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Non-pharmaceutical Intervention Strategies for Pandemic Influenza Outbreaks

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Non-pharmaceutical Intervention Strategies

for Pandemic Influenza Outbreaks

by

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Dedication

To my husband and my parents.

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Abstract

In case of a pandemic influenza outbreak, non-pharmaceutical interventions will likely be the only containment measure at the early stages of the pandemic when vaccines are not available. NPIs also offer an option for decreasing the probability of creating antiviral resistant viruses product of a mass prophylaxis campaign. In countries where there are not enough resources for vaccines and antivirals, NPIs may be the only mitigation actions available.

NPIs have been increasingly used in preparedness plans. We can see recommendations and guidelines regarding the use of NPIs in countries, health departments and universities. Also, researchers all around the world have study the impact of NPI's in pandemic influenza outbreaks, most of them using simulation as their modeling tool.

Our review of the aforementioned plans and literature shows that there is a lack of consensus in how to implement these interventions. They vary widely in the choice of key parameters such as intervention initiation threshold, duration and compliance. We believe that the lack of uniformity in NPI mitigation strategies arise from the uncertainty in the virus epidemiology and the current lack of scientific knowledge about the complex interactions between virus epidemiology with social behavioral factors and mitigation actions.

In this dissertation we addressed this problem by modeling pandemic influenza outbreaks using an agent-based simulation approach. The model incorporates detailed population demographics and dynamics, variety of mixing groups and their contact processes, infection transmission process, and non-pharmaceutical interventions. Using a statistical experimental design approach we examine the influence of characteristic parameters of virus epidemiology, social behavior, and non-pharmaceutical interventions on various measures of pandemic impact such as total number of infections, deaths and contacts. The experimental design approach also yields the knowledge of the extent of interactions among the above parameters. Using this knowledge we develop effective NPI strategies and demonstrate the

efficacy of these strategies on large-scale simulated outbreaks involving three different scenarios of virus transmissibility. The results show that significant improvements in the NPI based pandemic mitigation approaches can be attained by the strategies derived from our methodology.

1 Introduction

Influenza pandemics have occurred an average of three times every century since the 1500's. The most infamous been that of 1918 which infected about 50% of the U.S. population. There is an ominous expectation that a severe pandemic could occur and infect between 20 to 47 million persons in the U.S. alone. Such a scenario is more devastating than the one occurred during the H1N1 2009 epidemic ("swine flu"). In the absence of any control measures it has been estimated that it could cause around 200,000 deaths, 700,000 hospitalizations, 42 million outpatient visits, and an economic impact ranging between $71.3 and $166.5 billion in the U.S. [1]. A pandemic of such proportions worries public health officials. An emergency crisis like this would last much longer than most other emergency events and resources such as supplies of vaccines, antiviral drugs, healthcare providers, hospital beds and medical supplies would be limited.

An influenza virus can change significantly through random mutation. After a virus mutates, the immune system fails to recognize it. Virus mutation creates the threat of a highly pathogenic virus for which there is little or no pre-existing immunity in humans [2]. An influenza virus is named after its hemagglutinin (H) and neuraminidase (N) proteins. These proteins are the ones that allow the virus to invade a cell and reproduce, and also exit the cell and infect others. Inside an influenza virus there are 8 RNA segments, which can shift and mutate into new viruses.

The virus from the 1918 "Spanish Flu" most probably came from waterfowl and at some point entered human and pigs. Pigs are like the melting pots for influenza viruses since they can be infected by avian and human strains. In 1957, the re-assortment of an H2N2 avian virus and an H1N1 human virus resulted in the H2N2 influenza virus which had 3 new genetic segments from avian influenza and 5 RNA segments from 1918. Later on 1968, the H3 avian virus and the H2N2 human virus reasserted themselves creating the H3N2 Hong Kong Influenza which contained 2 genetic segments from avian influenza, one

from the H2N2 human virus and five from 1918's influenza virus. The 2009 H1N1 pandemic strain is a reassortment of avian, human, and swine influenza viruses.

Currently there are many flu viruses lurking around the world with the potential to mutate. The most notorious one being the avian influenza or bird flu H5N1. This virus is generally found in birds and in recent years there have been cases of human infections. But it could mutate and allow human to human infections, such a mutation could start a deadly worldwide pandemic. First cases occurred in Hong Kong in 1997 and human cases have since been reported in Asia, Africa, Europe, Indonesia, Vietnam, the Pacific and the near East. As of May 2^{nd} 2012, WHO has reported 603 confirmed cases and 356 of those have died.

Pandemic containment refers to keeping the number of new infections under control or within limits. In case of a pandemic that would be keeping the reproduction number R_0 under one or the infection attack rate (IAR) under 10%. Pandemic mitigation refers to the actions needed to reduce the severity, seriousness and painfulness caused by such a public health emergency. Pandemic containment and mitigation is of outmost importance because the flu virus spreads quickly. There are two ways a flu virus can enter the body, that is direct or indirect contamination. Direct contamination occurs when an infected person can directly pass the virus to an uninfected person (by coughing or sneezing). Indirect contamination occurs when an uninfected person touches a surface that has been contaminated by an infected person. Flu symptoms include fever, cough, sore throat, runny or stuffy nose, muscle or body aches, headaches, fatigue and vomiting and diarrhea. These symptoms can be so intense that it could limit a person of going to work, school or just run with their every day lives. Enough people missing work and school would pose a threat to our infrastructure and could seriously affect our quality of life. There is also the cost to society by the loss of education and business continuity.

Known approaches for pandemic mitigation and/or containment utilize both pharmaceutical interventions (PHIs) and non-pharmaceutical interventions (NPIs). PHIs include vaccines and antiviral drugs. NPIs include among other measures social distancing, quarantine, isolation, school and workplace closure, and travel restrictions.

The most effective mitigation measure is vaccination. However, there are certain challenges and limitations with the use of vaccinations at the early, critical stages of a pandemic. The major challenge arises from our inability to predict which virus strain will be the responsible for the next influenza pandemic. With the emergence of a new virus subtype, many limitations with the use of vaccines arises. Among the limitations include vaccine development, its production and distribution in a timely manner. For example, during the 2009 H1N1 outbreak, the development, production and distribution of a vaccine took nine months [3, 4].

Antivirals can be an effective containment and treatment measure. However, it would require a substantial level of stockpile for an effective antiviral campaign. Such a strategy can be infeasible due to prohibiting production and storage costs [5, 6, 7, 8]. Also, the use of a large-scale antiviral-based prophylaxis strategy can result in some strains of influenza becoming antiviral resistant while maintaining infectiousness [9, 10, 11]. Antiviral resistant virus are a threat since antivirals are the only means for treating influenza.

NPIs though often with certain delays, have the advantage of being available at the early phases of a pandemic. That early availability allows for reducing pressure on health services providers allowing them time to procure, distribute, and administer vaccines and antivirals [12]. NPIs will also likely be the only effective containment measure in developing countries that lack adequate resources for effective vaccination/antiviral campaigns [13].

Some of the NPIs (e.g., social distancing) have already been incorporated by many countries in their national pandemic preparedness plans [14, 15, 16, 17, 18]. Other major organizations that have also included NPIs in their preparedness plans are the World Health Organization (WHO) [19] and the Centers for Disease Control and Prevention (CDC) [17]. However, our review of the above plans and guidelines reveals that there is no consistent NPI strategy of when and how to implement these interventions. The plans and guidelines vary in their definitions of declaration thresholds, implementation stages, target population, and implementation logistics.

Some of the recent papers on simulation-based models for pandemic influenza mitigation, have examined various non-pharmaceutical intervention strategies. Our review of

these papers found differences in the assumptions regarding some of the key model parameters, such as intervention initiation, duration of the intervention phases, composition of risk groups, compliance levels, and other NPI related parameters (e.g., partial/full school closure, community contact rate increase during school closure [20]. The study by Aledort concludes that there is a general lack of scientific evidence and expert opinion regarding the use of NPIs during a pandemic [8]. We believe that the lack of consensus on the effectiveness of NPIs can be attributed to the differences in the underlying considerations of the existing simulation models that were used to examine NPIs. The differences include the composition of mixing groups, disease natural history, contact and infection transmission processes, and virus severity.

Effectiveness of NPIs have also been studied extensively in the literature. Different studies adopt different modeling approaches. There exist a number of mathematical models that examine the effectiveness of NPIs [21, 22, 23, 24, 25, 26]. However, mathematical approaches can not consider demographic and geographic features, they can not accommodate the process of individual to individual transmission and their daily schedules, and they are not capable of tracking infection spread, hence making it difficult to estimate basic reproduction number (R_0) and infection attack rates (IAR). Simulation-based models on the other hand, can consider demographic and geographic features of the region as well as individual health and family status, and daily schedules. Simulation models can also account for specific individual interactions and resulting infection spread, and can incorporate detailed infection-transmission processes and thus yields better estimates of R_0 and IAR.

Some of the recent papers on simulation-based models for pandemic influenza mitigation, have examined various non-pharmaceutical intervention strategies. In our literature review of these papers we also found a lack of consistency in the assumptions regarding some of the key model parameters, such as intervention initiation, duration of the intervention phases, composition of risk groups, compliance levels, and other NPI related parameters [27]. The study by Aledort concludes that there is a general lack of scientific evidence and expert opinion regarding the use of NPIs during a pandemic [8].

We believe that the lack of consensus on the effectiveness of NPIs can be attributed to the uncertainty on the virus epidemiology, and the complex interactions between virus epidemiology, social behavioral factors and mitigation actions. Developing good NPI strategies would require a better understanding of the science of the above interactions.

This dissertation have the following aiming, to establish the underlying relationships between the characterizing parameters of virus epidemiology, social behavior and non-pharmaceutical interventions. Use those results to develop guidelines for the design of effective NPI strategies and demonstrate the efficacy of such guidelines on large simulated outbreaks.

Chapter 2 presents a discussion on the current literature on the development and use of NPIs on simulated outbreaks. A detailed problem description along with the research objectives are presented in Chapter 3 and Chapter 4. Chapter 5 describes our methods and Chapter 6 presents our experimental study. A discussion along with conclusions are presented in Chapter 7.

2 Literature Review

In this section we present a comprehensive review and analysis of the prevailing types of NPIs found in the literature including case isolation, individual/household quarantine, school and workplace closure, and travel restrictions. We compile available model-based evidence on the effectiveness of these strategies, and examine how the choice of modeling assumptions and key NPI parameter values impact intervention effectiveness. We also discuss the effectiveness of NPIs when used in combination with PHIs.

2.1 Methods

This review considers only simulation-based models, which provide the most granular description of contact and infection transmission processes and social-behavioral considerations. There exist in the literature a number of mathematical models that also examine the effectiveness of NPIs [21, 22, 23, 24, 25, 26]. These papers are not included in our review.

We selected 203 articles from Pubmed published between 2005 through 2010 using the following keywords: simulation, quarantine, isolation, non-pharmaceutical interventions, travel restrictions, and social distancing. Paper abstracts were first examined to see if they met the selection criteria: simulation models, pandemic influenza, and NPI based mitigation. This reduced the number of articles to eighteen, which reduced to fifteen when the contents were further scrutinized to ensure that they included a description of the types of NPIs and their characterizing parameters. Four additional papers were added after reviewing the references for the selected fifteen articles, which brought the total number of reviewed papers to nineteen.

Selected papers were examined using the following key questions. What were the mitigation objectives? What types of NPIs were used? Were NPIs used in combination with PHIs? Which key parameters were used in defining the NPI strategies and the impact measures? Are the results and recommendations from different papers consistent?

2.2 Results

In this section we discuss how different modeling assumptions and parameter values guiding the disease natural history, contact processes, and infection transmission processes influence the effectiveness of NPIs. It may be noted that the number of assumptions and parameters involved in highly granular simulation based models are quite large. Mostly independent and disparate studies that are reviewed here consider a wide range of assumptions and parameter values and examine them on a variety of outbreak regions, transmissibility, severity, and NPIs. As a result, this paper contains a qualitative review and discussion. Studies cited in different parts of the paper are not meant to be exhaustive, but as a guide to the reader.

Table 1 summarizes the modeling assumptions regarding disease natural history and contact and infection processes that are made in the review papers. For each one of these assumptions, the key defining parameter values are tabulated. This table is intended to give a summary of each simulation model discussed in this review paper. For example, the model by Carrat et.al. [28] (see row 1 of Table 1) has the following features, 30% of the cases are asymptomatic; latent and incubation period are of same length; considers all major mixing groups, namely, households, schools, workplaces, and community; contact probabilities are dependent on age; mixing groups' contact probabilities are not affected when NPIs are in effect; infection process depends on both susceptible and infected individual's age, vaccination and antiviral status, as well as the infected individual's infectiousness status; virus severity is not considered in determining the infection probability.

Table 1: Summary of modeling assumptions for natural history, contact processes and infection transmission processes

Authors	Natural History		Contact Process				Infection Process		
			Mixing Groups (MG)	Contact Probability/Rates					
	Percentage of asymptomatic cases	Difference between incubation and latent periods (T Days)	Types	Uniform for all ages and MG	Function of specific attribute(s)	Do contact probability/rates change in MG not targeted by NPI? Y/N*	Characteristics of susceptible, infectious, and virus severity		
							Susceptible	Infectious	Virus Severity
Carrat et al. (2006)	30%	0	H,S,W,C	N	Age	N	Age Vaccination Antiviral	Age Vaccination Antiviral Infectiousness	N
Cauchemez et al. (2008)	50%	-	H,S,C	Y	-	Y	Age Immunity	Age Size of MG Infectiousness	Y
Chao et al. (2010)	33%	1 with 30% p 2 with 50% p 3 with 2% p	H,S,W,C	N	Age MG	Y	Vaccination Antiviral	Vaccination Antiviral	Y
Ferguson et al. (2005) (2006)	50%	0	H,S,W,C	Y	-	Y	Antiviral Vaccination	Antiviral Vaccination Infectiousness	Y
Germann et al. (2006)	33%	0.7	H,S,W,C	N	Age MG	Y	Antiviral Vaccination	Antiviral Vaccination	Y
Glass et al. (2006) Davey et al. (2008) Davey and Glass (2008)	50%	0.5	H,S,C	N	Age MG	Y	Age	Age	Y
Halder et al. (2010)	20% <18yrs. 32% > 18yrs.	1	H,S,W,C	Y	-	N	Age Antiviral	Antiviral	Y
Longini et al. (2005)	33%	0.7	H,S,W,C	N	Age MG	Y	Antiviral Vaccination	Antiviral Vaccination	N
Milne et al. (2008) Kelso et. al. (2009)	20% <18yrs. 32% > 18yrs.	1	H,S,W,C	Y	-	N	Age	Asymptomatic	Y
Sypsa and Hatzakis (2009)	33%	1	H,S,C	Y	-	Y	Age, MG Antiviral	Age, MG Antiviral Infectiousness	N
Wu et al. (2006)	33%	0.5	H,S,W,C	N	Isolation	N	Age	Infectiousness	Y
Yasuda et al. (2008) Yasuda and Suzuki (2009)	0%	-	H,S,W,C	N	MG	Y	-	-	-

Legend: Y – yes, N – no, H – households, S – schools, W – workplaces, C – community, p – probability, yrs – years

* For example: when schools and workplaces close, household and community contact probabilities/rates are increased

2.2.1 Disease Natural History [DNH]

A schematic of an influenza DNH model is shown in Figure 1. In many of the models reviewed, the incubation period is considered to outlast latency by a period T during which an individual is infectious but asymptomatic (see column 3 of Table 1). Under/overestimation of T can result in an increase/decrease in the prevalence of symptomatic cases at any given time during an outbreak [6, 7, 29, 30]. Most of the models also assume that up to 50% of individuals remain asymptomatic after completion of the incubation period (see column 2 of Table 1). Also, under/overestimation of the percentage of asymptomatic cases can lead to over/underestimation of the prevalence of symptomatic. Since in most of the reviewed models, the triggering thresholds of NPIs are based on the number (cumulative, prevalence or new incidences) of symptomatic cases, it's under/overestimation will lead to inaccurate assessment of NPI performance.

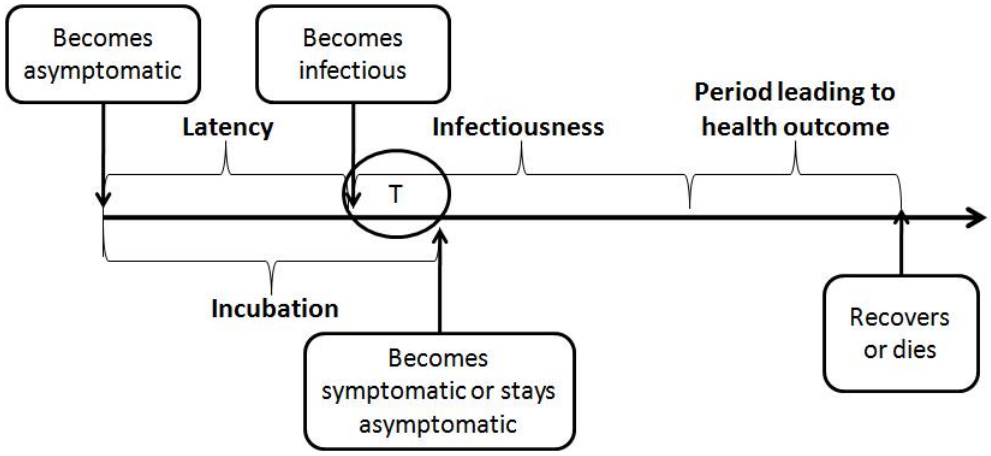


Figure 1: Schematic of an influenza disease natural history model. Figure depicts the schematic of pandemic influenza disease natural history. Once infected, an individual simultaneously enters the periods of latency and incubation. When incubation period is over, the individual may stay asymptomatic or become symptomatic. Both asymptomatic and symptomatic individuals will be infectious for a period of time before recovering or dying

2.2.2 Contact Processes [CP]

Key elements of CP models are composition of mixing groups and contact rates/probabilities. Most of the reviewed models considered four basic mixing groups: households

[H], schools [S], workplaces [W], and community [C] [6, 7, 12, 29, 30, 31] (see column 4 of Table 1). By ignoring any of these basic mixing groups, a model can misjudge NPI effectiveness since the CP in these basic groups are highly correlated. For example, closing of schools increase household and community contact rates [12, 31], which, if not considered, would underestimate the number of infections and thus overestimate NPI effectiveness. Moreover, partitioning of the population by mixing groups offers higher flexibility of how NPIs are implemented. An example could be considering each classroom as a separate mixing group instead of the whole school as one. This allows the implementation of partial school closure in addition to full closure [3]. The values of contact rates/probabilities also affect NPI effectiveness assessed by the models. Contact rates/probabilities vary among the mixing groups and also within the groups depending on age, health status, and other factors (see columns 5, 6, and 7 of Table 1). For example, contact rate is generally considered to be higher in schools than in workplaces [30, 32, 20]. If contact rates/probabilities are assigned lower than desired values, then the infections would be underestimated resulting in overestimation of NPI effectiveness and vice versa. Finally, the values of contact rates/probabilities used by a model should be supported by well-designed surveys and reputable data sources.

2.2.3 Infection Transmission Processes [ITP]

Infection probabilities along with the contact processes dictate ITP. Models that are reviewed in this paper obtain infection probabilities considering population heterogeneity (e.g., age and immunity), susceptibility and infection status of individuals, and virus transmissibility (see columns 8, 9, and 10 of Table 1). Consideration of population heterogeneity requires highly granular simulation-based models. An individual's infection susceptibility is affected by age [12, 31, 32, 20, 33] and status of vaccine/antiviral treatment [5, 6, 34, 35]. Not adjusting infection probabilities for age and vaccination/antiviral status can result in under/overestimation of the levels of infections, leading to incorrect estimates of NPI effectiveness. For example, if children are more susceptible to infection, not accounting for that would underestimate the impact of school closure. Past pandemics have shown that different age groups have different susceptibility to influenza viruses [7]. It has also been shown

that vaccine and antivirals decrease susceptibility in all age groups [7]. It is well known that viral shedding of an infected individual is influenced by the individual's time varying profile of infectiousness. This depends on immunity status and virus transmissibility and is often modeled by a lognormal distribution [5, 32].

