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# OPTIMAL DISTRIBUTION OF THE INFLUENZA VACCINE

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## ABSTRACT

Influenza is a serious public health concern and vaccination is the first line of defense. In a pandemic, individuals are prioritized based on their risk profiles and transmission rates to ensure effective use of the available vaccine. We use an agent-based stochastic simulation model, and optimize the age-specific vaccine distribution strategy. We use black-box optimization techniques to minimize the overall cost of the outbreak. Our numerical experiments show that the best policy returned by our approach outperforms alternative policies recommended by the Advisory Committee on Immunization Practices and Centers for Disease Control and Prevention.

## 1 INTRODUCTION

Influenza (flu) is a serious public health concern. Seasonal epidemics impact 5-15% of the world's population, resulting in 3-5 million cases of severe illness and up to 500,000 deaths annually. In a typical seasonal epidemic, between 5% and 20% of the US population gets the flu, of whom 200,000 are hospitalized and 36,000 die (CDC 2013). Elderly people, young children, pregnant women, and people with chronic medical conditions are at high risk for serious complications (Fiore et al. 2009). Influenza has also significant economic impacts, which include direct medical costs and working days lost. The annual economic burden of influenza epidemics based on statistical life projections amounts to $87.1 billion (95% CI: $47.2-$149.5) in the US (Molinari et al. 2007).

Influenza viruses frequently mutate. A pandemic is caused by an emerging influenza virus that spreads worldwide infecting a large proportion of the human population. Unlike seasonal influenza epidemics, pandemics reoccur intermittently, and usually cause high levels of mortality. Three influenza pandemics occurred in each century for the last 300 years. The 1918 Spanish influenza pandemic, the first of the two pandemics involving H1N1 influenza virus in the $20^{th}$ century, infected 500 million people across the world killing approximately 50 million or more (Taubenberger and Morens 2006).

Vaccination is the most effective pandemic response. Social distancing strategies (e.g. school closure, quarantine, isolation) and public health measures (e.g. improved hygiene, respiratory protection) can reduce the risk of exposure and infection (Ferguson et al. 2006; Germann et al. 2006), but can not reduce susceptibility among the population. Prophylaxis with antiviral medications also may prevent infection but requires large antiviral drug stockpiles and does not provide long-term immunity. By contrast, immunization with a well-matched pandemic vaccine would provide the most durable pandemic response. However, given current timeline for the development of a pandemic influenza vaccine and its production capacity, vaccine is not likely to be available in sufficient quantities before pandemic outbreaks occur, and thus potentially limited stocks may need to be prioritized.

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The national and global pandemic mitigation plans has been evaluated using compartmental mathematical models (Longini, Ackerman, and Elveback 1978; Chowell, Miller, and Viboud 2008; Chowell et al. 2009; Hill and Longini 2003; Tuite et al. 2010) and agent-based simulation models (Ferguson et al. 2005; Ferguson et al. 2006; Germann et al. 2006; Merler, Ajelli, and Rizzo 2009). In particular, Medlock and Galvani (2009) developed a compartmental SEIR (susceptible, exposed, infectious, recovered) model to determine the optimal age-specific vaccine allocations for the US population based on five outcome measures: deaths, infections, years of life lost, contingent evaluation, and economic costs. They calibrated the model for both the 1918 A (H1N1) and 1957 A (H2N2) pandemics. The optimal vaccine distribution in both cases was vaccinating people aged 5 to 19 and 30 to 39. The rationale behind this result is that children 5 to 19 are responsible for most transmission and for the spread of infection to their parents aged 30 to 39. Thus, both those most responsible for transmission and those most likely to be infected are prioritized, which in turn protects the rest of the population. Medlock and Galvani (2009) concluded that disease transmission must be explicitly considered when optimizing vaccine allocation.

