association between order lags and coverage is an important aspect of the supply chain and distribution. It is possible that time lags are a function of the system design or processes, which would suggest monitoring and/or designing the system for fast response within the states in an emergency is needed. There can be many decisions made at the state level that can affect lead-time including ordering frequency, number of delivery locations, on which days orders were placed, use of third parties, etc. Further study would be useful in this area. Our results on type of location to which vaccine was directed may provide some guidance on increasing coverage, e.g., in a campaign with limited resources and time pressures, sending to general access or public locations may be beneficial. As more adult and specialty providers, including pharmacies, take on the role as vaccinators, this strategy may change. This, too, remains an area

Table 2
Regression results for predicting the state level vaccination coverage for the adult population. The table contains the variable name, short description, point estimation of the variable's coefficient, coefficient's standard error, coefficient's t-value, and results of the significance test.

| Variable | Short description | Estimate | Std. error | t value | P(>|t|) |
|----------|-------------------|----------|------------|---------|--------|
| Indep2   | (Intercept)        | 2.66E−16 | 0.06807    | 3.9E−15 | 1.00E+00 *** |
| Indep5   | % Hispanic        | 0.378    | 0.07953    | 4.753   | 2.26E−05 *** |
| Indep1   | % women w/Pap     | 0.3599   | 0.07928    | 4.54    | 0.000045 *** |
| Indep6   | Max # sites       | 0.3002   | 0.07653    | 3.923   | 0.00031 *** |
| Indep7   | % to specialists  | 0.1807   | 0.07061    | 2.558   | 0.01412 *    |
| Indep4   | % weeks ILI high  | −0.4366  | 0.07362    | −5.931  | 4.61E−07 *** |
| Indep3   | Lead-time         | −0.4419  | 0.07401    | −5.97   | 4.04E−07 *** |

Significance codes: 0 < **** < 0.001 < *** < 0.01 < ** < 0.05. Adjusted R-squared: 0.7637, Reg. p-value: 6.035E−13.
where additional assistance is useful, such as collecting information on shipments by type of provider, examining the small number of states where registry information records the location of vaccine administration, or additional analysis on where vaccination occurred for different target groups.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.05.069.

References