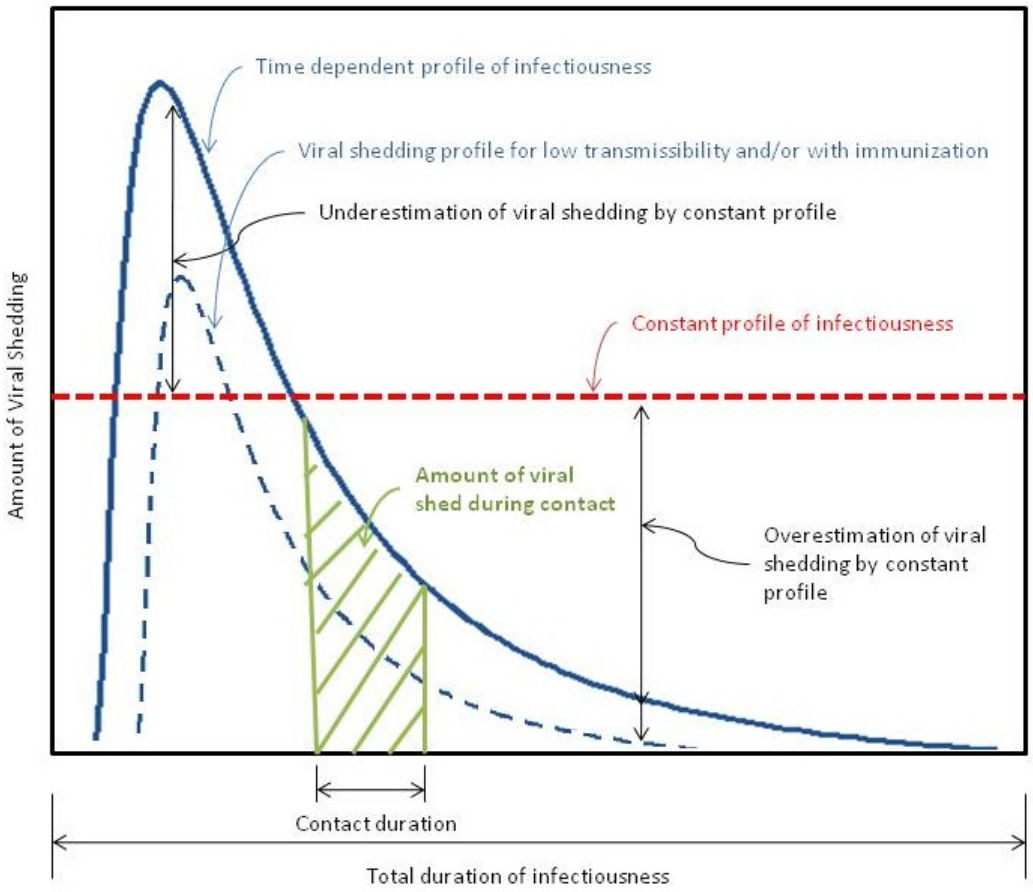


Figure 2: True time dependent profile of infectiousness. Figure depicts a schematic of a true time dependent profile of infectiousness along with a constant profile of infectiousness that is often assumed for model simplicity. The constant profile either underestimates or overestimates viral shedding depending on the time epoch during an infectious period. Immunization and virus transmissibility can alter the profile. Area of the shaded region indicates the total amount of viral shedding during a contact.

Consideration of a constant profile of infectiousness or not adjusting the time varying profile for the characteristics of an infected individual and virus transmissibility can lead to under/overestimation of infection transmission (see Figure 2 for a schematic of different profiles and their impact on infection probability). Other factors affecting the infection

probability are the day and the duration of contact between infected and susceptible. As shown in Figure 2, the area under the profile of infectiousness curve for the day and duration of contact determine the level of viral exposure dictating the infection probability [5, 35]. Even though the virus characteristics will not be known prior to or at the beginning of an outbreak, simulation models should study different "what-if" scenarios when assessing the effectiveness of NPIs and making recommendations.

2.3 Common NPIs

Our review shows that studies in the literature vary significantly in how NPIs are defined and modeled. In this section we summarize the definitions of the commonly used NPIs, the assumptions regarding their key parameters, and discuss their possible impact on performance. The papers that examine simultaneous application of multiple NPIs (layered) and combination of NPIs with PHIs are reviewed separately at the end of this section.

2.3.1 Quarantine Based NPIs

Case isolation [CI] refers to confining symptomatic individuals to their households away from other mixing groups [5, 7, 36, 37] or to a location other than home [6]. The effectiveness of CI depends on a number of parameters including initiation threshold, intervention duration, and compliance. Table 2 presents, for each model, a summary of definitions of NPIs discussed in this section, their defining parameters, and their performance as assessed by the models. When initiation threshold increases, CI effectiveness decreases and vice versa. As for the duration of CI, the reviewed papers consider it to be one of the following: the duration of the infectiousness phase [12], the duration of the disease period [6, 34], or the duration of the pandemic [30, 31, 20, 38]. None of the models examine the sensitivity of duration on effectiveness. Most of the reviewed models assume high compliance levels for CI. Blendon et al. [39] conducted a survey to determine the percentage of the population that was willing to stay at home for 7-10 days if infected with 94% responding affirmatively. However, this study was hypothetic and other studies have shown that in real life situations, conformance to NPIs will not be as optimistic.

Table 2: Summary of definition, parameters, and impact for case isolation, individual quarantine, household quarantine, and social distancing

Authors	Definition	Initiation Threshold	Intervention Duration	Compliance Level	Intervention Impact		
Davey et al. (2008)	SD : children/adults reduce non-school/ workplace and non-household contacts,; work contacts reduced; household contacts doubled	SD: 10 new cases	SD: ends when there are 0 cases/7 d and re-implemented when there are 10 new cases	50% - 90%	Compliance	B (IAR)	HQ (IAR)
					60%	28%	21.8%
						50%	44.2%
						62.9%	57.6%
	HQ: non-household contacts reduced; household contacts doubled	HQ: one diagnosed case in household	HQ: 10 d		90%	28%	9.8%
						50%	36%
						62.9%	49.9%
Davey and Glass (2008)	SD: non-household contacts reduced; household contacts doubled	10 new cases	Until pandemic slows to the point when only 0- 3 newly diagnosed cases occur in 7 d	50-90%	Compliance	B (IAR)	SD (IAR)
					90%	49.6%	1.6%
						71.4%	4.5%
Ferguson et al. (2005) Ferguson et al. (2006)	CI: infected reduce contacts	CI: 1 d upon becoming symptomatic	CI: 7d	CI: 90%	B (IAR)	CI (IAR)	HQ (IAR)
	HQ: contact rates of all household members of a case reduced; household contacts doubled	HQ: 1 d upon becoming symptomatic	HQ: 14 d	HQ: 50%	34%	27%	31%

Legend: CI – case isolation, IQ – individual quarantine, HQ – household quarantine, SD – social distancing, B – baseline, IAR – infection attack rate, d – days, MG – mixing groups, w- weeks

Table 2 (Continued)

Authors	Definition	Initiation Threshold	Intervention Duration	Compliance Level	Intervention Impact			
Germann et al. (2006)	SD: contact rates in all MG reduced; household contacts doubled	7 d after pandemic alert	Duration of pandemic	100%	**B(IAR)**	**SD (IAR)**		
					32.6%	25.1%		
					43.5%	39.2%		
					48.5%	44.6%		
					53.7%	50.3%		
Glass et al. (2006)	CI: all symptomatic cases withdraw to household SD: contact frequencies in all non-household and non-work MG reduced; household contacts doubled	CI: threshold of 10 new cases SD: threshold of 10 new cases	CI: duration of pandemic SD: duration of pandemic	CI: 90% SD: 90% contact reduction	**B (IAR)**	**SD (IAR)**	**CI (IAR)**	
					51%	29%	39.2%	
					66%	46%	-	
					75%	56%	-	
					86%	68%	-	
Kelso et al. (2009)	CI: adult/child withdraw to household SD: community contact reduction	CI: 0-8 w after introduction of 1st case SD: 0-8 w after introduction of 1st case	CI: duration of infection SD: duration of pandemic	CI: 90%-100% SD: 50%	**Initiation threshold**	**B (IAR)**	**CI (IAR)**	**SD (IAR)**
					0 w	32.5%	7%	15%
					8 w	32.5%	24%	24%
Longini et al. (2005)	HQ: infected case and certain percentage of susceptible restrict movement to their household or neighborhood cluster; household and neighborhood cluster contacts doubled	HQ : one infected case in a locality Interventions are implemented with a 7 – 21 d delay after introduction of first case	HQ: duration of pandemic	HQ: 70%	**Delay**	**R_0**	**B (cases per 1000)**	**HQ (cases per 1000)**
					14 d	1.4	211	0.17
						1.7	384	1

Legend: CI – case isolation, IQ – individual quarantine, HQ – household quarantine, SD – social distancing, B – baseline, IAR – infection attack rate, d – days, MG – mixing groups, w- weeks

Table 2 (Continued)

Authors	Definition	Initiation Threshold	Intervention Duration	Compliance Level	Intervention Impact			
Milne et al. (2008)	CI: infected individual withdraw to household SD: individuals reduce their contacts	CI: upon becoming symptomatic Interventions are implemented prior to the introduction of the first case in the community	CI: duration of pandemic SD: duration of pandemic	CI: 90% adults/ 100% children SD: 50%	R_0	B (IAR)	CI (IAR)	SD (IAR)
					1.5	33%	6%	16%
					2.0	55%	30%	41%
					2.5	65%	49%	55%
Sypsa and Hatzakis (2009)	SD: reduction in community contacts	SD: threshold of 1% attack rate	SD: Duration of pandemic	SD: 50%	B (IAR)		SD (IAR)	
					34.5%		20.4%	
Wu et al. (2006)	HQ: household contacts of a suspected case withdraw to household	HQ: when a member in the household developed symptoms, or was contacted by contact tracing or hospitalized	HQ: until no new symptoms developed in compliant household members for 7 d	50%	B (IAR)		HQ (IAR)	
					74%		49%	
Yasuda et al. (2009)	CI: home isolation of school children, a proportion of adults stayed home	CI: 2 d after the onset of symptoms	CI: duration of pandemic	CI: 33% adults 70%-100% children	Compliance		CI(number of cases)	
					0% (B)		3211	
					70%		2729	
					80%		2561	
					90%		2425	
					100%		2121	

Legend: CI – case isolation, IQ – individual quarantine, HQ – household quarantine, SD – social distancing, B – baseline, IAR – infection attack rate, d – days, MG – mixing groups, w- weeks

For example, in the study by Luliano et al. [40] only $35 - 89\%$ would stay at home while ill and in Johnson et al. [41] 87% of ill children visited a place outside of home while ill during the A/H1N1 pandemic of 2009. In general, compliance can be significantly affected by a variety of demographical, economic, and social behavioral factors. To address this uncertainty, analyses of sensitivity of the compliance rate were performed [36, 37, 38], and it was shown how CI effectiveness decreased as compliance decreased.

We also observed from our review that for low virus transmissibility scenarios, CI alone could reduce IAR and the number of infected cases. However, with increased transmissibility, CI is less effective. In most of the models, CI alone did not contain the pandemic (i.e., did not reduce IAR below 10% [12, 34]). The only study that claimed containment by using CI alone was by Kelso et al. [12]. Their success was likely due to the facts that CI was implemented immediately following the detection of one infected case, a low transmissibility virus was considered along with a high compliance rate ($90 - 100\%$).

Using CI, Ferguson et al. [35, 5] achieved a reduction of IAR from 34% to 27%, while Kelso et al. [12] achieved a reduction from 32.5% to 7%. This difference in NPI effectiveness is due to the differences in modeling assumptions as well as the choice of key NPI implementation parameters. Ferguson et al. assumed 50% of asymptomatics while Kelso et al. assumed 20% asymptomatics for those younger than18 years and 32% for those older than 18 years. As discussed earlier, underestimation of asymptomatic cases can lead to overestimation of symptomatic cases, which can improve NPI performance. For example, initiation thresholds in both studies are a function of the number of symptomatic cases. Ferguson et al. uses one day after becoming symptomatic as an initiation threshold, while Kelso et al. implements CI immediately after introduction of the first case. CI effectiveness is obviously guided by the rule "sooner implemented the better." Other difference observed in the above models is the difference in the value of T (difference between the latency and incubation period). In Ferguson et al. both latency and incubation period are the same length and T is therefore zero. In Kelso et al., T is considered to be one day.

Contact process also varies in the above models. When a person is in case isolation, it would be expected for the contact probabilities in other mixing groups to be zero while increasing at home. Ferguson et al. increases contact probabilities in other mixing groups while Kelso et al. keeps them constant. Not increasing the contact probabilities at home would underestimate the number of infections in the household leading to overestimations of NPI performance (as in Kelso et.al.). Definitions and assumptions of the key implementation parameters of CI also differ in the above models. In Ferguson et al. a person in isolation reduces contacts while in Kelso et al. the person is withdrawn to household. Allowing

the infected to have contact while in isolation is clearly a major factor in the difference in results among the above models. One possible reason why CI alone was not able to contain pandemic outbreaks in most models is that CI targeted only the symptomatic individuals, leaving the asymptomatic individuals to continue the spread.

Other quarantine measures that also target asymptomatic individuals include contact tracing [6], quarantine zones [35], and household quarantine [HQ]. We limit our discussion to HQ, which is most prevalent in the papers that we have reviewed. HQ involves restriction of movement of household members of an infected case. Some of the models considered a complete restriction of movement [6, 7, 34], while the rest assumed a partial restriction [5, 36, 37]. The duration of HQ intervention among the selected papers vary significantly from seven days [34] to fourteen days [5]. In other models, HQ lasted either until the pandemic slowed to the point where no more than three new cases were diagnosed in seven consecutive days [37] or until the pandemic ended [7]. Most of the papers implemented HQ immediately after the detection of an infected case while some considered a one day delay [5, 6, 34]. As in the case of CI, compliance is an important determinant on the effectiveness of HQ. The study by Blendon et al. [39] showed that 85% of the population is willing to stay home for 7-10 days if a member of the household is diagnosed with pandemic influenza. Again, this survey is hypothetical and recent studies regarding A/H1N1 outbreak of 2009 have shown that conformance will be dependent on the population's perception of severity [40]. The models reviewed in this paper considered compliance ranging from 50% to 90%. As compliance weakened so did the HQ effectiveness.

The diverging nature of the reported values of HQ effectiveness can be attributed to a rather wide range of parameter values used in defining HQ. Davey et al. [37] reported a reduction in IAR from 28% to 21.8% using household quarantine with 60% compliance. Longini et al. [7] with 70% compliance for HQ achieved a reduction from 211 cases per 1000 to 0.17 cases per 1000. The primary between the above models is in the value of the parameter for asymptomatic cases (50% for Davey et al., 33% for Longini et al.). However, some of the key assumptions that we believe have contributed to the difference in results are as follows: Davey et al. reduced non-household contacts while doubling household contacts; in

Longini et al., movements of the infected cases and a certain percentage of the symptomatic cases were restricted to their households. As non-household contacts were not allowed, we believe that Longini et al. achieved better results applying household quarantine. Duration of HQ should be a major contributor to the difference in IAR reduction. Davey et al. implemented household quarantine for 10 days, whereas Longini et al. implemented HQ for the duration of the pandemic. Larger duration in Longini et al. produced better performance, as it is well known that when NPIs are relaxed, new pandemic waves start to emerge increasing IAR [42]. So even when HQ was implemented with a 14 day delay, stringent application of HQ resulted in a sharper reduction of IAR in Longini et al. when compared to Davey et al.

Social distancing (SD) generally refers to the modes of reduction of contacts of individuals in all mixing groups other than household [30, 31, 37]. Examples of means of SD include cancelation of public mass gatherings (concerts, churches) and wide dissemination of pandemic related news. Results summarized in Table 2, show that the effectiveness of SD depends greatly on the transmissibility of the virus. We noted that SD alone was not able to achieve pandemic containment in all of the studies except in Davey et al. [36, 37], in which contacts were reduced by 90% for low and medium transmissibility scenarios. Comparing results from German et al. [30] and Glass et al. [31] we observe the significance of the values of initiation thresholds on NPI effectiveness. Though both models are quite similar in their modeling assumptions apart from assumptions (except for percentage of asymptomatics: 33% in Germann et al. and 50% in Glass et al.). Germann et al. achieved a small reduction in IAR (e.g., 53.7% to 50.3%) while Glass et al. achieved a relatively high reduction (e.g., 51% to 39.2%.) We note that Germann et al. initiated intervention 7 days after pandemic alert while Glass et al. had a threshold of 10 new cases which was met within a short time after the outbreak. We believe that early initiation in Glass et al. made SD more effective in reducing IAR.

2.3.2 Closure Based NPIs

School closure (SC) involves closing of schools, school related activities, and childcare programs. SC, while reducing contacts in the aforementioned mixing groups, increases household contacts [5, 12, 37] and community contacts [34]. The extent of SC can vary widely from a nationwide closure [30] to partial closure of all schools in a region, individual schools, or one or more classes within a school [3]. The reported performances of SC also vary significantly due to differences in significant assumptions regarding closure initiation threshold and duration, and students' contact behavior during a closure (i.e., whether the students remain strictly at home or continue to make contacts in the community).

Some of the reviewed papers showed outbreak containment via SC alone [30, 32, 28, 37, 43], concluding that SC effectively reduces IAR. However, SC results in a significant loss of productivity since many working adults stay home with the children [28]. Other conclusions about SC include the following: SC could be an ideal strategy except for the long length of closure necessary [37]; SC is highly effective for low transmissibility scenarios and when attack rates are higher in children than adults [30, 32, 20]; SC is effective in reducing peak attack rates and slowing the spread of the pandemic even when the overall IAR is not significantly reduced [5, 44, 45]; SC could be a successful strategy only if children are kept at home and not allowed to contact others in the community [31].

Table 3 shows a summary of results for school closure and workplace closure (discussed later) from the selected papers. Definitions of closures along with the assumptions regarding the key parameters guiding the closure policies are also presented in Table 3. The results show that there is little consensus among the conclusions arrived at by the studies on the level of effectiveness of SC during a pandemic influenza. However, in general, SC is shown to be an effective measure to reduce peak attack rate and to delay time of occurrence of the peaks [5, 30, 20, 44], which can reduce stress on the health care delivery system.

For example, Germann et al. [30] achieved a reduction in IAR from 48.5% to 37.9%, whereas Davey and Glass [36] achieved a reduction from 49.6% to 2% (containment).