However, the homogeneous mixing assumption of compartmental models describes the dynamics of an epidemic when large numbers of individuals are infected, rather than the initial or final stages of an outbreak, when stochastic person-to-person transmission among small numbers of individuals are involved (Germann et al. 2006). Moreover, they generally do not incorporate the granularity that can be modeled in a simulation such as specific household structures and work environments (Andradóttir et al. 2014). Therefore, agent-based models may be more suitable to include a complicated natural history of disease or detailed intervention strategies. Nevertheless, enumerating all-possible vaccine distribution policies with such models is not possible due computational burden of the process; therefore, novel simulation optimization approaches are needed to address vaccine distribution for influenza pandemics.

In this paper, we use numerical optimization techniques to determine the optimal age-specific vaccine distribution based on a discrete time, stochastic simulation model of influenza outbreak within a community-structured population. Rather than comparing the efficacy of just a few specific vaccination policies, as it is often done in simulation modeling, our approach returns one of the best performing vaccine distributions, essentially searching over all possible age-specific vaccination policies. In the literature, Patel, Jr., and Halloran (2005) used a genetic algorithm and a random mutation hill climbing heuristic to optimize the age-specific vaccine distribution to mitigate an influenza pandemic generated by a stochastic simulation model with 10,000 individuals. We consider a more realistic population, in particular the metropolitan Seattle where approximately 560,000 residents live (US Census Bureau 2000).

## 2 METHODS

### 2.1 Epidemic Simulation Model

Epidemic simulations model the spread of an infectious disease in a population through the contacts between susceptible, infectious, and immune individuals. Such models help understand the dynamics and patterns of disease propagation. They also provide useful tools for analyzing the effect of various interventions.

We use a stochastic simulation model of influenza transmission in the metropolitan Seattle where approximately 560,000 residents live (Chao et al. 2010). The simulation generates a synthetic population of census tracts, and each tract consists of communities of 500–3000 individuals. Each community is populated by randomly generated households of size 1–7 based on the US family size distribution (US Census Bureau 2000). Individuals are categorized into five age groups: preschool (0-4), school (5-18), young adults (19-29), middle aged adults (30-64), and the elderly (65 and over). Each person is a member of various social mixing groups including family, household cluster, neighborhood, community, workplace, playgroup and school, as appropriate. The simulation runs in two time steps per day. At night, everyone can contact with other individuals in their families, household clusters, home neighborhoods, and home communities. During the day, most children attend school or a playgroup, where there is a relatively high probability of transmission. Each community has two elementary schools, one middle school, and one high

school. Preschool-age children usually belong to either a playgroup or a neighborhood preschool. The number of employed working-age adults (aged 19-64 years-old), and tract-to-tract worker flow data are extracted from the Census 2000. Employed individuals are assigned to neighborhoods within their work tracts to simulate community contacts during the day, and to a work group of about 20 people to represent their close contacts at the workplace. The contact probability of two individuals in the same social mixing group is the probability that they will have sufficient contact for transmission during a time step. Chao et al. (2010) calibrated contact probabilities so that the final age-specific attack rates are similar to 1957 Asian A (H2N2) influenza pandemic, which is hereafter referred to as Asian-like influenza.

The model randomly infects 10 people at the beginning of the simulation. Once infected, an individual becomes infectious for six days, and her infectiousness is proportional to the log of the daily viral titers (Chao et al. 2010). Asymptomatic incubation period lasts for one, two, or three days with 0.3, 0.5, and 0.2 probabilities, respectively. After incubation, 67% of infected individuals become symptomatic (Carrat et al. 2008). Symptomatic individuals are twice as infectious as asymptomatic individuals. Infected individuals recover six days after infection and become immune. Vaccinated individuals have a reduced likelihood of becoming infected (40%), of becoming ill given infection (67%), and of transmitting infection (40%) (Halloran, Longini, and Struchiner 2010).

We use the same vaccine efficacy for each age group except those aged 65 and over for whom the relative efficacy is reduced by 40%. We assume that each vaccinated person receives one dose of vaccine. The vaccine effectiveness increases exponentially starting the day after vaccination, and it takes two weeks to reach maximum efficacy. Because of this delay, vaccines can be administered four weeks before the pandemic (pre-vaccination) or during the epidemic with a certain response delay (reactive vaccination).