Table 3: Summary of definitions, parameters, and impact for school closure and workplace closure

Authors	Definition	Initiation Threshold	Intervention Duration	Compliance Level	Intervention Impact		
Carrat et al. (2006)	SC: schools close WC: workplaces close	SC: infected reaches threshold of 5/1,000 population WC: infected reaches threshold of 5/1,000 population	SC: 10 d after the last infected case WC: 10 d after last infected case	SC: 100% WC: 100%	B (IAR)	SC (IAR)	SC + WC (IAR)
					46.8%	9.7%	1.1%
Cauchemez et al. (2008)	SC: schools close	SC: When daily incidence > 20/100,000 population	SC: duration of pandemic	SC: 100%	B (IAR)		SC (IAR)
					31%		14% - 18%
Chao et. al. (2010)	SC: school group contacts eliminated, community contacts doubled	SC: one infected case in school or community	SC: 60 d closure vs. permanent closure for pandemic duration	SC: 100%	Duration	B (IPP)	SC (IPP)
					60 d	6%	3.5%
					Permanent	6%	2%
Davey et al. (2008)	SC: school contacts reduced, household contacts doubled, adult stayed with children < 11 yrs.	SC: infected reaches threshold of 10 new cases per total data	SC: until there are no new cases in 7d and re-implemented when threshold is reached	SC: 60% - 90% (only extreme cases are presented)	Compliance	B (IAR)	SC (IAR)
					60%	28%	2.8%
						50%	25.1%
						62.9%	49.8%
					90%	28%	2.2%
						50%	22.7%
						62.9%	47.2%
Davey and Glass (2008)	SC: school contacts reduced, household contacts doubled, adult stayed with children < 11 yrs.	SC: : infected reaches threshold of 10 new cases	SC: Until pandemic slows to the point when only 0- 3 newly diagnosed cases occur in 7 d	SC: 90%	Compliance	B (IAR)	SC (IAR)
					90%	49.6%	2%
						71.4%	17.6%
Ferguson et al. (2005) Ferguson et al. (2006)	SC + WC: school s close and can re-open if threshold is reached. School and workplace contacts eliminated, household contacts increased	SC + WC: 1 d after a case is detected	3 w	SC: 100% WC: 50%	B (IAR)		SC + WC (IAR)
					27%		23%
					34%		31%
Germann et al. (2006)	SC: Nationwide closure of schools, other contacts remain unchanged	SC: 7 d after pandemic alert	SC: duration of pandemic	SC: 100%	B (IAR)		SC (IAR)
					32.6%		1%
					43.5%		29.3%
					48.5%		37.9%
					53.7%		46.4%
Glass et al. (2009)	SC: school contacts reduced, children/teenager contacts doubled WC: workgroup contacts reduced	SC: : infected reaches threshold of 10 new cases WC: infected reaches threshold of 10 new cases	SC: duration of pandemic WC: duration of pandemic	SC:90% WC: 50%	B (IAR)	SC (IAR)	WC (IAR)
					51%	41%	48%
					66%	61%	63%
					75%	73%	72%
					86%	85%	84%

Legend: SC - school closure, WC - workplace closure, B –baseline, IAR – infection attack rate, IPP – illness prevalence peak, yrs.– years, w- weeks, d – days

Table 3 (Continued)

Authors	Definition	Initiation Threshold	Intervention Duration	Compliance Level	Intervention Impact			
Halder et al. (2010)	SC: 1. case was isolated with a set of classmates 2. individual SC 3. all SC For all 3: adult stay with children <12 yrs	1 and 2: threshold of one new case 3: threshold of 0.1% of the population	1,2 and 3: 1 to 4 w	1,2 and 3: 100%	**B (IAR)**	**Best SC scenario 2 (IAR)**		
					32.5%	30%		
Kelso et al. (2009)	SC: school contacts eliminated, adult stayed with children WC: worker had the choice of staying home	SC: 0-8 weeks after introduction of first case WC: 0-8 weeks after introduction of first case	SC: duration of pandemic WC: duration of pandemic	SC: 100% WC: 50%	**Initiation threshold**	**B (IAR)**	**SC (IAR)**	**WC (IAR)**
					0 w	32.5%	14%	24%
					8 w	32.5%	24%	29%
Milne et al. (2008)	SC: school contacts eliminated, adult stayed with children WC: worker had the choice of staying at home	SC: implemented prior to the introduction of the first case WC: implemented prior to the introduction of the first case	SC: duration of pandemic WC: duration of pandemic	SC: 100% WC: 50%	**R_0**	**B (IAR)**	**SC (IAR)**	**WC (IAR)**
					1.5	33%	13%	24%
					2.0	55%	45%	48%
					2.5	65%	60%	60%
Sypsa et al. (2009)	SC: all schools closed	SC: threshold of 1% cumulative clinical attack rate	SC: duration of pandemic	SC: 60%	**B (IAR)**		**SC (IAR)**	
					34.5%		3.7%	
Yasuda et. al. (2008)	SC: all schools closed	SC: 4 w after pandemic starts	SC: 2 w	SC: 100%	**B (# of cases)**		**SC (# of cases)**	
					2951		2696	
Yasuda and Suzuki (2009)	SC: all students stayed home WC: percentage of adults stayed home	SC: 1 - 2 weeks after pandemic starts WC: 2 d after onset of symptoms	SC: 7d WC: 7d	SC: 100% WC: 33% adults	**Duration**	**B (# of cases)**	**SC + WC (# of cases)**	
					1 w	3211	1812	
					2 w	3211	1766	

Legend: SC - school closure, WC - workplace closure, B –baseline, IAR – infection attack rate, IPP – illness prevalence peak, yrs.– years, w- weeks, d - days

The key differences between the above models are as follows. Germann et al. assumes 33% asymptomatic while Davey and Glass assume 50%. A higher number of asymptomatic generally translate to a later intervention initiation and lower reduction in IAR. Davey and Glass still achieved a better SC performance. One possible reason for this is that Germann et al. defined SC as a nationwide closure of schools with other contacts remaining unchanged, while Davey and Glass reduced school contacts, doubled household contacts and considered that an adult stayed home. This clearly shows that for SC to be effective, children must be confined to home and not allowed to make contacts in the community.

The initiation threshold appears to be another key reason behind the difference in SC performance in the above studies. Germann et al. initiated SC seven days after pandemic alert, and Davey and Glass started the intervention after threshold reached 10 new infected cases. In both studies the duration of intervention was reasonably long. For Davey and Glass maintained SC until pandemic slowed to the point when only 0-3 newly diagnosed cases occurred in 7 days. Germann et al. kept SC in place for the duration of the pandemic. In recent studies on the effect of SC (conducted during the A/H1N1 pandemic outbreak) [42], it was shown that R (reproduction number) increased when school closure was lifted and before summer vacation started. SC is an effective measure when implemented early, but when removed, can result in new waves of infection unless PHIs are introduced.

Workplace closure (WC) eliminates contacts at workplaces but increases household and community contacts [5]. In some of the reviewed papers, WC considers workplace non-attendance with reduced contact rates as workers have the option to stay home [12, 31, 20].

In general, WC is shown to be less effective than SC [12, 31, 20]. In the reviewed papers, WC by itself didn't cause a significant reduction in IAR. Glass et al. [31] had a reduction in IAR from 51% to 48% while Kelso et al. [12] from 32.5% to 24%. These reductions are lower compared to those achieved by SC. Clearly the children make more contacts at schools than adults at work. Hence, independent of modeling and parameter assumptions, WC by itself wasn't shown to be very effective.

When WC was used in conjunction with SC, better results were reported in comparison to either of the interventions alone [20]. The study by Carrat et al. [43] achieved containment by applying school and workplace closure to a pandemic with a base IAR of 46.8% and reducing it to 1.1%. The study by Ferguson et al. [5], achieved some reduction of IAR, but didn't achieve containment, as the base IAR of 34% was reduced to 31% IAR.

There could be multiple reasons why Ferguson et al. did not achieve a considerable IAR reduction as in Carrat et al. Ferguson et al. assumed a 50% asymptomatics (30% in Carrat et al.) leading to increased delay in WC initiation. Unlike in Carrat et al., Ferguson et al. increased household contact rates as they eliminated school and workplace contacts. In Ferguson et al., institutions were closed one day after the first case is detected, which is much

sooner than Carrat et al. strategy of reaching 0.5% infected in the population. However, they used much shorter closure duration of three weeks, which is likely to have caused new spikes in infection after each WC completion and resulting higher IAR. Our conjecture is that the benefits of shorter initiation threshold in Ferguson et al. were outweighed by the shorter duration of WC. Lack of IAR reduction in Ferguson et al. should also have been impacted by the consideration of a relatively low (50%) WC compliance as compared to the 100% compliance considered in Carrat et al.

When considering WC, it is important to seek a balance between pandemic containment and the total cost of this intervention. The cost of SC and WC should account for lost productivity, lost educational opportunities, and the cost of business continuity.

2.3.3 Travel Restriction Based NPI

Among the reviewed papers, travel restriction (TR) is the least explored NPI. Table 4 shows a summary of the TR implementations [5, 30, 44] and the corresponding results. The study in [5] used border control and area quarantine, where border control attempts to reduce the number of infected individuals entering the country, and area quarantine is the reduction of travel between the affected and unaffected zones. TR was modeled as the reduction of travel to as little as 10% of the normal number of trips made by an individual in [30]. The model in [44] considered elimination of travel via train lines. None of the above studies achieved a significant outcome. In order for TR to be effective in reducing IAR, it must be implemented prior to the introduction of infected cases into the community, which could be difficult to accomplish in practice. However, TR has been shown to be effective in delaying the spread, which gives time for PHIs to be developed and deployed.

2.3.4 Layered NPIs: Combinations of NPIs and PHIs

A number of the reviewed papers show that layered NPI strategies, in which multiple NPIs are applied together, performed better than one intervention at a time in reducing the infection attack rate, the total number of infections, and the peak attack rate (for a summary see Table 5). Layered strategies also help to delay the occurrence of pandemic peaks.

Table 4: Summary of definitions, parameters and impact for travel restrictions

Authors	Definition	Initiation Threshold	Intervention Duration	Compliance Level	Intervention Impact			
					Compliance	BC (peak delay)	AQ (peak delay)	BC + AQ (peak delay)
Ferguson et al. (2005) Ferguson et al. (2006)	BC: number of infected individuals entering the country is controlled AQ: reduction of travel from affected zones to unaffected zones and vice versa	BC: day 30 of global pandemic declaration AQ: 2 days from detection of an infected case in a zone	BC: duration of pandemic AQ: 7 d	BC: 90% - 99.9% AQ: 75% - 100%	75%	-	1 w	-
					90%	1.5 w	-	-
					99%	3 w	-	-
					99.9%	6 w	-	No delay in peak but extends pandemic
Germann et al. (2006)	Travel reduced to 10% of the normal number of trips	Immediately after pandemic alert	Duration of pandemic	100%	B (IAR)		TR (IAR)	
					32.6%		32.8%	
					43.5%		44%	
					48.5%		48.9%	
					53.7%		54.1%	
Yasuda et al. (2008)	PT: prohibition of travel in the virtual Chuo Line	Intervention was implemented after pre-pandemic spread	2 w	100%	B (# of cases)		TR (# of cases)	
					2951		2837	

Legend: BC – border control, AQ – area quarantine, PT – prohibition of traffic, d – day, w – weeks, TR – travel restrictions, B – baseline

However, some of the reviewed studies were not successful in containing pandemic influenza with a layered strategy (add references). It was shown by the studies that achieved containment (add references) that for a multi-layered approach to work, it has to be implemented early in the pandemic and with high compliance levels.

This is often problematic as early implementation, higher compliance, and a possible extended duration of interventions may result in public disapproval and a high societal cost.

NPIs were also studied in combination with PHIs in some of the selected papers. Studies that achieved containment implemented NPIs together with PHIs such as vaccination, antiviral treatment, and antiviral prophylaxis [3, 7, 30, 32, 37, 38, 44, 46]. In general, based on the papers reviewed, it can be concluded that the best strategy to mitigate pandemic influenza outbreaks is to combine NPIs with PHIs. But even this combination of interventions may not be sufficient for containment for high transmissibility viruses.

Table 5: Summary of definitions, parameters, and impact of using layered NPIs and combinations of PHIs and NPIs*

Author/Year	Definition	Initiation Threshold	Intervention Duration	Compliance Level	Results on Intervention Impact		
Carrat et al. (2006)	C: HQ, AP and AT AP: prophylaxis of households	AP: beginning of simulation AT: beginning of simulation	AP: 10 d AT: 5d	AP: 70% AT: 90%	B (IAR)		C (IAR)
					46.8%		17%
Davey et al. (2008)	C: SC, HQ, SD , AP and AT	C: threshold of 10 new cases AP: until household member became infected AT: immediately after diagnosis	C: until there are no new cases in 7 d and re-implemented when there are 10 new cases AP: 10 d AT: 5 d	AP: 60% - 90% AT: 60% - 90%	Compliance	B (IAR)	C (IAR)
					60%	28%	1.2%
						50%	1.5%
						62.9%	2.2%
					90%	28%	1.1%
						50%	1.4%
						62.9%	1.5%
Ferguson et al. (2005) Ferguson et al. (2006)	C: HQ , SC, WC, AP and AT	AP: 1 d delay from onset of symptoms AT: 1 d delay from onset of symptoms	AP: 10 d AT: 5 d	AP: 90% AT: 90%	B (IAR)		C (IAR)
					34%		13%
					13%		7.6%
Germann et al. (2006)	C: SD, SC, TR, AP, AT and V	AT and AP: first symptomatic case in a household V: starting at day 0 of pandemic	AP: 10 d AT: 5 d	AP: 100% children, 60% adults AT: 60%	B (IAR)		C (IAR)
					32.6%		0.02%
					43.5%		0.03%
					48.5%		0.06%
					53.7%		0.1%
Glass et al. (2006)	Layered NPI: SC, SD, WC	For details see Tables 3 and 4	For details see Tables 3,and 4	For details see Tables 3 and 4	B (IAR)		C (IAR)
					51%		2%
					66%		3%
					75%		6%
					86%		25%
Halder et al. (2010)	C: SC, AT and AP	AT: upon being diagnosed AP: upon household contact being diagnosed	AT: 5 d AP: 10 d	AT: 100% AP: 100%	B (IAR)		C (IAR)
					32.5%		9%

Legend: CI – case isolation, IQ - individual quarantine, HQ – household quarantine, SD - social distancing, SC – school closure, V – vaccination, AP – antiviral prophylaxis, AT – antiviral treatment, B – baseline, C – combination, w – weeks, IAR – infection attack rate, CT – contact tracing

*For NPI details see previous tables

Table 5 (Continued)

Author/Year	Definition	Initiation Threshold	Intervention Duration	Compliance Level	Results on Intervention Impact
Halloran et al. (2008)	C: SC, WC, CI, HQ, SD	C: 1%-10% cumulative illness attack rate	AT: 5d AP: 10 d	AT: 5% stop taking antivirals after 1d AP: 5% stop taking antiviral after 2 d	Model: 1 / 2 / 3 — B(IAR): 42.4%, 52.4%, 58.8%, 46.8%, 52.4%, 58.8%, 44.7%, 51.1%, 56.5% — C (IAR): 7.3%, 15.5%, 27.4%, 2.8%, 4.1%, 8.5%, 3.9%, 9.7%, 20.4%
Kelso et al. (2009)	Layered NPI: WC, SC, SD, CI	For details see Tables 3 and 4	For details see Tables 3 and 4	For details see Tables 3 and 4	Duration: 0 w, 8 w — B (IAR): 32.5%, 32.5% — C (IAR): 2%, 20%
Longini et al. (2005)	C: AP, AT, V and HQ	C: 14 d delay from introduction of first case AT: 1 d delay upon becoming symptomatic AP: 1 d delay upon contact becoming symptomatic V: prior to pandemic	AT: 1 d AP: 1 d	AT: 80% AP: 80% V: 50%	R_0: 1.4, 1.7 — B (cases per 1,000 population): 211, 384 — C (cases per 1,000 population): 0.02, 0.03
Milne et al. (2008)	Layered NPI: SC, CI, WC, SD	For details see Tables 3 and 4	For details see Tables 3 and 4	For details see Tables 3 and 4	R_0: 1.5, 2.0, 2.5 — B (IAR): 33%, 55%, 65% — C (IAR): 2%, 2%, 3%
Sypsa and Hatzakis (2009)	C: CI, SC, SD, AT, AP	C: threshold of 1% cumulative clinical attack rate	C: duration of pandemic	AT: 100% AP: 80%	B (IAR): 34.5% — C (IAR): 1.8%
Wu et al. (2006)	C: HQ, CI, AT, AP	AT and AP: one d delay upon becoming symptomatic	AT and AP: two doses for symptomatic individuals per day, one for non-symptomatic individuals	AT and AP: 50%	B (IAR): 74% — HQ + CI (IAR): 43% — HQ + AT + AP (IAR): 44% — HQ + CI + AT + AP (IAR): 40% — HQ + CI + AT + AP + CT (IAR): 34%
Yasuda et. al. (2008)	C: SC, TR and V	V: prior to pandemic	-	V: 30%	B (# of cases): 2951 — SC + TR (# of cases): 2359 — SC + V (# of cases): 1578 — SC + TR + V (# of cases): 955
Yasuda and Suzuki (2009)	C: CI, SC, V and AP	V: before pandemic	-	V: 30% AP: 40%	B (# of cases): 3211 — C (# of cases): 1027

Legend: CI – case isolation, IQ - individual quarantine, HQ – household quarantine, SD - social distancing, SC – school closure, V – vaccination, AP – antiviral prophylaxis, AT – antiviral treatment, B – baseline, C – combination, w – weeks, IAR – infection attack rate, CT – contact tracing

*For NPI details see previous tables

2.4 Conclusions

Employing NPIs at the earlier stages of a pandemic can reduce and delay the pandemic peak, thus allowing time to develop and distribute PHIs, which are costly and unlikely to be available at the beginning of a pandemic. NPIs are of particular significance for underdeveloped countries that lack resources for developing or acquiring a supply of vaccines and antivirals.

Many countries in their preparedness plans have incorporated NPIs, but the interventions vary significantly in their key implementation parameters. These variabilities can be attributed to the cultural and social differences in how NPIs are perceived and complied with, methods of implementation, and the capacities of the nations to absorb the economic impact of the interventions. The inconsistencies among the plans are also due to the lack of a cohesive scientific approach to model and assess NPIs. Models vary widely in part because of the complexities of multi-scale societal structures, human behavior, and uncertainty of virus epidemiology. Other variations arise from modeling methods, assumptions, definitions, parameter values, test-beds, and choice of impact measures. This paper highlights the above disparity by providing a systematic review of a segment of the NPI literature that uses simulation as their underlying model.

To analyze the commonly used NPIs, we grouped them in four categories: quarantine, closure, travel restrictions, and combinations. Quarantine based NPIs include case isolation, household quarantine, and social distancing. These perform better at lower transmissibilities, when implemented early, and for high compliance rates. However, there are many economic and social limitations of implementing quarantine based NPIs. For example, even though enforcement of these interventions for a prolonged time improves IAR reduction, it may result in loss of individual freedom and income. Hence, quarantine based NPIs must consider a wide range of compliance levels, ability for quarantined individuals to acquire food and medicine, and the limit for the loss of income that individuals/families can sustain.

Closure based NPIs include closing of schools and workplaces. The models of school closure vary from 'selected classrooms' to 'all classrooms', a 'cluster of schools' to 'all schools'

in a region, and nationwide closure. The models also vary in the choice of initiation threshold and closure duration. Literature shows that school closure is highly effective for low transmissibility scenarios and when attack rates are higher in children than adults. School closure was shown to consistently reduce peak attack rates and delay pandemic spread. It also impacts workplaces, since working adults may have to stay home to supervise children. A prolonged school closure may also have a significant impact on the academic progress of the students. Hence, a prolonged school closure must have associated measures to alleviate loss of productivity, loss of income, and academic disruption.

Literature considers both full and partial workplace closure. This intervention by itself does not significantly reduce pandemic impact. However, workplace closure used in combination with school closure achieved better results than either measure alone. A prolonged closure of workplaces could adversely impact society by impairing supply of basic goods and services and inflicting a high cost of lost productivity and wages. Hence, workplace closure must be supported by plans to ensure business and service continuity.

Travel restrictions include border control, area quarantine, reduced public transportation, and reduced personal travel. None of these were found to yield a significant reduction in the IAR, but they did help to delay pandemic spread. Travel restrictions were shown to be effective only when they are implemented prior to the introduction of infected cases into a community. This poses a challenge for public health officials as convincing the public to accept travel restrictions may be difficult. Moreover, travel restrictions are ineffective in preventing travels of those who are either asymptomatic or are in their latent phases of infection.

A layered NPI strategy refers to a combination of various simultaneous interventions. Except for some high transmissibility scenarios, layered NPIs were shown to be successful in containing pandemic outbreaks. Some studies considered combining layered NPI with PHI, which produced better results than using layered NPI only.

There have been many recent studies on NPI effectiveness during the 2009 H1N1 pandemic [42]. In Mexico, SC was shown to reduce transmission in $29 - 31\%$, and it was shown that R increased when school suspension was resumed. A decrease in R from 2.2

to 1 coincided with the suspension of educational activities and other social distancing measures (closure of movie theaters and restaurants and cancellation of public gatherings). These findings support the effectiveness of early mitigation efforts and also the importance of school cycles in the transmission of pandemic influenza. These results were also shown during the A/H1N1 pandemic in Hong Kong where a 25% reduction in transmission was achieved following the closure of schools. A $13 - 40\%$ reduction in R was seen in Belgium, Great Britain and the Netherlands during holiday period [42].

The study by Hatchett et al. [47] analyzed the impact of NPIs during the 1918 pandemic. From this study it was shown that outcomes of NPI effectiveness were correlated with the quality and timing of intervention. For example, Philadelphia reported cases on September 17 but didn't implement any NPIs until October 3. St. Louis reported cases on October 5 and implemented NPIs on October 7. Philadelphia had a peak death rate of 257/100,000 compared to St. Louis peak death rate of 31/100,000. This study also shows that implementation of layered NPIs resulted in lower peak death rates, across cities. Implementation of three or fewer NPIs had a peak weekly death rate of 146/100,000, whereas cities that implemented four or more NPIs had a peak weekly death rate of 65/100,000. Early school, church or theater closure as well as early bans on public gatherings were also associated with lower peak excess death rates. This study also showed the importance of duration of intervention, no city experienced second waves while its main battery of NPIs were in place, second waves occurred only after the relaxation of interventions.

Even though there are many differences in modeling assumptions, implementation parameters, and the resulting recommendations of the papers that are reviewed here, the following general conclusions can be of benefit to the public health officials.

- NPI effectiveness is directly correlated with time of implementation. Pandemic preparedness is important in order to minimize deployment delay and maximize effectiveness.
- When planning for NPI implementation, duration of interventions should be kept as long as necessary. It has been shown that when the interventions are relaxed, new pandemic waves emerge.

- NPIs should be layered. We noted from this review that layered NPIs have a better effectiveness than any one intervention by itself.
- School closure may be the most effective of NPIs. When planning for SC, extra measures should be taken to ensure children don't continue to increase their contacts in the community.

A notable omission that we have observed in the reviewed literature is the use of *cost to society* as a measure of performance. Clearly, there is a need for further research to develop a unified approach to design, implement, and assess performance of NPIs.

3 Problem Description and Research Objectives

Non-pharmaceutical interventions are increasingly being used in national pandemic preparedness plans. Many countries are already incorporating the use of NPIs in their pandemic influenza preparedness guidelines. Some of these countries include Australia, China, Japan, Canada, Mexico and the U.S. among others. All of these plans can be found in the United Nations Office for the Coordination of Humanitarian Affairs (OCHA) website [18]. All of these countries recognize the importance of non-pharmaceutical interventions during a pandemic influenza outbreak. The threat of a pandemic influenza outbreak is not only of national concern, in the U.S., the health departments in every state have their own preparedness plans, with their own recommendations and guidelines. Many universities have also developed their pandemic preparedness plans comprising NPIs [48, 49, 50]. Also, non-pharmaceutical interventions can be found in the World Health Organization (WHO) community measures [19] and in the Centers for Disease Control and Prevention (CDC) guidelines [17].

As discussed in our literature review [27], NPIs are also being studied by researchers around the world. But available research approaches and the resulting guidelines offer widely varying recommendations for the choice of critical NPI design parameters. Some of these parameters include thresholds for pandemic declaration and intervention initiation, and duration and target population for each intervention.

For example, major agencies like WHO and CDC adopt different andemic declaration thresholds. WHO uses a six-phased approach. Phases 1-3 compromise mostly animal infections and few human infections, and it correlates with preparedness. Phase 4 entails a sustained human to human transmission and Phase 5 and 6 a widespread human infection. It is evident that response is needed during phases 4 to 6 on the WHO scale. CDC on the other hand, divides the pandemic into categories based on the case fatality ratio (CFR), and give recommendations based on these categories.

As regards school closure, CDC only recommends less than four weeks of closure when pandemic is in a category 2-3 and less than 12 weeks for categories 4-5. Many researchers on the other hand, recommend to start school closure right away and sometimes for indefinite periods of time. A lack of uniformity in the recommendations examined above can be attributed to the uncertainty in the virus epidemiology and the current lack of scientific knowledge about the complex interactions between virus epidemiology with social behavioral factors and mitigation actions.

At the early stages of a pandemic, virus epidemiology parameters such as reproduction number (R_0), infection attack rates (IAR) and case fatality ratios (CFR) will be largely unknown.

Figure 3 shows a set of selected parameters concerning virus epidemiology, social behavior and NPIs which are likely to have significant interactions.

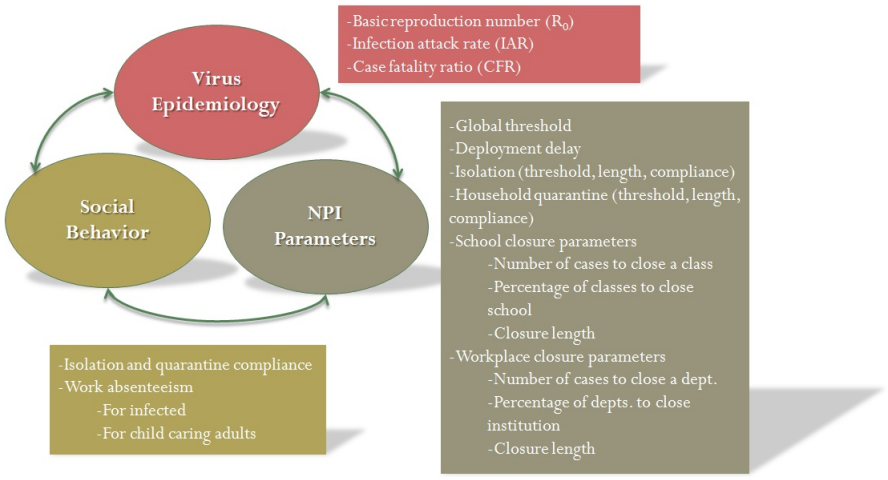


Figure 3: Interacting parameters affecting pandemic outbreaks

This dissertation has the following three objectives:

- To establish the underlying relationships between the characterizing parameters of virus epidemiology, social behavior and non-pharmaceutical interventions.
- To develop guidelines for design of effective NPI strategies using the results from the first objective.
- To demonstrate the efficacy of NPI guidelines developed in the second objective on large-scale simulated outbreaks involving millions of people in urban areas.

4 Methodology

Our methodology is driven by a simulation-based model, an earlier version of which was presented in Uribe et al. [29]. The simulation is capable of modeling millions of individuals and track their daily schedules. The simulation model incorporates the population dynamics, disease natural history, contact and infection transmission processes and mitigation actions. A schematic of the simulation is given in Figure 4. The major components of the simulation model are described next.

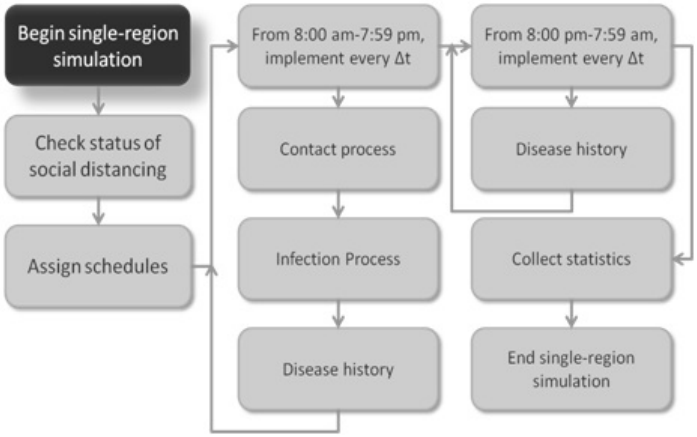


Figure 4: Simulation schematic representation

4.1 Simulation Model

The simulation model begins by creating mixing groups and individuals. Individuals are created based on demographic data with a set of attributes. Adults and children have the following common attributes: age, gender, household, health condition (poor, moderate, good), and disease status. Adults in addition have parenthood and workplace as attributes, and children have school.

Mixing groups include households which are characterized by the number of adults and children. Other mixing groups considered in our simulation are workplaces which

include office, factories, stores, educational institutions and restaurants. We also consider after work places such as grocery stores, restaurants, entertainment centers and churches.

Daily schedules are assigned to each individual based on their attributes. These schedules are hourly time discrete weekday and weekend schedules. Table 6 shows the schedules for unemployed and employed adults during the week, weekday schedule for children and the weekend schedule which is the same for all individuals.

Table 6: Schedules

Employed adult weekday schedule	**Unemployed adult weekday schedule**	**Children weekday schedule**	**Weekend schedule for all individuals**
0 - 8hr: home	0 - 8hr: home	0 - 8hr: home	0 - 16hr: home
8 - 17hr: work	8 - 19hr: errands	8 - 15hr: school	17 - 19hr: errands
17 - 19hr: errands	19 - 24hr: home	15 - 17hr: after school	19 - 24hr: home
19 - 24hr: home		17 - 24hr: home	

As the schedule progresses through the hours of the day, the simulation model traces each individuals movement among the mixing groups and track their contacts. The pandemic is triggered by introducing one or more infected cases into the region. After a contact is made between a susceptible and an infected, the susceptible becomes infected with a certain probability as determined by the infection transmission process.

4.2 Disease Natural History

As shown in Figure5, when a susceptible individual becomes infected, s/he enters the latency and incubation period simultaneously. Infectiousness starts at the end of the latency period and symptoms show at the end of the incubation period. It is important to note that some individuals will remain asymptomatic. For example, in our numerical study 33% of those infected remain asymptomatic. After the infectiousness period is over, an individual either recovers or dies with a certain probability. We assume that recovered individuals will develop immunity and can not be susceptible again.

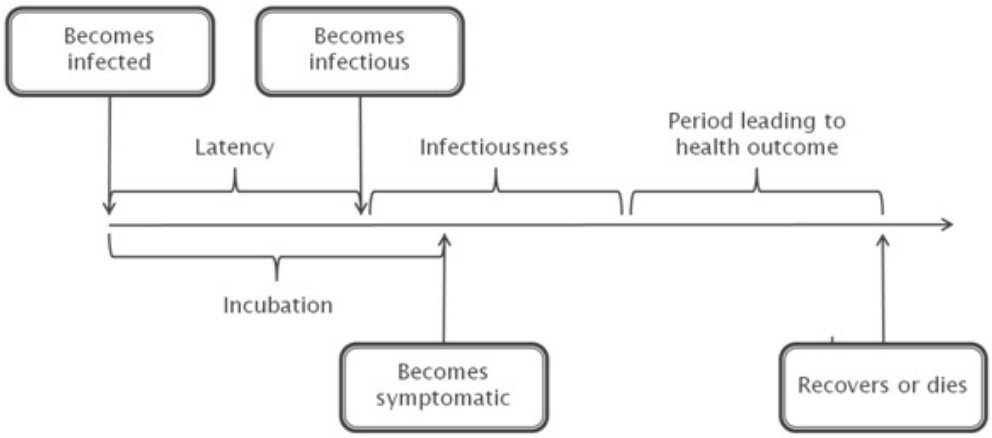


Figure 5: Influenza disease natural history

4.3 Contact Process

Every individual is assigned an hourly schedule which dictates the mixing group the individual is part of at a certain point in time during a day. At every hour, the population in each mixing group is compromise of susceptible and infected individuals. The simulation tracks how many individuals are infected and susceptible in each mixing group, and determines the number of contacts using the contact probabilities given in Germann et al. [30]. Contact probabilities are based on age and mixing group. For example, an infected child contacting a susceptible child in a household will have a different contact probability than an infected adult contacting a susceptible adult in a workplace. The infection transmission process, described next, determines which contacts will result in infections.

4.4 Infection Transmission Process

When an individual $\boldsymbol{j}$ becomes infected, s/he enters into the latency period. At the end of latency, the period of infectiousness begins which changes over time. We assume that the profile of infectiousness follows a lognormal distribution function $f(t, \delta, \gamma)$, where $\boldsymbol{t}$ denotes the elapsed time of the infectiousness period in hours and δ and γ are the distribution parameters [5].

Figure 6 shows an example of the time varying profile of infectiousness, which is given by the following function:

$$f(t,\delta,\gamma) = \frac{1}{t\gamma\sqrt{2\Pi}}(e^{\frac{-(\ln t-\delta)^2}{2\gamma^2}}), t > 0. \tag{1}$$

As shown in Figure 6, we use a truncated (at t=10 days) version of the lognormal function as it is assumed that infectiousness does not last more than 10 days. The idea of a time varying profile of infectiousness is that an infected individual will shed greater amounts of virus particles during the beginning of its infectiousness period and the quantity of virus particles shed will diminish as the individual progresses through the infectiousness period.

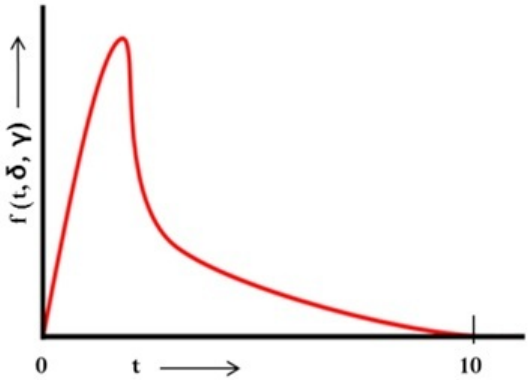


Figure 6: Time varying profile of infectiousness

We assume that the total amount of virus shed by an infected individual is guided by a *calibrated parameter* ρ. The value of ρ varies with the virus transmissibility scenario. At hour $\boldsymbol{t}$, the j^{th} infected individual is in its t_j^{th} hour of infection and the amount of viral shed that is ingested by a susceptible contact until hour $t_j + 1$ is given by $VS_j(t)$. It is assumed that the amount of viral shed is divided equally among the total number of susceptible contacts n_j at any hour. Then we have that

$$VS_j(t) = \int_{t_j}^{t_j+1} \frac{\rho \cdot f_j(u,\delta,\gamma)}{n_j+1} du, \tag{2}$$

where $n_j + 1$ indicates that the j^{th} infected individual will also ingest a share of the viral shed.

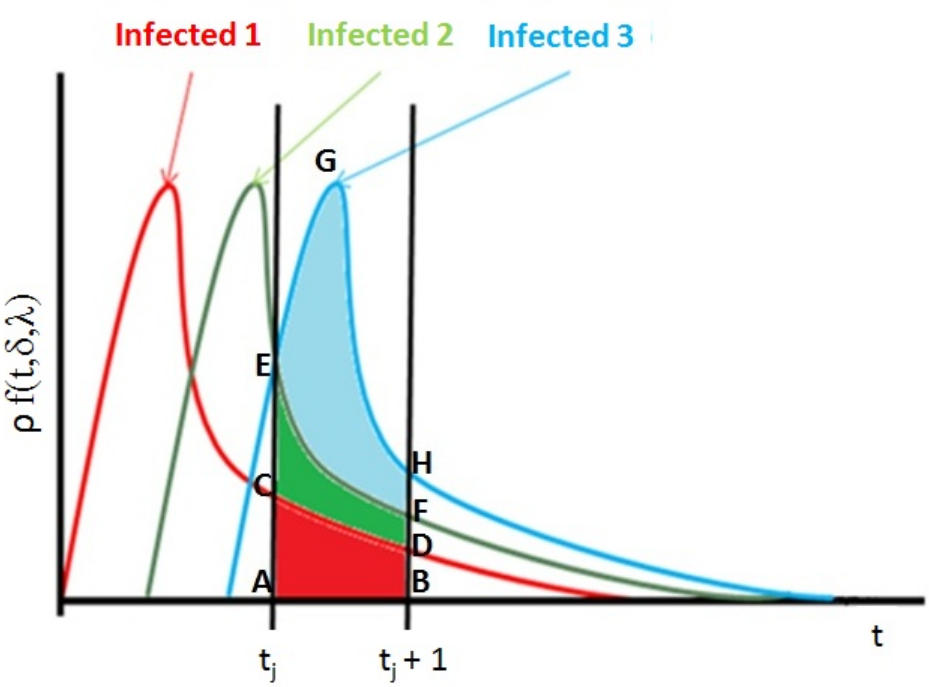


Figure 7: Viral load accumulated by a susceptible. Example of viral load accumulated by a susceptible individual that has been contacted by three infected individuals

A susceptible individual i may have contacts with $m_t \geq 1$ infected individuals during any hour t, where each infected individual is at a different stage of infectiousness. During any contact period beginning at time t and ending at $t+1$, the susceptible individual i will accumulate a viral load equal to the sum of the ingested virus from each one of its infected contacts. We obtain the viral load of susceptible i during hour t and $t+1$ as

$$VL_i(t) = \sum_{j=1}^{m_t} VS_j(t). \tag{3}$$

Figure 7 presents a graphical example of a susceptible individual i that has been contacted by three different infected ($j = 1, 2, 3$) during the period of time starting at t and ending at $t+1$. Note that the y axis in the figure denotes total amount of viral shed by the infected individuals ($\rho \cdot f_j(t, \delta, \gamma)$). We assume virus epidemiology of an outbreak dictates the value of ρ, and the profile distribution parameters δ and γ. For any outbreak, these parameters are assumed to be identical for all infected individuals. At time t, the corresponding elapsed period of infectiousness are t_1,t_2, and t_3, respectively, for the three infected. Infected number one will shed a total amount of virus given by the area ABCD.

Similarly, for infected two and three the total amount of viral shed will be given by the areas ABEF and ABGH, respectively. The sum of the above three areas represents the total amount of viral shed by the three infected.

The proportion of this total amount that will be ingested by susceptible i depends on the number of other susceptible contacts of these three infected during the hour being considered.

A susceptible individual i that does not get infected during hour t (time from t to $t+1$) keeps accumulating viral load through the hours of a day until infection. The total viral load accumulation for susceptible i until time t of the day is given by $VLA_i(t)$ as follows

$$VLA_i(t) = \sum_{u=1}^{t} VL_i(u). \tag{4}$$

For susceptible contacts not infected by the end of the day, we assume that the value for the total viral load accumulation VLA_i becomes zero at the start of the following day.

We liken the infection process to the Poisson failure process of a machine containing thousands of parts. Just as failure of a subset of parts can cause machine malfunction, virus invasion of some of the cells in the human body can cause infection.

Define T as the time required for a susceptible individual i with total accumulated viral load VLA_i to get infected. We assume that T is exponentially distributed with a rate of $\lambda_i = VLA_i$. The assumption as shown in Figure 8 is that a susceptible individual i with a certain amount of VLA in his system for a long period of time will eventually get infected, and that the probability of getting infected increases as the value of VLA increases.

Then, the probability that a susceptible individual i will get infected during time t to $t+1$ is

$$P_i(T \leq 1) = [1 - e^{-VLA_i(t)\cdot 1}] \cdot \alpha, \tag{5}$$

where α is an age based factor [5] and is shown in Table 7. Note that our methodology somewhat overestimates the infection probability as the rate $VLA_i(t)$ keeps increasing during the hour. The value of the rate used in Equation 5 is the maximum value at the end of the hour.

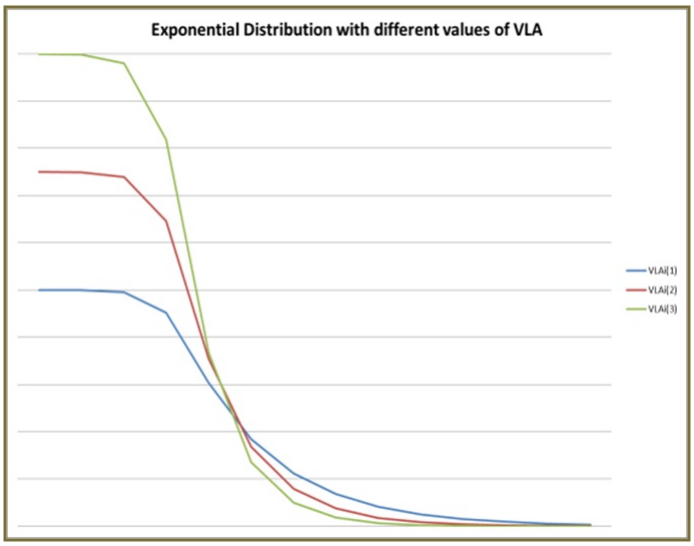


Figure 8: Exponential distribution for time to get infected T for a susceptible i at hours 1, 2 and 3 with rates $VLA_i(1) < VLA_i(2) < VLA_i(3)$

Table 7: Age based factor for infection probabilities

Age lower bound	Age upper bound	Scale factor
0	5	1.5
6	12	1.14
13	17	1.63
18	24	1.76
25	44	1
45	64	0.52
65	100	1.44

4.5 Non-pharmaceutical Interventions

In our simulation we consider four different non-pharmaceutical intervention strategies. These interventions are case isolation, household quarantine, school closure, and workplace closure. In this section we discuss each one of them by providing their definitions, key implementation parameters, and how they are modeled in the simulation.

4.5.1 Case Isolation

In our simulation, case isolation refers to confining symptomatic individuals into their household. Those infected cases that have been diagnosed by a doctor are expected

to obey isolation, when in effect, with a certain compliance probability. The compliance probability its assumed to depends on the extent of illness and work status.

Using expert opinion (from doctors) we divided the period of infectiousness in three phases. The length of the phases (days) and the probability that the sick person would want to stay home and not continue with his/her regular schedule are shown in Figure 9.

The probability of an infected individual obeying isolation also depends on his/her work status [51]. An unemployed individual has a higher probability of obeying than an employed. Therefore, case isolation compliance probability is obtained as the product of the probability that the individual is too sick to continue with his/her regular schedule AND the probability that the individual will obey the isolation recommendation.