To validate their simulation model, Chao et al. (2010) ensured that 1) simulated final age-specific attack rates and percentage of transmission attributed to each mixing group match to those of Asian-like influenza; 2) simulated household secondary attack rates match to those in the literature; 3) the calibrated contact probabilities and the estimated statistics such as average time between infection and transmission to susceptible are consistent with the values reported in the literature.

### 2.2 Optimization Problem

The outcome measure used to quantify the success of a vaccination program is fundamental when evaluating different strategies. Example outcome measures frequently used in the literature include number of infections, number of deaths, years of life lost and economic cost, which is also used in our study. We consider costs associated with vaccination and infection of unvaccinated and vaccinated individuals (see Table 1).

Table 1: Costs in 1995 US dollars. Cost of vaccination includes cost of the vaccine, cost of time lost to work, and weighted cost of side effects. Cost of infection includes weighted costs of illness without medical care, outpatient visits, and hospitalization (Medlock and Galvani 2009).

| Cost | Age Group | Value ($) |
|---|---|---|
| Vaccination | all | 37.26 |
| Infection of unvaccinated | 0-18 | 275.30 |
| | 19-64 | 328.98 |
| | 65+ | 492.56 |
| Infection of vaccinated | 0-18 | 231.58 |
| | 19-64 | 264.71 |
| | 65+ | 404.54 |

Given a limited supply of influenza vaccine, a particular population, and parameters for a single wave influenza pandemic, the optimization problem decides the portion of each age group that should be *allowed* for vaccination to minimize the overall cost of the pandemic.

Let $p_i$ and $n_i$ be the portion allowed for vaccination and the total number of individuals in age group $i = 1, \ldots, 5$, respectively. To evaluate the optimal distribution of available vaccine doses $V$, we find the optimal $p_i$ so that the cost of the pandemic is minimized, subject to the constraints $0 \leq p_i \leq 1$. We do not explicitly enforce $\sum_{i=1}^{5} n_i p_i \leq V$ in the optimization model, because the number of individuals allowed for vaccination might exceed the amount of available vaccine. Note that the actual number of people vaccinated in each age group is determined in the simulation model based on random arrival patterns of individuals. However, the simulation model guarantees that no more than $p_i$ portion of age group $i$ is vaccinated.

Influenza transmission from person to person is a complex process. In addition, given an introduction of influenza into a population, there is high variation in the probability of an epidemic outbreak as well as its size and duration. Thus, the mathematical models for influenza epidemics should capture a detailed contact structure and be stochastic (Patel, Jr., and Halloran 2005). The epidemic process is non-linear since the incidence of new infections depends on the current number of both infected and susceptible people in the population at a particular time. All of these factors render traditional gradient-based optimization methods, such as the Newton–Raphson method, inapplicable.

We solve the optimization problem numerically using mesh adaptive direct search (MADS) algorithm (Abramson et al. 2014). Starting with an initial solution MADS iteratively tries to improve the current best solution by generating a trial point on the mesh. If the trial point cannot improve the best solution, a finer mesh is generated in the next iteration. The MADS algorithm is suitable for our problem, because it is a derivative-free technique (Audet and Dennis 2006).

## 3 RESULTS AND DISCUSSION

### 3.1 Optimal Vaccine Distributions

In our numerical experiments, we consider ten configurations with three different vaccine coverage levels $\sum_{i=1}^{5} n_i/V = 0.2, 0.3, 0.4$, three different response delay times: prevaccinate, vaccinate on the first day of the epidemic, and vaccinate after 10 days from the onset of the epidemic, and six different basic reproductive ratio $R_0 = 1.4, 1.6, 1.8, 2.0, 2.2, 2.4$, defined as the expected number of secondary infections caused by a single infectious individual in a completely susceptible population (Anderson and May 1991). If $R_0 < 1$, then each infected individual produces, on average, less than one new infected individual, and we therefore predict that the infection will not spread. On the other hand, if $R_0 > 1$, the infection is able to invade the susceptible population. The mesh adaptive direct search is started from the initial solution $p_i = 0.5$, $i = 1, \ldots, 5$. For each solution, the simulation model is run 8 times with different random number seeds, and the average cost is calculated. Table 2 presents the settings of each configuration and the associated optimal solution. Replications are performed in parallel on a computer with 3.40 GHZ CPU with 8 cores and 12 GB memory. Each replication is performed on single core. Small stochastic variability across the replications because of the large population size (i.e. 560,000 residents) indicates that 8 runs are adequate.

As seen in Table 2, vaccinating school children is the main focus in each configuration. This result is due to the fact that Asian-like influenza had the highest illness attack rate in school children, followed by preschool children with adults having a lower attack rate (Longini et al. 1978). The model does not allocate any vaccine to young adults if the coverage is 20% (Configuration 1). However, a small portion of young adults get vaccinated when the coverage reaches 30% (Configurations 2 and 3). Note that when the epidemic spread is relatively slow in Configuration 5, the optimal solution is to vaccinate only 75% of the school children. On the other hand, when $R_0 = 1.8$ in Configuration 6, the vaccine is allocated to both preschool children and young adults in addition to school children to slow down the fast spreading epidemic. In general, the priority of the young adults increases as R0 increases in Configurations 7, 8 and 9. Surprisingly, the optimal solution does not differ much between Configuration 4 with 10-day response delay and Configuration 10 with prevaccination. Preschool children are not vaccinated in both of those configurations, and young adults are given higher emphasis than they are given in Configuration 2.

Table 2: Ten configurations considered in the numerical experiments.

| Configuration | Coverage | $R_0$ | Response Delay | Optimal Solution | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | 0-4 | 5-18 | 19-29 | 30-64 | 65+ |
| 1 | 0.2 | 1.6 | no delay | 0.048 | 0.946 | 0.000 | 0.001 | 0.000 |
| 2 | 0.3 | 1.6 | no delay | 0.050 | 1.000 | 0.055 | 0.000 | 0.000 |
| 3 | 0.4 | 1.6 | no delay | 0.050 | 1.000 | 0.055 | 0.000 | 0.000 |
| 4 | 0.3 | 1.6 | 10-day delay | 0.000 | 1.000 | 0.305 | 0.000 | 0.000 |
| 5 | 0.3 | 1.4 | no delay | 0.000 | 0.750 | 0.000 | 0.000 | 0.000 |
| 6 | 0.3 | 1.8 | no delay | 0.850 | 0.994 | 0.200 | 0.000 | 0.000 |
| 7 | 0.3 | 2.0 | no delay | 0.666 | 0.992 | 0 | 0.290 | 0.000 |
| 8 | 0.3 | 2.2 | no delay | 0.584 | 0.999 | 0.291 | 0.287 | 0.000 |
| 9 | 0.3 | 2.4 | no delay | 0.760 | 0.999 | 0.999 | 0.000 | 0.001 |
| 10 | 0.3 | 1.6 | prevaccinate | 0.000 | 1.000 | 0.500 | 0.000 | 0.000 |

Table 3: The portion of each age group that is allowed for vaccination under alternative policies.

| Strategy | 0-4 | 5-18 | 19-29 | 30-64 | 65+ |
|---|---|---|---|---|---|
| ACIP | 1.000 | 1.000 | 0.167 | 0.000 | 0.000 |
| FCDC | 1.000 | 0.000 | 0.000 | 0.429 | 1.000 |
| NCDC | 1.000 | 1.000 | 0.000 | 0.429 | 1.000 |
| Uniform | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| No vaccination | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |

### 3.2 Comparison with Alternative Strategies

The current US pandemic vaccine prioritization strategy is based on the severity of the disease (Schwartz and Orenstein 2009). Pandemic Severity Index identifies five categories based on the case fatality rate (CDC 2007). The mortality as a result of a Category 1 pandemic, defined by a case fatality rate of $< 0.1\%$, would be slightly greater than a severe seasonal influenza epidemic. Therefore, the proposed US vaccine prioritization strategy for less severe pandemics (Categories 1 and 2) is similar to recommendations for annual influenza vaccination. The US Centers for Disease Control and Prevention (CDC) recommended the vaccination of children aged 6 months to 5 years old and of adults aged 50 and over for seasonal influenza. These recommendations were expanded in 2008 to include children through age 18 (CDC 2008). Moreover, the CDC's Advisory Committee on Immunization Practices (ACIP) proposed guidelines for vaccinating against the novel swine-origin influenza that prioritize young people aged 6 months to 25 years, excluding the elderly due to their reduced susceptibility (CDC 2009).