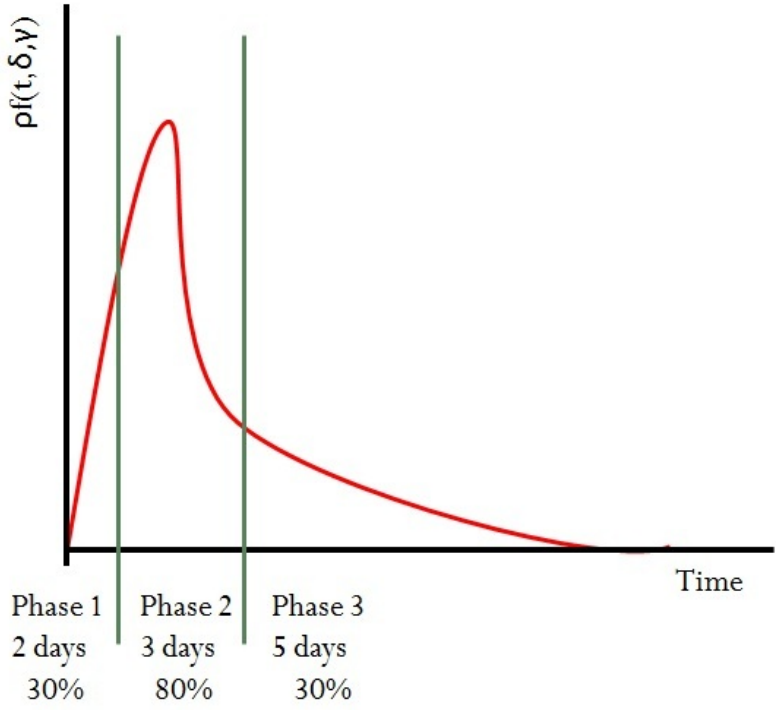


Figure 9: Infectiousness profile. Infectiousness profile divided in phases with its respective staying at home probabilities

If an individual complies with isolation then s/he stays at home all day. If the individual does not comply with isolation then s/he follows regular schedule. If the individual is employed, does not comply with isolation, and his/her workplace is closed, then the individual is considered to stay at home and s/he spends five hours out of home for errands.

Children are assumed to comply with isolation with a 100% probability. A child younger than 13 years of age is assumed to be supervised by an adult when isolated at home. If an adult is already at home, that adult takes care of the child. However, if there are no adults in the household, then the simulation randomly selects an adult member of the household to provide supervision.

In the simulation model we use three parameters to characterize case isolation, which are initiation threshold, intervention duration, and isolation compliance.

4.5.2 Household Quarantine

In the simulation model, household quarantine is the restriction of movement of household members of an infected case. Is important to note that the said infected case is one who has been diagnosed by a doctor and who is in compliance with isolation. Household quarantine compliance probabilities for uninfected household members are adopted from the literature [51], which depends on the individual's employment status. If a quarantined household have members that are 13 years or younger, they stay at home with a 100% probability under adult supervision.

If an individual is not infected, is part of a quarantined household, and s/he complies with the measure, then the daily schedule changes to stay at home without any errands. If an individual does not comply with the intervention and his/her workplace or school (for those older than 13 years) is not closed, then that individual continues with the regular assigned schedule. If an individuals workplace/school is closed, then s/he is assigned a new schedule for staying home with five hours of errands.

We parameterized household quarantine in our simulation model using intervention initiation threshold, duration, and quarantine compliance.

4.5.3 School Closure

We model a partial school closure approach. We divide the school into smaller mixing consisting of individual classrooms. Children belonging to these smaller mixing groups (classrooms)are considered to remain in it all the time except during the lunch hour

when they interact with other classrooms members. In our model a school closes when one or more classrooms are closed. A classroom is closed when a threshold of new infected in the classroom is reached.

When a school is closed, students comply with closure and stay at home with a 100% probability. If the student is younger than 13 years old s/he stays at home with an adult.

Our partial school closure approach considers three key implementation parameters which are the number of new infected cases to close a class, the number of classes to close a school, and closure duration. Note that when a school opens after its closure duration could close again if thresholds are met by new infections.

4.5.4 Workplace Closure

Workplace closure is modeled after school closure. We divide the workplaces into smaller mixing groups comprising individual departments. An individual only contacts those in his/her department except during lunch break. A department is closed after a threshold of new infected cases is reached, similarly, the workplace closes after a certain percentage of the departments has closed.

If an individual's workplace is closed, and s/he is neither subjected to isolation/ household quarantine nor supervising a child as discussed earlier, then that individual follows the stay at home schedule with five hours of errands. However, if the individual is subject to isolation or household quarantine, then the rules of these interventions apply.

Our workplace closure approach considers three key implementation parameters which are threshold of new infected cases to close a department, the percentage of closed departments to close the entire workplace and closure duration. Note that when a workplace opens after its closure duration could close again if thresholds are met by new infections.

4.6 Experimental Approach for Design of NPI Strategies

We use an experimental approach for the design of NPI strategies. In particular we used the tools of statistical design of experiments and regression analysis. Using the results

obtained from the experiment we examined the significance of the impact of all parameters (as shown earlier in Figure 3) and their interactions on the measures of performance of the NPI strategies. The performance measures that can be used in this experimental approach include total number of infected, total number of deaths, total number of contacts, total cost, among others.

4.6.1 Factorial Design

Factorial designs allow study of the effect of two or more factors and their interactions on a measure of performance. The effect is defined as the change in response produced by a change in the level of the factor [52].

A full factorial design can grow in size quickly depending on the number of factors and may not always be feasible. In such cases, fractional factorial designs can be used, where a subset or a fraction of the full factorial design is used.

In our numerical study, we use fractional factorial designs to reduce the computational time required to examined a large number of factors. Since we were not interested in three-way or higher level of interactions, we used fractional factorial designs in which main effects and two-way interactions were not confounded.

In this section we describe the basics of a factorial design for two level and three level experiments. We also discuss how to derive regression equations using information from the factorial analysis and obtain optimal design parameters by optimizing the regression equations.

4.6.2 Two-Level Experiments

Suppose you have two factors A and B. Each factor have two levels as shown in Table 8. The value of A at the high level is A^+, and at the low level is A^-. Similarly for factor B, the value of B at the high level is B^+, and at the low level is B^-. The effect of changing factor A is given by $A^+B^- - A^-B^-$ and the effect of changing factor B is given by $A^-B^+ - A^-B^-$.

Table 8: Low and high level values for a two factor factorial design

Factor	**Low level**	**High Level**
A	A^-	A^+
B	B^-	B^+

Let y_{ij} be the response when factor A is at the i^{th} level and factor B is at the j^{th} level. Table 9 shows a general arrangement for the two-factor factorial design with only one replicate. In this table, both row and column treatment factors are of equal interest. In particular, we want to test the following hypotheses: the equality of row treatment effects, the equality of column treatment effects and determining wether row and column treatment interact. These hypotheses can be tested using a two-factor analysis of variance.

Table 9: General arrangement for two-factor factorial design

	Factor B	
Factor A	1	2
1	y_{11}	y_{12}
2	y_{21}	y_{22}

Table 10 presents a general Analysis of Variance (ANOVA) table for the two-factor factorial design. Here, a is the total number of levels of factor A and b is the total number of levels for factor B, with n replicates. Where the sum of squares SS_T, SS_A, SS_B SS_{AB} SS_E computation is shown in Equations 6 through 11.

$$SS_T = \sum_{i=1}^{a}\sum_{j=1}^{b}\sum_{k=1}^{n} y_{ijk}^2 - \frac{y_{...}^2}{abn} \tag{6}$$

$$SS_A = \frac{1}{bn}\sum_{i=1}^{a} y_{i..}^2 - \frac{y_{...}^2}{abn} \tag{7}$$

$$SS_B = \frac{1}{an}\sum_{j=1}^{b} y_{.j.}^2 - \frac{y_{...}^2}{abn} \tag{8}$$

To obtain SS_{AB} is better to do so in two stages. First, compute the sum of squares between the ab cell totals (sum of squares due to subtotals):

$$SS_{Subtotals} = \frac{1}{n}\sum_{i=1}^{a}\sum_{j=1}^{b} y_{ij.}^2 - \frac{y_{...}^2}{abn}, \tag{9}$$

then compute SS_{AB} as

$$SS_{AB} = SS_{Subtotals} - SS_A - SS_B. \tag{10}$$

Finally SS_E is computed by substraction as

$$SS_E = SS_T - SS_{AB} - SS_A - SS_B. \tag{11}$$

Using the P-values for the test statistics, significance of the different factors can be determined. Graphs of the average responses at each treatment combination also helps with experiment interpretation.

Table 10: The analysis of variance table for the two-factor factorial

Source	**SS**	**Degrees of Freedom**	**Mean Square**	F_0
A treatments	SS_A	$a-1$	$MS_A = \frac{SS_A}{a-1}$	$F_0 = \frac{MS_A}{MS_E}$
B treatments	SS_B	$b-1$	$MS_B = \frac{SS_B}{b-1}$	$F_0 = \frac{MS_B}{MS_E}$
Interaction	SS_{AB}	$(a-1)(b-1)$	$MS_{AB} = \frac{SS_{AB}}{(a-1)(b-1)}$	$F_0 = \frac{MS_{AB}}{MS_E}$
Error	SS_E	$ab(n-1)$	$MS_E = \frac{SS_E}{ab(n-1)}$	
Total	SS_T	$abn-1$		

Before adopting any conclusions from the aforementioned analysis of variance, model adequacy should be checked. The most used tool is residual analysis. The residuals for the two-factor factorial design we have been discussing so far are

$$e_{ijk} = y_{ijk} - \widehat{y}_{ijk}, \tag{12}$$

where $\widehat{y}_{ijk}$ is the fitted value and is the average of the observations of the ij^{th} cell. Residuals should follow a normal distribution and the expected value of the residuals should be approximately zero.

To estimate the parameters of the model as shown in Equation 13 we use least squares. This is the model that we later optimize to get the optimal parameter values and design an effective NPI strategy.

$$y = \beta_0 + \beta_A x_A + \beta_B x_B + \epsilon \tag{13}$$

For information in how to vary this model to a 2^k factorial and 2^k fractional factorial design please refer to Montgomery [52].

4.6.3 Three-Level Experiments

We had the intuition that many of the NPI parameters were not linear. For this, we designed a three-level experiment. A 3^k design, have 3^k treatment combinations with $3^k - 1$ degrees of freedom. The sum of squares can be determined for k main factor effects each with two degrees of freedom, $k2$ two-factor interactions, each with four degrees of freedom, etc., and one k-factor interaction with 2^k degrees of freedom. All these sum of squares and interactions are computed by the methods discussed in the previous section for factorial designs.

In a three level design, any h-factor interaction has 2^{h-1} orthogonal two-degrees-of-freedom components. For example the interaction AB has two components. One is AB and the other is AB^2. This partitioning is very useful when you don't have enough degrees-of-freedom for your analysis. Each of the components in the interaction AB has two degrees-of-freedom, and the values of the components can be calculated as follows

$$AB = x_A + x_B(mod3), \tag{14}$$

and

$$AB^2 = x_A + 2x_B(mod3), \tag{15}$$

where x_A and x_B are the values of the factors A and B, which are 0, 1 or 2.

In the experiments we are not calculating purely the interaction between A and B, but by calculating one of the two components (less degrees of freedom) you can get conclusions about if the interaction is significant or not. We also use interaction plots.

For the regression equations, if factors A and B are quantitative (in our experiments all factors are quantitative), instead of decomposing the effect into linear and quadratic components a regression analysis on the original scale of the factors (0, 1, and 2) can be performed. Using x_A and x_B as the values for the factors, then x_A^2 can be used for the quadratic effect and $x_A x_B$ for the interaction effect. The regression equation for this example would be

$$y = \beta_0 + \beta_A x_A + \beta_B x_B + beta_{A^2} x_A^2 + \beta_B x_B^2 + \beta_{AB} x_{AB}. \tag{16}$$

We estimate the regression model using the traditional least squares regression models with the coded variables. After that, the optimization is performed and the optimal factors in the actual scale are calculated by interpolation.

4.7 Derivation of Optimal NPI Parameters from Regression Equations

For the optimization of the regression equations derived from the two and three level fractional factorial experiments, we use Microsoft Excel Solver. Solver uses the simplex method with bounds on the variables, and the branch and bound method for linear and integer problems. This method was implemented by John Watson and Dan Fylstra, of Frontline Systems, Inc [53].

5 Experimental Design

5.1 Test-bed

For our simulated outbreaks we use demographic data from Hillsborough County, Florida. The population is approximately 1.1 million. Tables 11 and 12 show the distribution of adult and children by age for the Hillsborough County as given by the U.S. Census Bureau for the 2010 census.

Table 11: Distribution of adult population by age given by the U.S. census bureau 2010

Age group	**Adult population distribution by age**
23-29	0.16
30-64	0.67
65-88	0.17

Households are created by using the distribution of the population by household type also from the census of 2010. Table 13 shows the distribution of population by households for Hillsborough County.

Table 12: Distribution of children population by age given by the U.S. census bureau 2010

Age group	**Children population by age**
0-5	0.24
6-9	0.23
10-14	0.25
15-17	0.13
18-22	0.15

Table 13: Distribution of regional population by households given by the U.S. census bureau 2010

Number of adults	**Number of children**	**Population by household type**
1	0	0.28
1	1	0.04
2	0	0.31
1	2	0.04
2	1	0.13
1	3	0.01
2	2	0.13
1	4	0.01
2	3	0.06

After individuals are created, then all mixing groups are created. Table 16 shows the composition of mixing groups in Hillsborough County as given by the census of 2010.

Contact probabilities are based on Germann et.al [30] and are dependant on age and mixing group. Table 17 list all the contact rates used in our simulation.

Table 14: Mortality probability for different age groups

Age group	**Mortality probability**
0-19	0.007
20-64	0.069
65 +	0.162

Table 15: Values for calibration factor depending on transmissibility scenario

Scenario	ρ
Low	1000
Medium	5000
High	24000

The disease natural history values for each one of the infection phases were taken as follows: a latent period of 29 hours, an incubation period of 46 hours, and an infectiousness

period ranging between 29 and 127 hours [54]. After an infected individual ends their infectiousness disease phase, s/he either recovers or dies with a certain probability that depends on age and is shown on Table 14. These probabilities are based on literature [1].

Table 16: Composition of mixing groups

MG type	**Description**	**Distribution**
0	Household	0.066
1	Factory	0.058
2	Office	0.302
3	Pre-school	0.005
4	Elementary school	0.010
5	Middle school	0.203
6	High school	0.097
7	College	0.106
8	Afterschool center	0.007
9	Grocery store	0.026
10	Restaurant	0.087
11	Entertainment center	0.032
12	Church	0.001

As for our infection transmission process, the value of the parameters for the log-normal distribution are $\delta = -0.72$ and $\gamma = 1.8$ days [5]. We model three different scenarios, a low, medium, and high transmissibility scenarios. These scenarios are given by our calibrated factor ρ. This factor is calibrated to give scenarios with an IAR of 33% for a low transmissibility scenario, and 50% and 67% for medium and high, respectively. We based these scenarios in our literature review. Table 15 shows the values of ρ used to create different pandemic influenza outbreaks.

Table 17: Hourly contact rates by age and mixing group

MG type	Infected age lower bound	Infected age upper bound	Susceptible age lower bound	Susceptible age upper bound	Contact probability
0	0	18	0	18	0.074
0	0	18	19	99	0.029
0	19	99	0	18	0.029
0	19	99	19	99	0.042
1	19	99	19	99	0.005
2	19	99	19	99	0.005
3	0	4	0	4	0.035
4	5	18	5	18	0.004
5	5	18	5	18	0.003
6	5	18	5	18	0.003
7	19	22	19	22	0.003
8	5	18	5	18	0.004
9	0	99	65	99	0.00007
9	0	99	19	64	0.00005
9	0	99	5	18	0.00002
9	0	99	0	4	0.00001
10	0	99	65	99	0.00007
10	0	99	19	64	0.00005
10	0	99	5	18	0.00002
10	0	99	0	4	0.00001
11	0	99	65	99	0.00007
11	0	99	19	64	0.00005
11	0	99	5	18	0.00002
11	0	99	0	4	0.00001
12	0	99	65	99	0.00007
12	0	99	19	64	0.00005
12	0	99	5	18	0.00002
12	0	99	0	4	0.00001

5.2 Factors

For our two level design we use 16 different factors. From our analysis we selected the significant ones for the three level experiment. In this section we discuss the 16 factors used in our experiment.

Table 18 present a summary of all the factors, the variable name we assigned to them in our experiments, and the units of each one of them.

Table 18: Summary of factors with their variables and units

Factors	**Acronym**	**Measurement Units**
Global threshold	GT	Number of infected cases
Deployment delay	GD	Days
Case isolation threshold	ID	Days
Case isolation duration	IP	Days
Case isolation compliance for workers	ICW	Percentage
Case isolation compliance for non-workers	ICNW	Percentage
Household quarantine threshold	HD	Days
Household quarantine duration	HP	Days
Household quarantine compliance workers	HCW	Percentage
Household quarantine compliance non-workers	HCNW	Percentage
Cases to close a class in a school	CMS	Number of infected cases
Classes to close a school	MS	Number of closed mixing groups in a school
School closure duration	PMS	Days
Cases to close a department in a workplace	CMW	Number of infected cases
Departments to close a workplace	MW	Percentage of closed mixing groups in a workplace
Workplace closure duration	PMW	Days

5.2.1 Global Threshold

Global threshold functions as the pandemic flag. It is the number of cases needed for public health officials to declare that the pandemic influenza outbreak has arrived to

a region. It is assumed that a pandemic has been declared elsewhere but public health officials in the studied region wait until this number of cases is reached before deploying interventions.

5.2.2 Deployment Delay

Deployment delay is the time needed for interventions to be deployed. Once a pandemic is declared, it is assumed that some time will be needed for interventions to be fully in place.

5.2.3 Case Isolation Threshold

The case isolation threshold is, for an individual that has been diagnosed, when should that infected individual start isolation. For example, should s/he starts immediately upon being diagnosed or a day after.

5.2.4 Case Isolation Duration

Pandemic influenza disease natural history may last between 5 and 10 days. The purpose of isolation is to prevent an infected individual from contacting others while infectious. It is examined how the duration of case isolation affects the effectiveness of the intervention.

5.2.5 Case Isolation Compliance

Case isolation compliance is different for workers and non-workers. Workers compliance tends to be lower since it is harder for workers to miss work and have the risk of losing their jobs and/or wages. We divide this factor into two: *compliance for workers* and *compliance for non-workers*.

5.2.6 Household Quarantine Threshold

As with the case isolation threshold. We examine when a household should be quarantined. Right after a member of has been diagnosed or after some time.

5.2.7 Household Quarantine Duration

As with case isolation we take into consideration the disease natural history of influenza when assigning values to the levels of this factor. The purpose of household quarantine is to prevent and infected individual and members of his/her household to make contacts while infectious (or suspected of being infectious). We examine how the duration of household quarantine affects the effectiveness of the intervention.

5.2.8 Household Quarantine Compliance

Household quarantine compliance values (just like with case isolation) are different for workers and non-workers. Therefore, this factor is actually divided into two, which are, *household quarantine compliance for workers* and *household quarantine compliance for non-workers.*

5.2.9 School Closure

As discussed in Chapter 4 Section 4.5.3, school closure have three different factors. These factors are the *number of cases to close a class*, the *number of classes to close a school* and *school closure duration.*

5.2.10 Workplace Closure

As discussed in Chapter 4 Section 4.5.4, workplace closure have three different factors. These factors are the *number of cases to close a department*, the *percentage of departments to close a workplace* and *workplace closure duration.*

5.3 Fractional Factorial Two-Level Experiment

We use a 2^{16-7} two-level factorial design. This yields a total of 512 experiments. We ran 5 replicates for each one of the experiments. A replicate in our simulation model is achieved by changing the value of the seed. In total, for the two level experiment we ran 2,560 simulations. Each simulation takes an average of 15 minutes to run. In this experiment, all main factors and all two-way interactions are not confounded.

Table 19: Two-level experiment

Factor	Low level	High level
GT	10	50
GD	3	7
ID	0	1
IP	7	10
ICW	0.53	0.75
ICNW	0.57	0.84
HD	0	1
HP	7	10
HCW	0.53	0.75
HCNW	0.57	0.84
CMS	1	3
MS	1	3
PMS	21	42
CMW	3	5
MW	0.3	0.5
PMW	7	14

Table 19 presents all factors with their low and high levels. We did this experiment for three different scenarios, low, medium and high.

5.4 Fractional Factorial Three-Level Experiment

From the two-level design analysis, we found the significant factors for each one of the scenarios. Based on this information, we then conducted a three-level experiment. We also ran 5 seeds for each one of the scenarios. Table 20 presents all the factors considered with their real values and the coded values.

For the low, only seven of those factors presented in Table 20 were significant. The experiment is then a 3_{IV}^{7-3} with 81 runs per experiment. The factors considered for the low transmissibility scenario were GD, ID, CMS, MS, PMS, CMW, and PMW.

With this design we can estimate all main factor effects and the following factors related to two-way interactions: $(GD)(ID)^2$, $(GD)(CMS)^2$, $(GD)(PMW)^2$, $(ID)(MS)^2$, $(ID)(PMW)$, $(CMS)(MS)$, $(CMS)(PMW)^2$, $(MS)(PMW)$, $(PMS)(PMW)^2$, $(CMW)(PMW)$,$(GD)(CMW)$, $(ID)(PMS)$,$(CMS)(PMS)$, $(MS)(CMW)$, and $(PMS)(CMW)$.

Table 20: Three-level experiment

	Uncoded Value			Coded Value		
Factor	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**
GT	10	30	50	0	1	2
GD	3	5	7	0	1	2
ID	0	1	2	0	1	2
CMS	1	2	3	0	1	2
MS	1	2	3	0	1	2
PMS	21	30	42	0	1	2
CMW	3	4	5	0	1	2
PMW	7	10	14	0	1	2

Therefore with this experiment we can derive some information about the following interactions: $(GD)(ID)$, $(GD)(CMS)$, $(GD)(PMW)$, $(ID)(MS)$, $(ID)(PMW)$, $(CMS)(MS)$, $(CMS)(PMW)$, $(MS)(PMW)$, $(PMS)(PMW)$, $(CMW)(PMW)$, (GD) (CMW), $(ID)(PMS)$, $(CMS)(PMS)$, $(MS)(CMW)$, and $(PMS)(CMW)$.

For the medium and high scenarios, only seven of those factors presented in Table 20 were significant, but different from the low transmissibility scenario. The experiment is then a 3_{IV}^{7-3} with 81 runs per experiment. The factors considered for the medium and high scenarios were GT, GD, ID, CMS, MS, PMS, and CMW.

With this design we can estimate all main factor effects and the following factors related to two-way interactions: $(GT(GD)^2$, $(GT(ID)^2$, $(GT)(CMW)^2$, $(GD)(CMS)^2$, $(GD)(CMW)$,$(ID)(CMS)$, $(ID)(CMW)^2$, $(CMS)(CMW)$, $(MS)(CMW)^2$, (PMS) (CMW), $(GT)(PMS)$, $(GD)(MS)$, $(ID)(MS)$, $(CMS)(PMS)$, and $(MS)(PMS)$.

Therefore with this experiment we can derive some information about the following interactions: $(GT)(GD)$, $(GT)(ID$, $(GT)(CMW)$, $(GD)(CMS)$, $(GD)(CMW)$, $(ID)(CMS)$, $(ID)(CMW)$, $(CMS)(CMW)$, $(MS)(CMW)$, $(PMS)(CMW)$, (GT) (PMS), $(GD)(MS)$, $(ID)(MS)$, $(CMS)(PMS)$, and $(MS)(PMS)$.

6 Results

In this chapter we present the results from our simulation experiment. First section presents a brief overview of the results we get from our simulation. The second and third sections present results from our two and three level experiments results for three different transmissibility scenarios. For each of this scenarios we have derived optimal NPI strategies. The last section presents a comparison between the optimal strategies derived from the two and three-level experiment across all scenarios considered.

6.1 Simulation Results

At the end of a simulation, we can gather a number of performance measures. Table 21 show some of these results for baseline (no intervention) and for a non-optimal NPI strategy. In addition to the results presented in Table 21, we can also get other performance measures such as cost, visits to doctors, and total of mixing groups closed.

Baseline refers to no intervention. The NPI shown has a global threshold of 10 cases, a deployment delay of three days, a case isolation threshold of one day, a case isolation duration of seven days, a case isolation compliance for workers of 53%, and a case isolation compliance for non-workers of 83.6%. This strategy also has a household quarantine threshold of one day, a household quarantine duration of 7 days and a household quarantine compliance of 53% and 83.6% for workers and non-workers respectively. Regarding school closure parameters, this non-optimal NPI strategy closes classes after a threshold of three new infected cases is reached in a class, closes schools after three classes have closed for a duration of 21 days. Workplaces departments close after three new cases have been diagnosed in the department, workplace closes after 30% of departments are closed for a duration of 7 days.

As shown in Table 21, NPIs succesfuly reduce IAR and CFR as well as contacts, infections and deaths for all scenarios. Even though they extend pandemic duration, it can

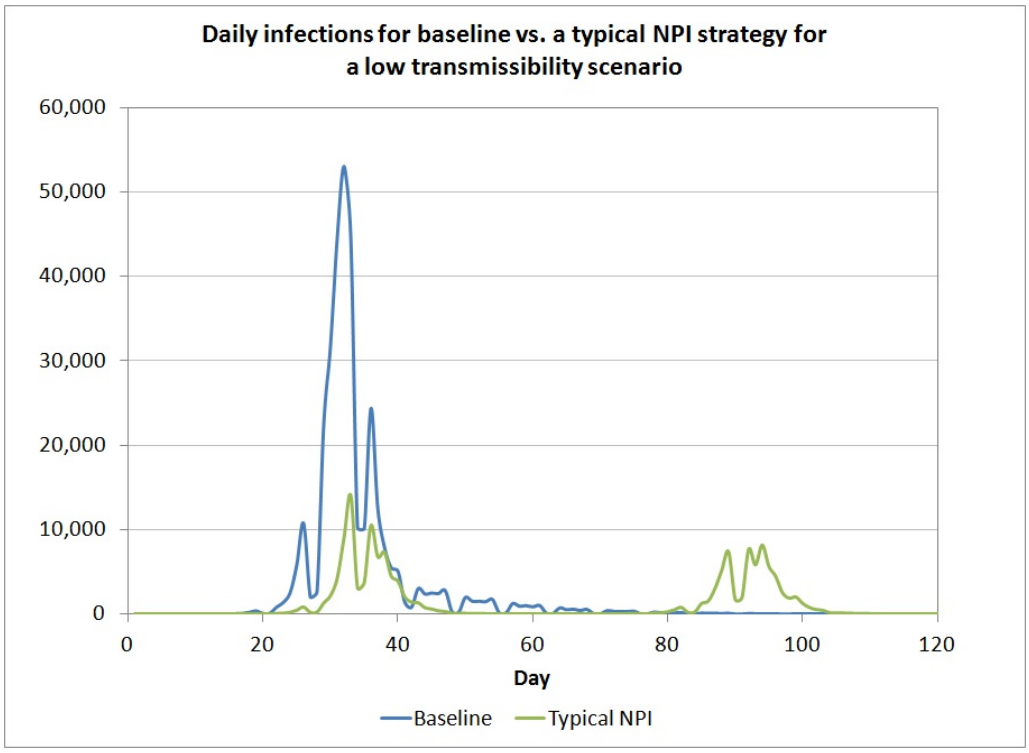
Table 21: Simulation results for baseline (no intervention) and a non-optimal NPI strategy

Performance Measure	**Low**		**Medium**		**High**	
	Baseline	NPI	Baseline	NPI	Baseline	NPI
IAR	33.06%	20.62%	50.80%	36.91%	64.53%	46.08%
CFR	0.69%	0.37%	1.76%	1.10%	2.55%	1.60%
Pandemic Duration (Days)	135	350	93	350	83	271
Total Contacts	1,177,393	738,716	1,047,302	709,958	1,063,751	682,295
Contacts 0-19 yrs.	818,912	618,661	520,883	484,052	482,881	432,625
Contacts 20-64 yrs.	294,046	102,973	416,307	181,986	486,013	203,731
Contacts 65-99 yrs.	64,435	17,082	110,112	43,920	112,857	45,939
Contacts Households	238,684	344,169	236,850	361,050	234,411	336,832
Contacts MG Types 1-2	231,051	37,785	392,793	106,101	439,368	118,571
Contacts Schools	699,427	352,987	403,908	235,560	372,678	217,948
Contacts MG Types 9-12	8,231	3,775	13,751	7,247	17,294	8,944
Total Infections	335,071	208,959	514,844	374,132	654,051	467,026
Infections 0-19 yrs.	225,467	156,849	230,127	201,319	229,952	210,941
Infections 20-64 yrs.	91,959	43,135	228,753	137,328	344,381	206,455
Infections 65-99 yrs.	17,645	8,975	55,964	35,485	79,718	49,630
Infections Households	37,562	65,107	92,217	141,603	136,127	203,884
Infections MG Types 1-2	46,600	7,019	168,185	49,784	249,929	73,968
Infections Schools	249,304	136,043	247,838	178,982	256,796	183,242
Infections MG Types 9-12	1,605	790	6,604	3,763	11,199	5,932
Total Deaths	7,009	3,764	17,851	11,111	25,858	16,238
Deaths 0-19 yrs.	1,041	744	1,090	975	1,077	1,047
Deaths 20-64 yrs.	4,095	2,059	10,681	6,332	16,018	9,725
Deaths 65-99 yrs.	1,873	961	6,080	3,804	8,763	5,466

be expected vaccines will be available sometime during the pandemic and it would not be extended for such a long period of time.

The majority of contacts are made by the age group 0-19 years, followed by adults 20-64 years. Most of these contacts happen at schools and workplaces types 1-2. Consequently the majority of infections happen at schools and workplaces. With school closure and workplace closure strategies in place, the number of infections at households increases.

Figure 10 shows graphs for daily infected, deaths and contacts for a low, medium, and high transmissibility scenario. In these graphs the blue line represents the baseline and the green line the typical NPI strategy. As it can be observed from these graphs, the typical NPI strategy looses effectiveness for a medium and a high transmissibility scenario. Using these graphs we can also observe that NPIs can reduce peak attack rates and death rates. When NPIs are lifted and then put in place again it causes new pandemic waves to emerge as evident from the daily infections graphs.



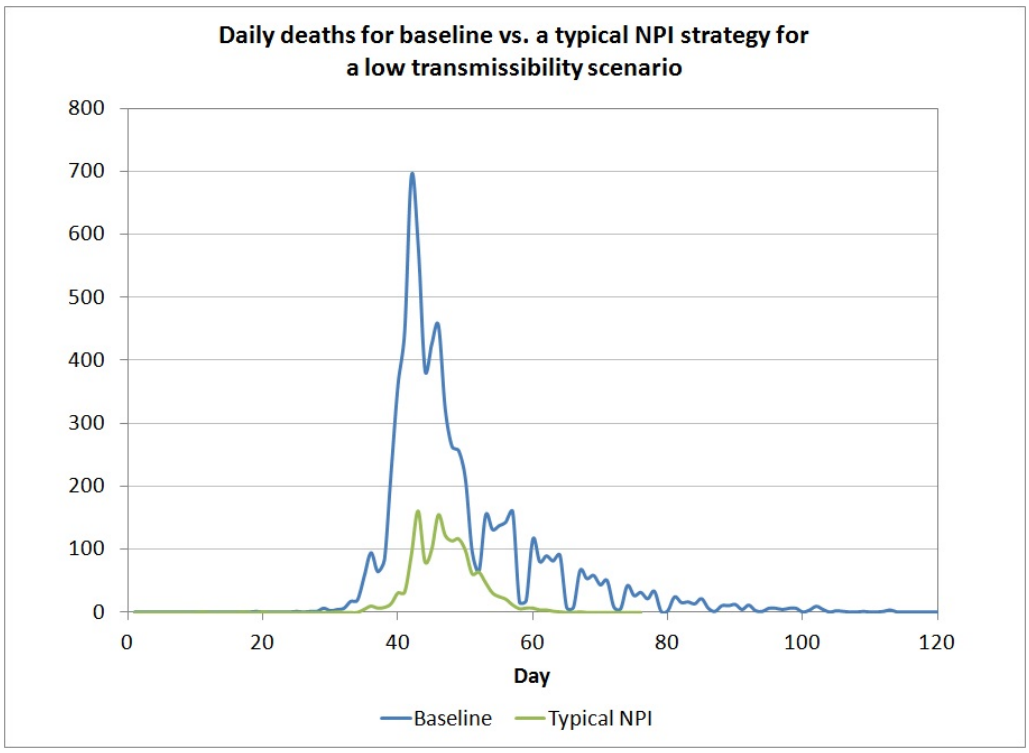
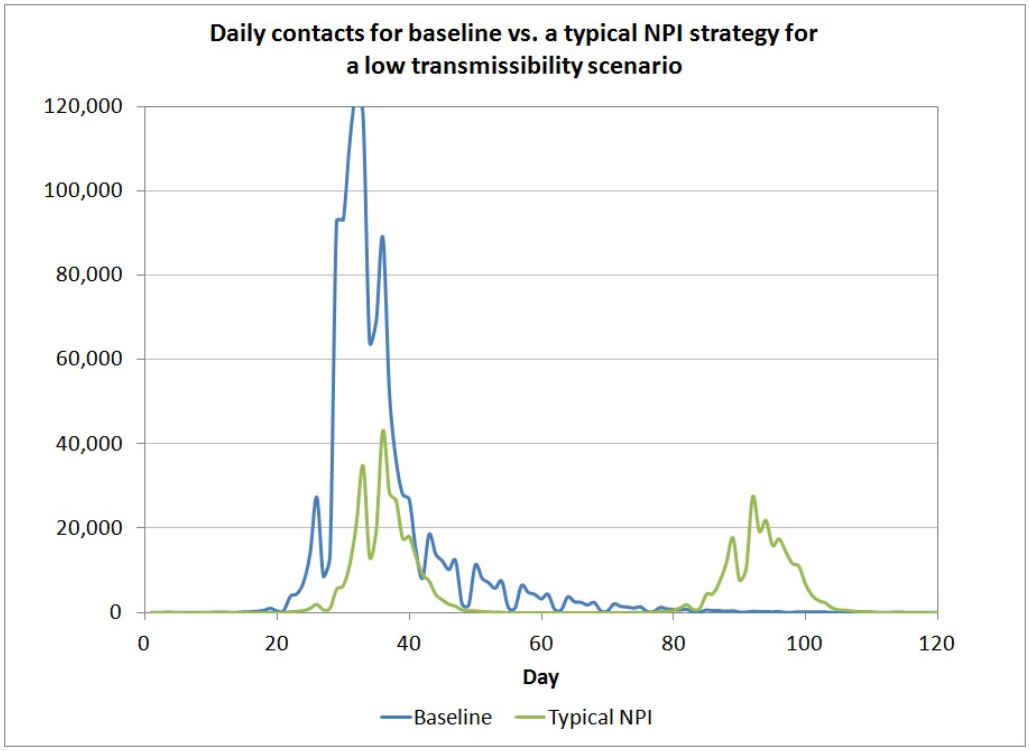
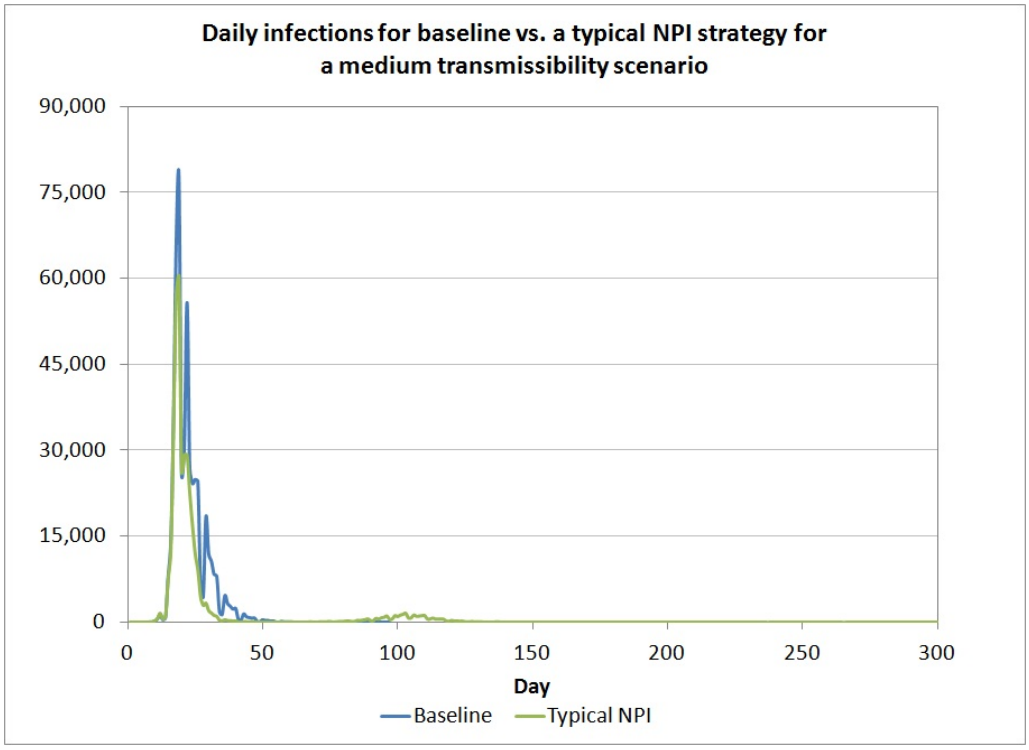


Figure 10: Daily infections, deaths and contacts for baseline and a non-optimal NPI strategy for three transmissibility scenarios





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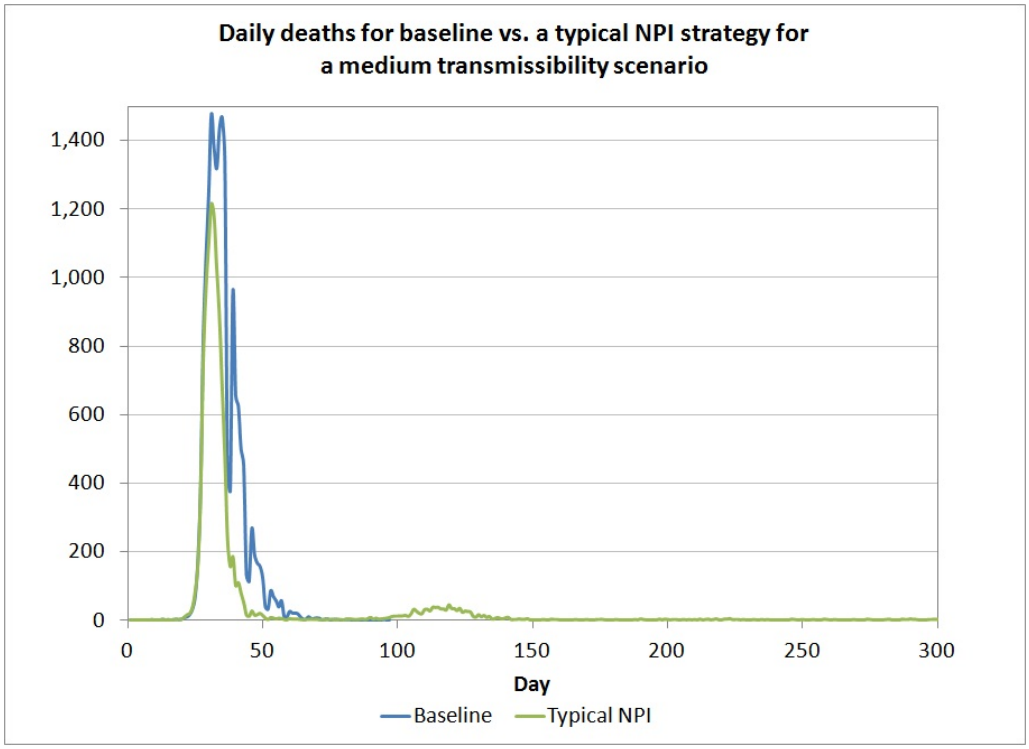