We compare our optimal vaccine distribution policies with five alternative vaccination policies: ACIP guidelines, former CDC (FCDC), new CDC (NCDC), uniform (i.e. distribute the vaccine on first-come-first-served basis), and no vaccination. In our numerical experiments, we set the portion of each age group that is allowed for vaccination under those policies as in Table 3.

Figures 1 and 2 depict the attack rate in Configuration 2 and percentage of vaccinated people from each age group under different policies, respectively. Our optimal policy and ACIP guidelines both emphasize vaccinating school children, and they clearly outperform other policies with respect to attack rate. However, in Figure 2, ACIP guidelines vaccinate significantly more preschool children and young adult than our optimal policy. As a result, implementing our optimal policy is less costly than implementing ACIP guidelines. Note that attack rates under our optimal policy are below the attack rates under the ACIP

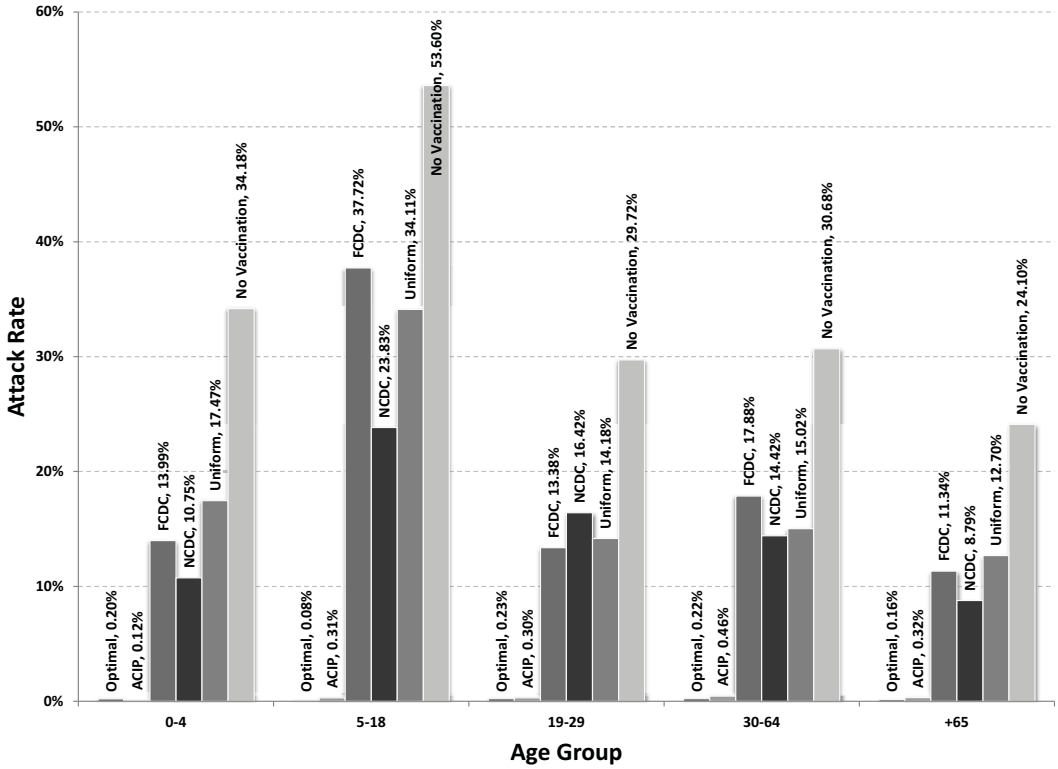


Figure 1: The percentage of infected people from each age group in Configuration 2.

guidelines in all age groups except the preschool children, where the ACIP guidelines perform slightly better.