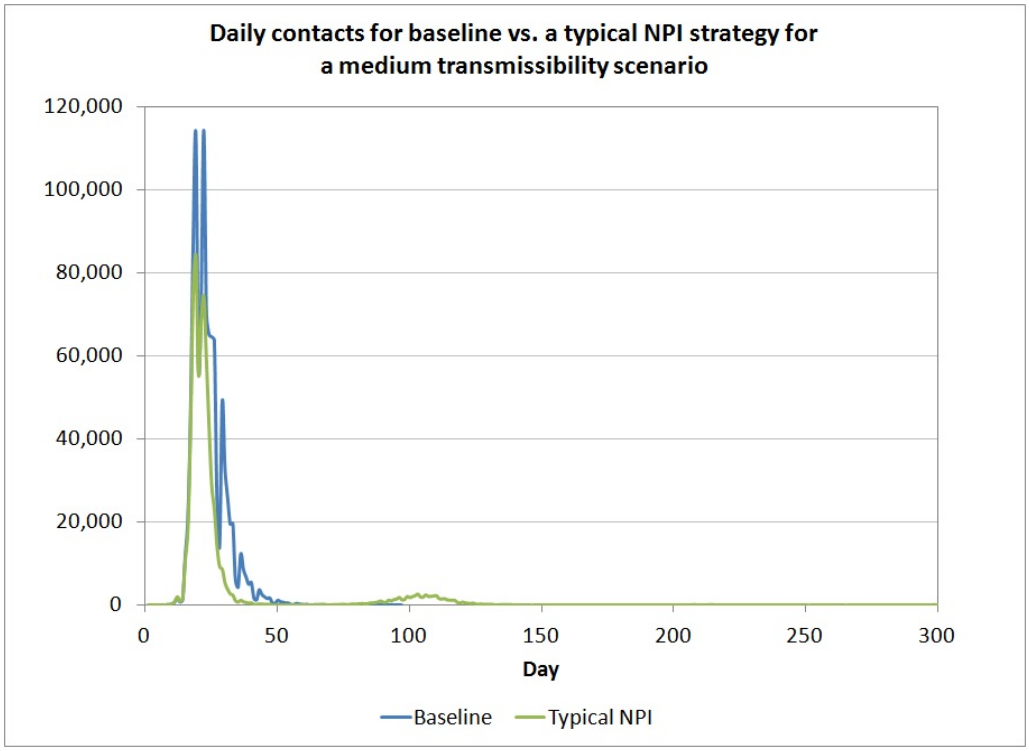

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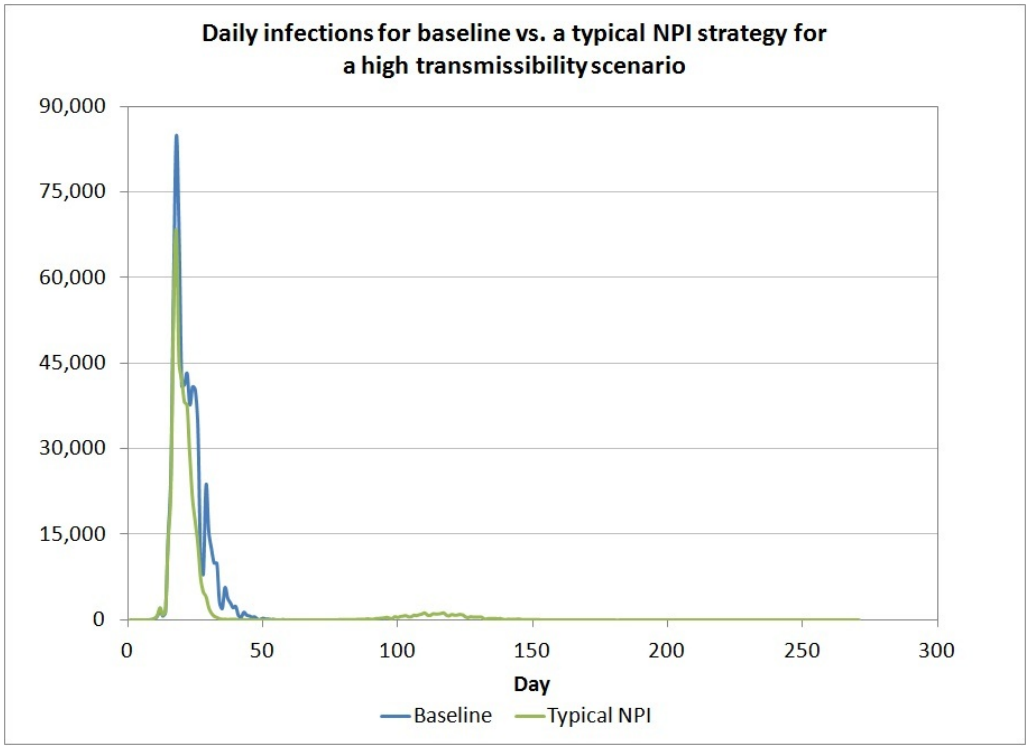

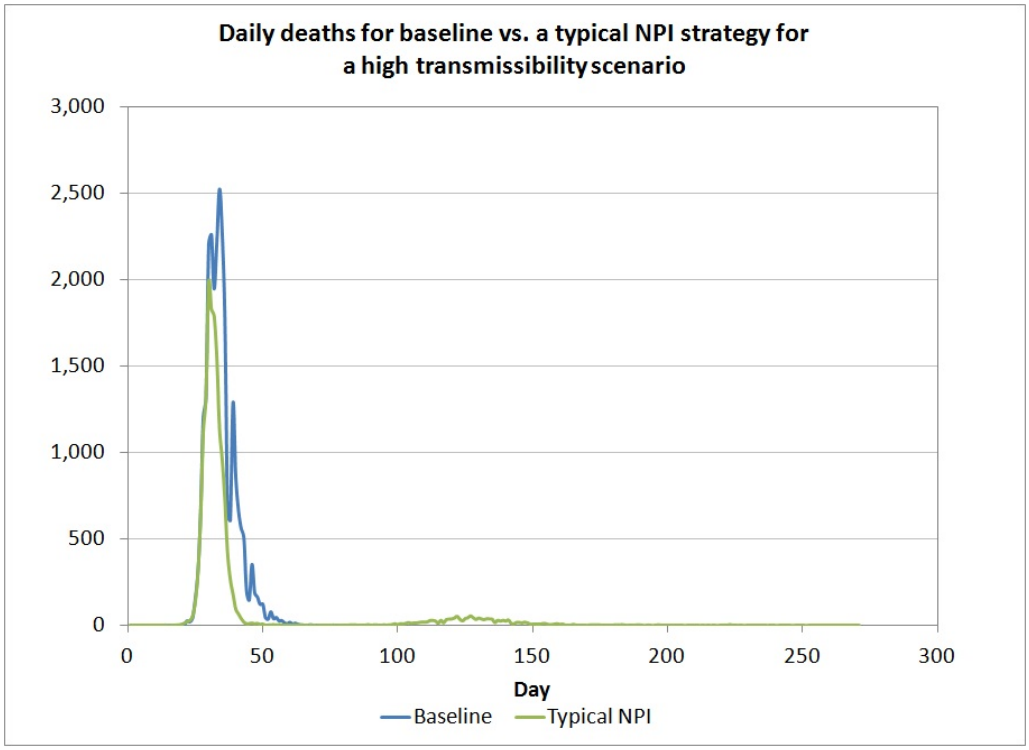

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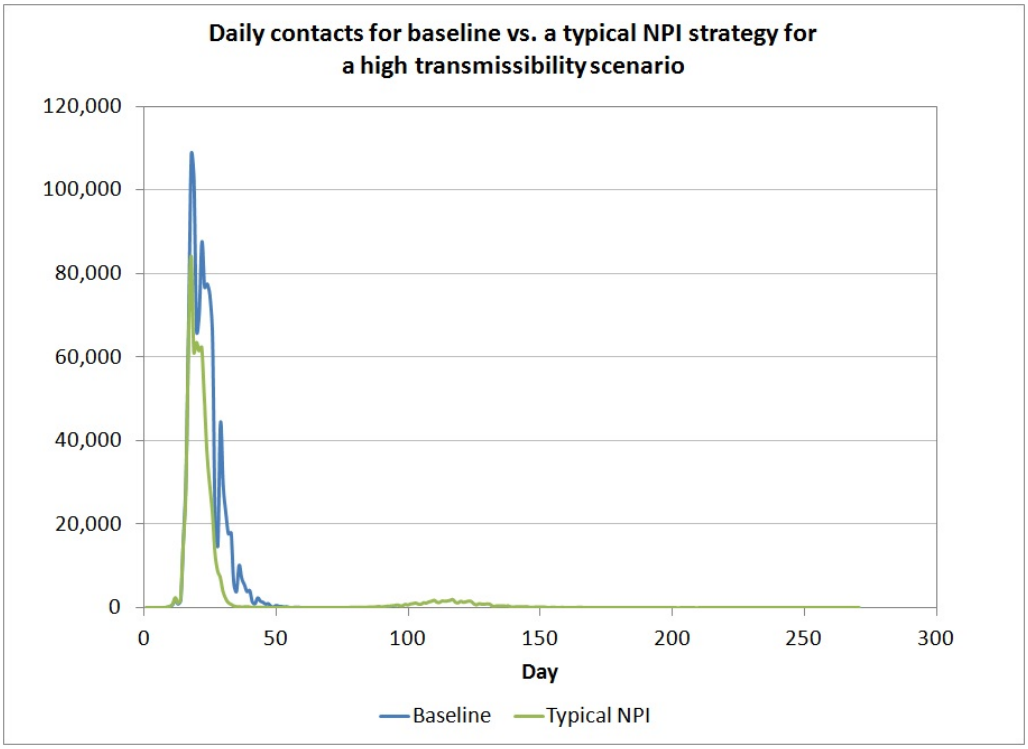


Figure 10: (Continued)

6.2 Two-Level Experiment Results

In this section we present the results for the two-level experiment for the three transmissibility scenarios considered.

6.2.1 Low Transmissibility Scenario

The ANOVA table for the two-level design for the low transmissibility scenario is shown in Table 22. The level of significance that we used to determine significant factors was 0.01, which are the factors marked with two and three stars in the significance level column. Table 23 shows the main effects factors that resulted to be significant. In this table, the mean number of infected at low and high levels are also presented. Figure 11 shows this graphically.

As expected an increase in factors such as global threshold, number of cases to close a class, number of classes to close a school, and number of cases to close a department,

Table 22: ANOVA Table for the low transmissibility scenario two-level fractional factorial experiment using total number of infected as the measure of performance

Factor	Df	F value	Pr(>F)	Signif.
GT	1	5.1854	0.0228614	*
GD	1	15.1545	0.0001017	***
ID	1	96.8494	< 2.2e-16	***
CMS	1	3038.729	< 2.2e-16	***
MS	1	170.3362	< 2.2e-16	***
PMS	1	659.7989	< 2.2e-16	***
CMW	1	77.0384	< 2.2e-16	***
PMW	1	7.7726	0.0053445	**
MW	1	1.2812	0.2577931	
HCW	1	0.7842	0.3759574	
IP	1	0.185	0.6671288	
ICW	1	0.0102	0.9196462	
ICNW	1	0.739	0.3900679	
GT:ID	1	3.1965	0.073918	.
GT:MS	1	3.5117	0.0610531	.
GT:CMW	1	5.407	0.0201362	*
ID:CMS	1	59.4727	1.78E-14	***
ID:PMS	1	13.1178	0.0002983	***
ID:CMW	1	7.0436	0.0080055	**
CMS:MS	1	21.9719	2.92E-06	***
CMS:PMS	1	360.8237	< 2.2e-16	***
CMS:CMW	1	34.3149	5.30E-09	***
CMS:PMW	1	4.7352	0.029644	*
MS:PMS	1	43.1378	6.19E-11	***
MS:CMW	1	5.1544	0.0232726	*
PMS:CMW	1	66.8691	4.56E-16	***
PMS:PMW	1	5.4814	0.0192985	*
PMW:MW	1	3.6698	0.0555204	.
GT:GD	1	0.7782	0.3777921	
GD:ID	1	1.7465	0.1864395	

Factor	Df	F value	Pr(>F)	Signif.
GT:CMS	1	0.278	0.598056	
GD:CMS	1	1.2686	0.260129	
GT:HCW	1	0.3644	0.546126	
ID:HCW	1	0.5748	0.448423	
GT:MW	1	0.1847	0.667409	
ID:MW	1	0.1484	0.700085	
GT:IP	1	0.1235	0.72535	
GT:ICW	1	0.0095	0.922202	
IP:ICW	1	0.1761	0.674799	
GT:PMW	1	0.7079	0.400224	
PMW:HCW	1	0.0475	0.827496	
GT:PMS	1	0.2314	0.630509	
MS:MW	1	0.8569	0.354702	
ID:ICW	1	0.0226	0.880533	
ID:ICNW	1	0.4059	0.524111	
ICW:ICNW	1	1.0516	0.305247	
IP:ICNW	1	0.1003	0.751501	
PMW:IP	1	0.0406	0.840276	
PMW:ICNW	1	0.1733	0.677271	
GT:GD:ID	1	4.9027	0.026905	*
GT:GD:CMS	1	4.7625	0.029179	*
GT:ID:HCW	1	3.3397	0.067744	.
GT:ID:MW	1	5.2194	0.02242	*
GT:IP:ICW	1	55.4185	1.33E-13	***
GT:PMW:HCW	1	7.0664	0.007904	**
GT:MS:PMS	1	4.5603	0.032818	*
GT:MS:MW	1	6.9855	0.008269	**
GT:PMS:CMW	1	5.7348	0.016705	*
ID:ICW:ICNW	1	4.0939	0.043145	*
PMW:IP:ICNW	1	30.3845	3.91E-08	***
Residuals	2499			

results in an increase in mean number of infected. Similarly, an increase in school and workplace closure duration results in a decrease in mean number of infected.

Table 23: Significant main effects observations using infected as the measure of performance for the low transmissibility scenario for the two-level fractional factorial experiment

Factor	**Low level**	**High level**	**Observation**
GD	56,060.11	61,817.11	An increase in deployment delay from 3 to 7 days results in an increase of 0.57% in total number of infected.
ID	66,215.46	51,661.76	An increase in case isolation threshold from 0 to 1 day results in a decrease of 1.44% in total number of infected.
CMS	18,177.97	99,699.25	An increase in the number of cases to close a class from 1 to 3 cases results in an increase of 8.04% in total number of infected.
MS	49,288.14	68,589.08	An increase in the number of classes to close a school from 1 to 3 classes results in an increase of 1.90% in total number of infected.
PMS	77,931.92	39,945.29	An increase in school closure duration from 21 to 42 days results in a decrease of 3.75% in total number of infected.
CMW	52,448.55	65,428.67	An increase in the number of cases to close a department from 3 to 5 cases results in an increase of 1.28% in total number of infected.
PMW	61,000.09	56,877.13	An increase in workplace closure duration from 7 to 14 days results in a decrease of 0.41% in total number of infected.

The percentage in decreased number of infected is shown in Table 23. School closure proves to be the most significant intervention, with a small increase in number of cases to close a class, a large increase in total number of infected was observed. A small increase in school closure duration, results in a large decrease in the total number of infected. Since majority of contacts and infections happen in schools and among children, this result was expected. A result that was not expected is the behavior of the case isolation threshold. Isolating individuals one day after becoming symptomatic resulted in a decrease in the total number of infected. Analyzing the behavior of individuals during NPIs as discussed before, once NPIs are in place, the number of infections in household increases, making it

more effective to have an infected individual during its first day of infectiousness contacting others at work or community instead of home where contact probabilities are higher. Table 24 shows the significant interactions for the low transmissibility scenario. In this table the values of the mean infected at each point of the graph is presented along with the percentage of increase or decrease in the total number of infected.

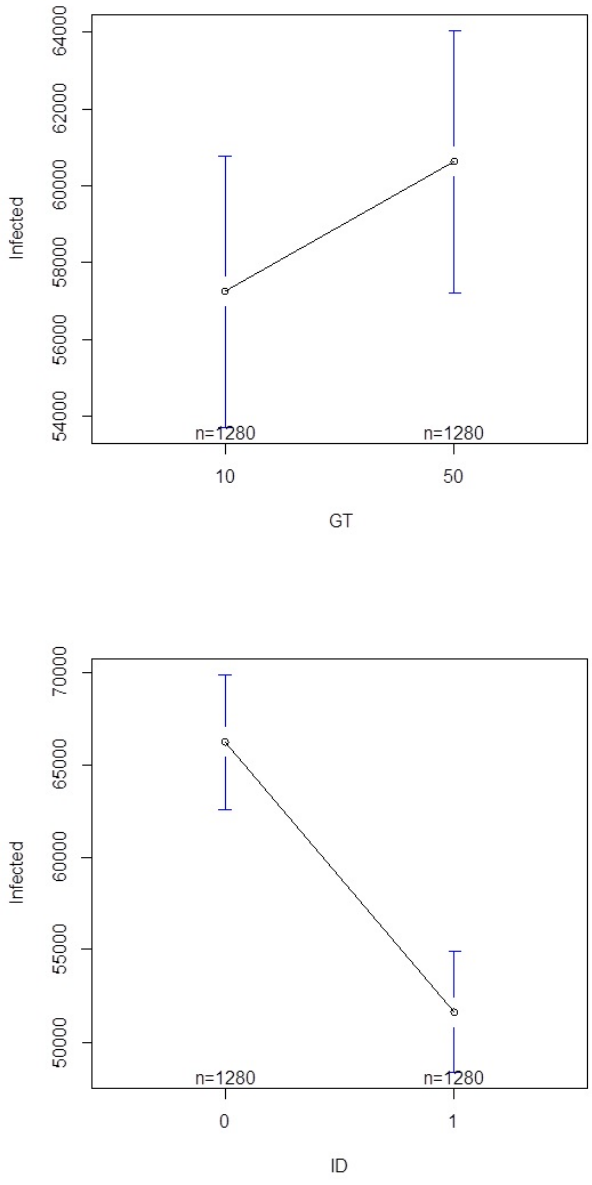
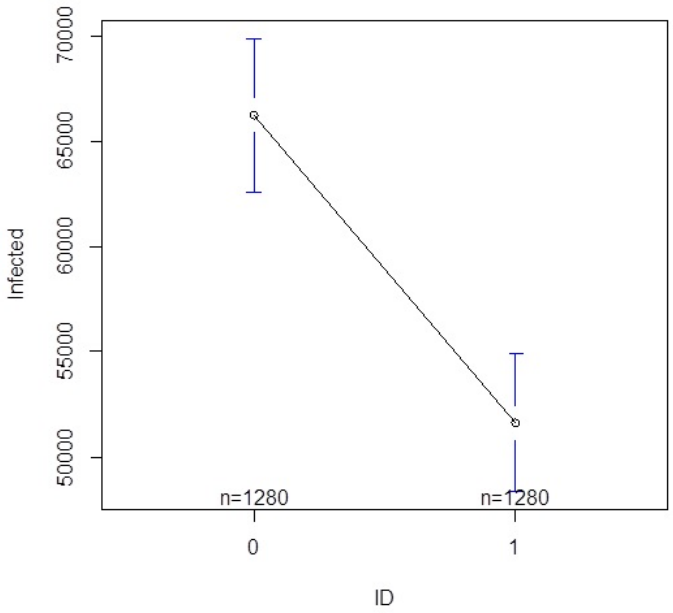


Figure 11: Main factor effects for the low transmissibility scenario for the two-level fractional factorial experiment



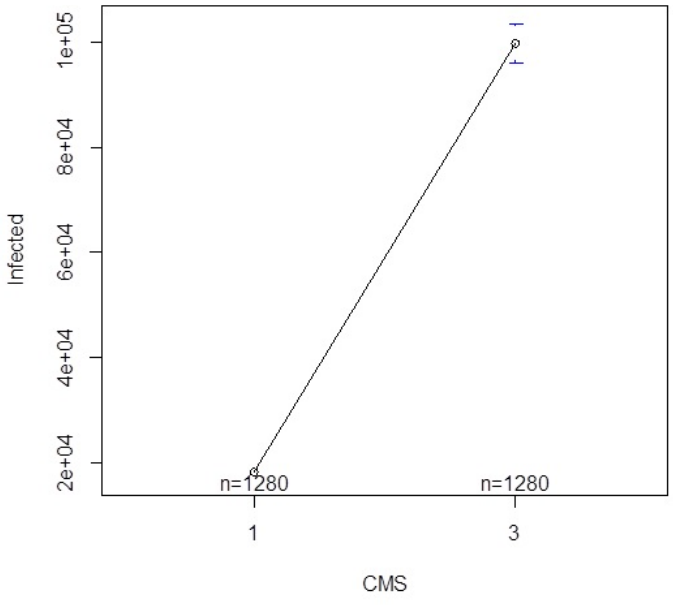
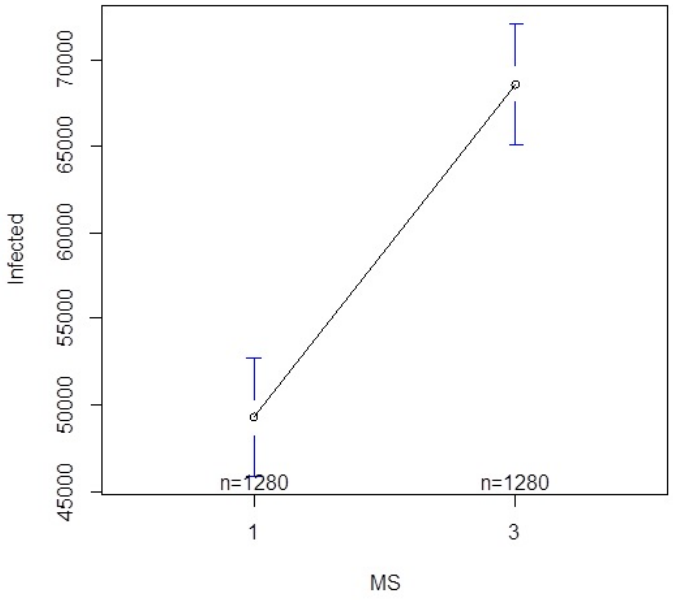