Finally, Figure 3 shows the reduction in total cost of infection and vaccination relative to no vaccination for all configurations. The cost reduction achieved by our optimal policy is around 90% for all configurations. Cost reductions under the ACIP guidelines are close to those achieved under our optimal policy except configurations 1 , 6, 7, 8 and 9. Since $R_0$ value gets higher in configurations 6-9, usage of our optimal policy becomes even more important when the disease propagation is aggressive. Note that the coverage level is as low as 20% in configuration 1. As a result, we conclude that our optimal policy distributes the available vaccine supply more efficiently than the ACIP guidelines.

## 4 CONCLUSION

We developed a simulation-optimization approach to determine the optimal age-specific distribution of limited vaccine supply to mitigate an influenza pandemic outbreak. Our results indicate that targeted vaccination of school children has the benefit of reducing the burden of disease in this age group and the also reduces the attack rate in the entire population. Despite various modeling approaches and assumptions, several studies have found that vaccinating schoolchildren could reduce the overall incidence of influenza in the population and the overall number of deaths expected (Basta et al. 2009; Mylius et al. 2008; Patel, Jr., and Halloran 2005). Our optimal policies under different coverage, epidemic spread, and response delay configurations outperform CDC and ACIP recommendations, although ACIP guidelines for swine-origin H1N1 performs substantially better than other CDC guidelines.

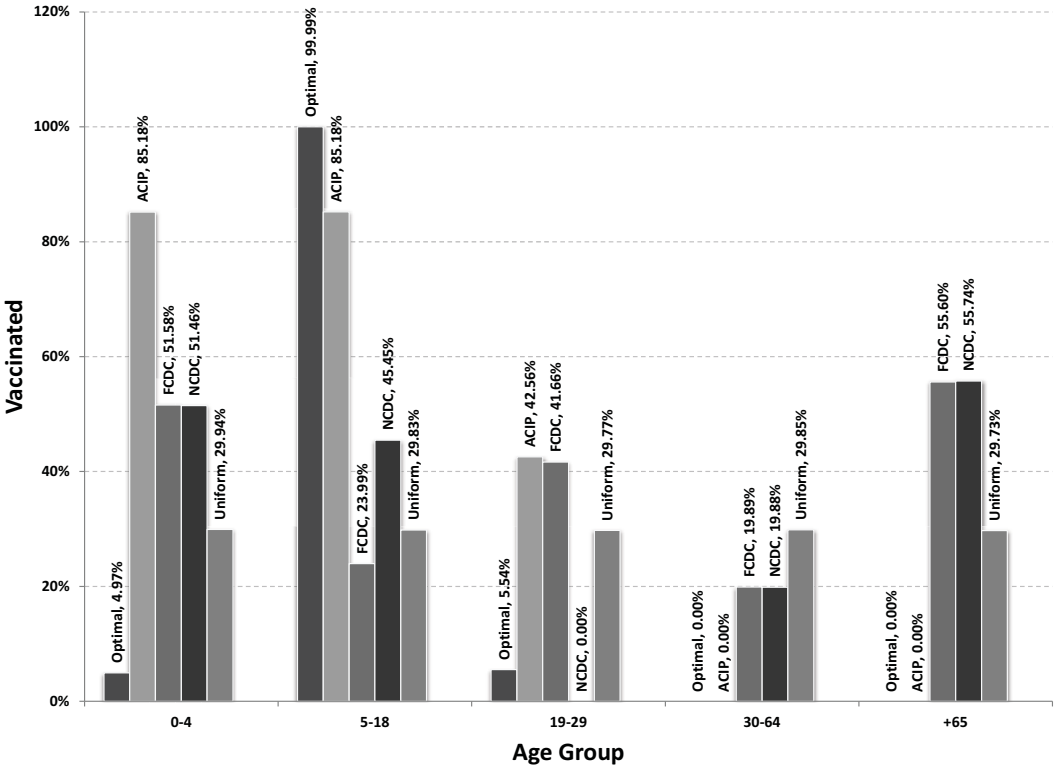


Figure 2: The percentage of vaccinated people from each age group in Configuration 2.

There are many limitations to our model with respect to choice of parameter estimates and the incorporation of biological, environmental, operational, political, and economic features. We illustrate an age-specific distribution scheme but do not further consider other sub-groups such as those people with chronic medical conditions and pregnant women. Disease-related mortality was also neglected, under the assumption that deaths would occur at the latter stages of the infectious period and thus not significantly affect the spread of disease.

When the next pandemic strain of influenza is identified, vaccine development and production should proceed as quickly as possible. Once the age-specific illness attack rate patterns are identified, the epidemic simulation can be calibrated with the current US population structure. Then the optimization model can be used to investigate the best vaccine distribution given the available supply. The proposed simulation optimization approach is generally applicable to other infectious diseases and population structures. In addition, it provides a benchmark for analytic models to measure the potential optimality gap caused by simplifying assumptions such as homogenous population mixing.

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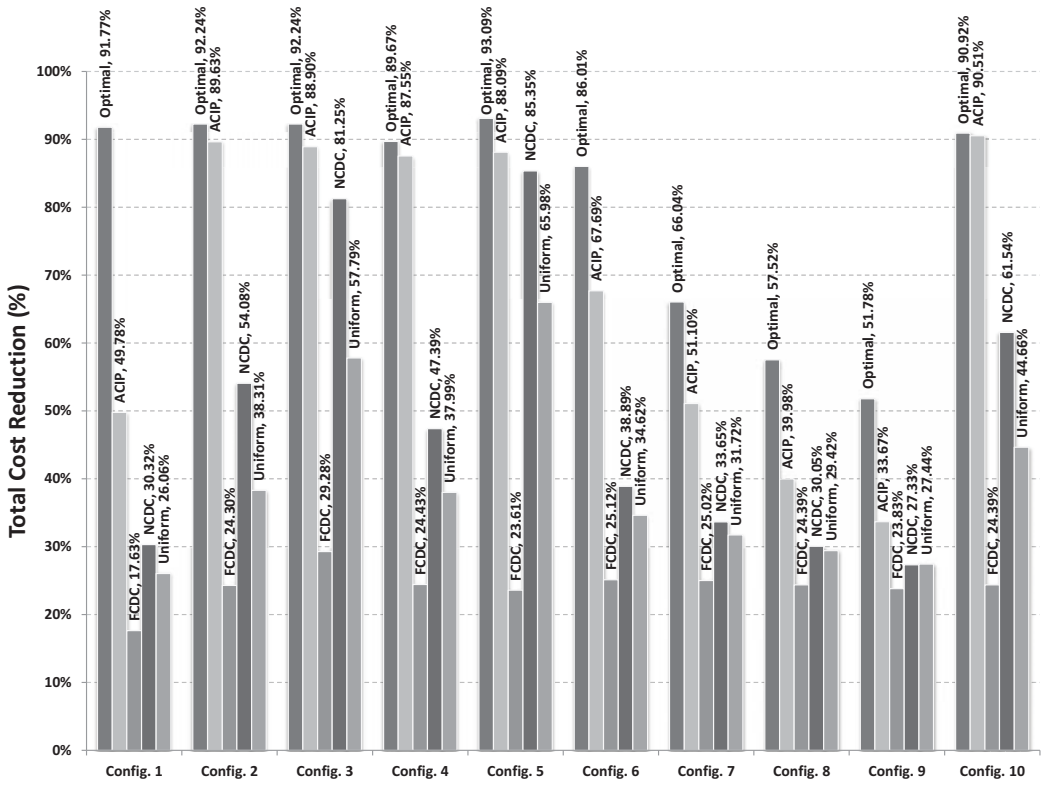


Figure 3: The cost reduction percentage of policies for each configuration.

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