Figure 11: (Continued)



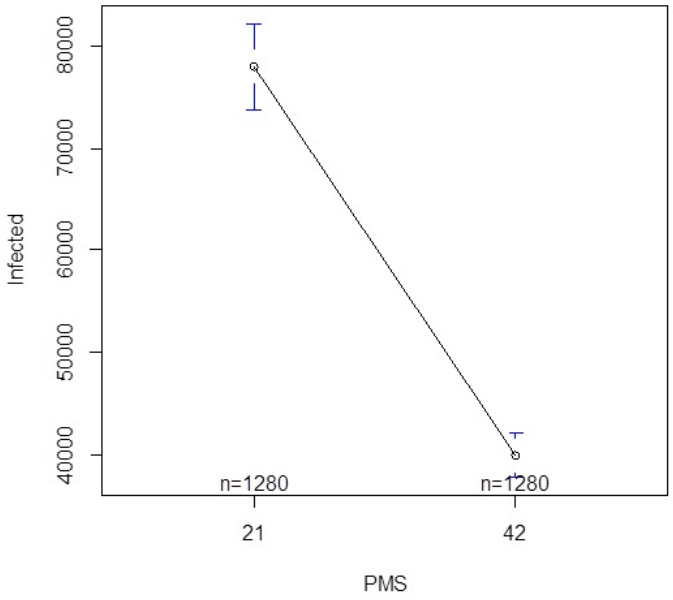
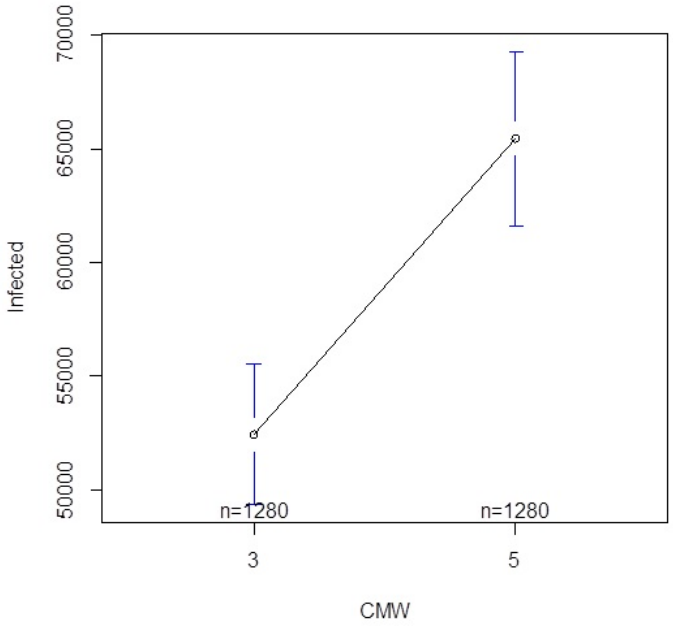


Figure 11: (Continued)



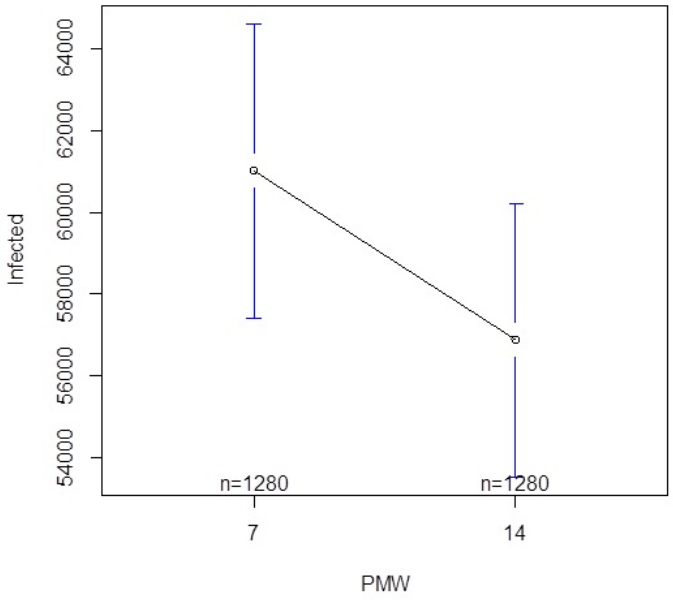


Figure 11: (Continued)

Table 24: Significant interactions observations for the low transmissibility scenario for the two-level fractional factorial experiment

Interaction	**Low, Low**	**High, Low**	**Low, High**	**High, High**
ID x CMS	19,752.47	16,603.47	11,2678.44	86,720.05
ID x PMS	87,886.86	67,976.99	44,544.05	35,346.53
ID x CMW	57,762.98	47,134.12	74,667.93	56,189.4
CMS x MS	11,993.5	86,582.77	24,362.44	112,815.72
CMS x PMS	23,125.62	132,738.23	13,230.33	66,660.26
CMS x CMW	16019.4	88,877.71	20,336.55	110,520.78
MS x PMS	73,137.96	82,725.89	25,438.32	54,452.27
PMS x CMW	65,395.32	39,501.79	90,468.53	403,88.8

Interaction	**Interpretation**
ID x CMS	When number of cases to close a school is one, an increase in case isolation threshold from 0 to 1 day results in a decrease in total number of infected by 0.31%. When number of cases to close a school is three, an increase in case isolation threshold from 0 to 1 day results in a decrease in total number of infected by 2.56%.
ID x PMS	When school closure duration is 21 days, an increase in case isolation threshold from 0 to 1 day results in a decrease in total number of infected by 1.96%. When school closure duration is 42 days, an increase in case isolation threshold from 0 to 1 day results in a decrease in total number of infected by 0.91%.
ID x CMW	When cases to close a workplace is three, an increase in case isolation threshold from 0 to 1 day results in a decrease in total number of infected by 1.05%. When cases to close a workplace is five, an increase in case isolation threshold from 0 to 1 day results in a decrease in total number of infected by 1.82%.
CMS x MS	When total number of classes to close a school is one, an increase in the number of cases to close a school from 1 to 3 cases results in an increase in total number of infected by 7.36%. When total number of classes to close a school is 3, an increase in the total number of cases to close a school from 1 to 3 cases results in an increase in total number of infected by 8.73%.
CMS x PMS	When school closure duration is 21 days, an increase in cases to close a class from 1 to 3 cases results in an increase in total number of infected by 10.81%. When school closure duration is 42 days, an increase in cases to close a class from 1 to 3 cases results in an increase in total number of infected by 5.27%.
CMS x CMW	When classes to close a school is 3 classes, an increase in cases to close a class from 1 to 3 cases results in an increase in total number of infected by 7.19%. When classes to close a school is 5 classes, an increase

Table 24 (Continued)

	in cases to close a class from 1 to 3 cases results in an increase in total number of infected by 8.90%.
MS x PMS	When school closure duration is 21 days, an increase in number of classes to close a school from 1 to 3 classes results in an increase in total number of infected by 0.95%. When school closure duration is 42 days, an increase in number of classes to close a school from 1 to 3 classes results in an increase in total number of infected by 2.86%.
PMS x CMW	When number of cases to close a workplace is 3 cases, an increase in school closure duration from 21 to 42 days results in a decrease in total number of infected by 2.55%. When number of cases to close a workplace is 5 cases, an increase in school closure duration from 21 to 42 days results in a decrease in total number of infected by 4.94%.

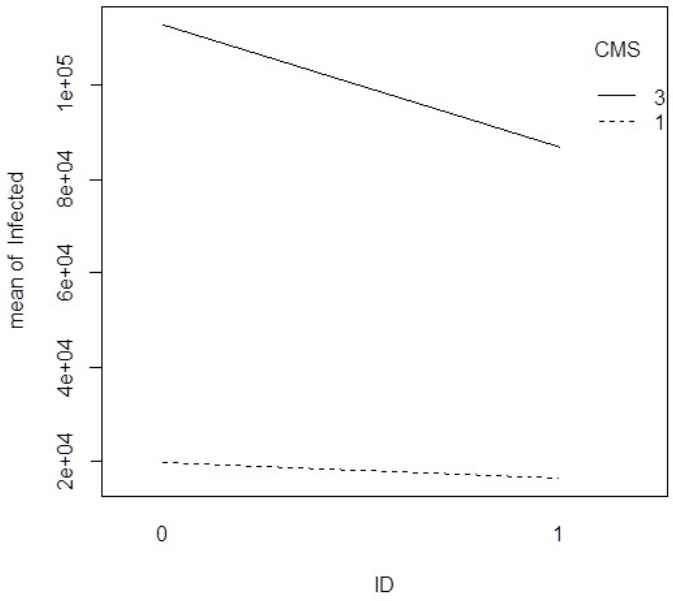
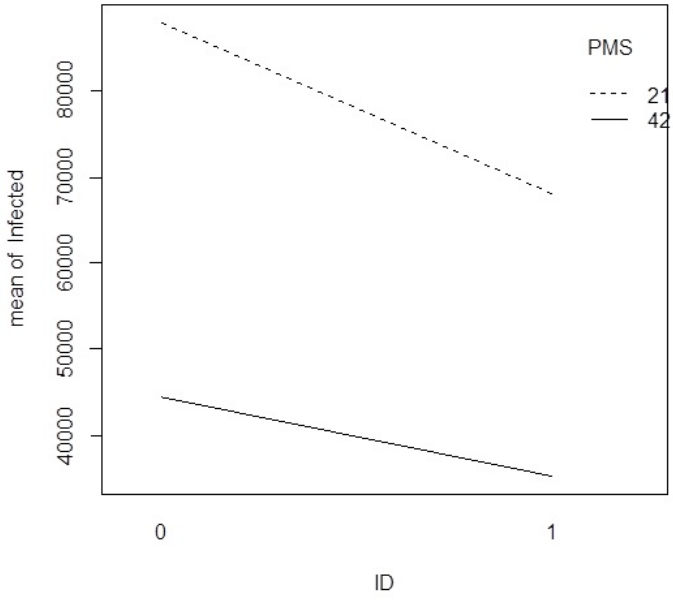


Figure 12: Interaction effects for the low transmissibility scenario for the two-level fractional factorial experiment



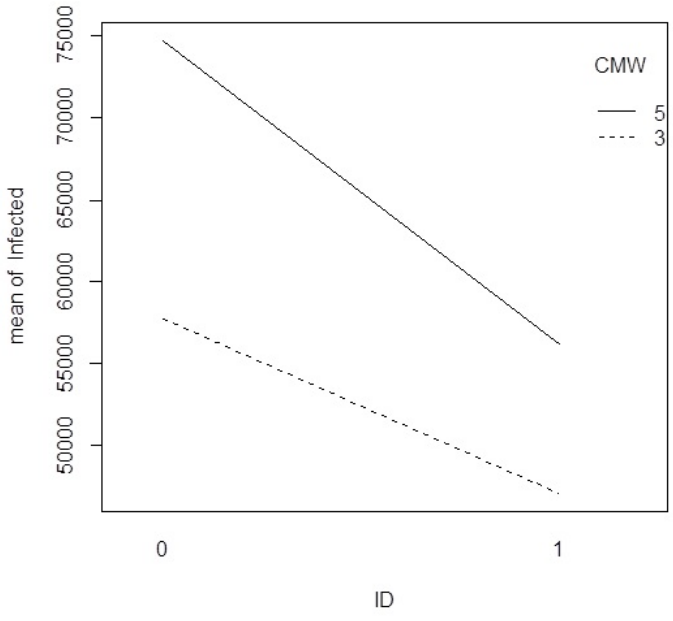
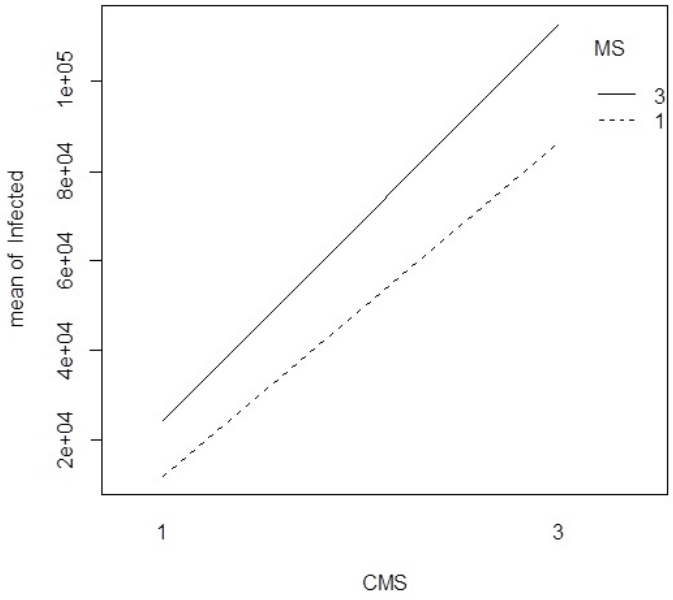


Figure 12: (Continued)



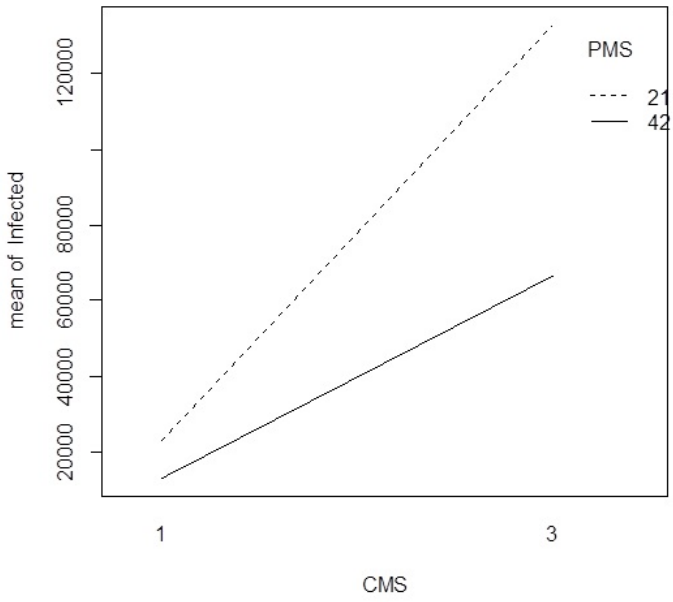
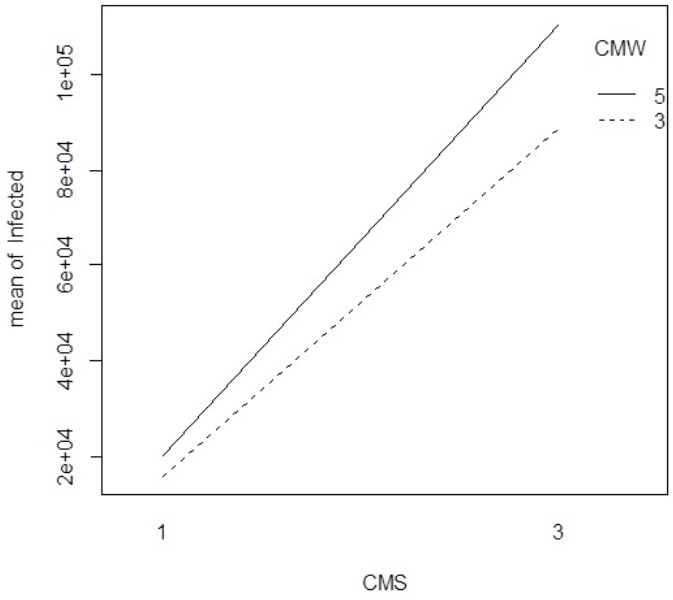


Figure 12: (Continued)



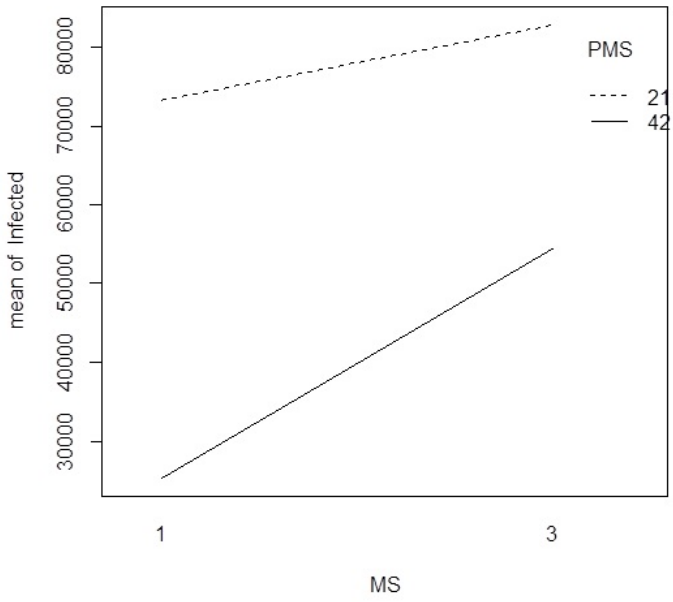


Figure 12: (Continued)

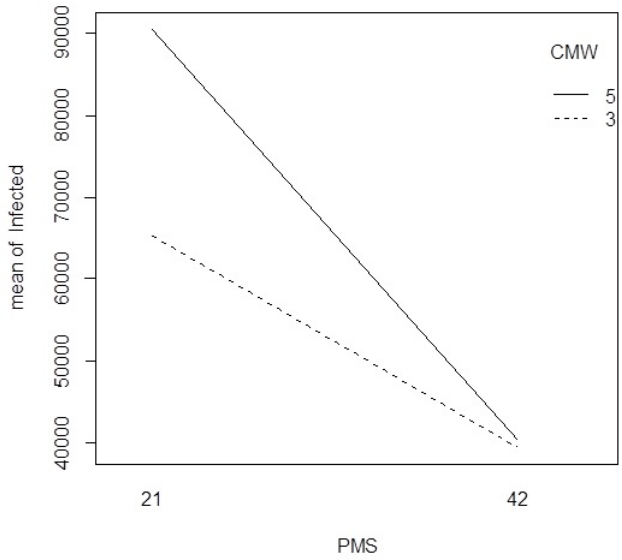


Figure 12: (Continued)

The most notable interaction results are ID x CMS, CMS x PMS, and MS x PMS. As seen in Figure 12, case isolation threshold has a major impact when the number of cases to close a classroom in a school is three as opposed to one. As discussed before, when an individual is in its first day of infectiousness is better to not keep him at home where contact probabilities are higher. When we wait too long to close a school, is better (from these results,) to keep kids in school for that first day of infectiousness than at home. Contacts at school are high, but the probability of contacting someone at home is higher. Add to this that the infected individual is in its day where viral shedding is higher, and the probability of infecting someone at home is greater than at school.

Figure 12 shows the interaction between the factors number of cases to close a class and school closure duration. The number of cases to close a class has a big impact in total number of infections independent of the duration of school closure. However, an increase in classes to close a class from 1 to 3 when school closure duration is 21 days results in a 10.86% increase in total number of infected, as opposed to 5.27% when school closure duration is 42 days. This shows that for small periods of school closure it is important to close classes

immediately after observing one infected case in a class. However, as shown in Figure 12, when having a longer period of school closure is better to close a school immediately after one class has been closed. A stringent duration is more beneficial when schools are closed immediately after closing a class. The number of classes to close a school is not of major impact for short closure durations.

The regression analysis for the low transmissibility scenario two-level fractional factorial experiment is shown in Table 26.

This model has an R-square value of 65.2%. The graph for residual analysis and the normal probability plot for residuals is shown in Figure 13. Even including all the factors in the low transmissibility model only increases the R-square value to 67.81%. Low R-square value tells us that the linear regression is not enough to characterize variation in total number of infected across changes in all factors considered. However, the optimization of the regression equation still resulted in a policy that significantly improves performance compare to baseline and the non-optimal NPI strategy. The optimal strategy is shown in Table 25.

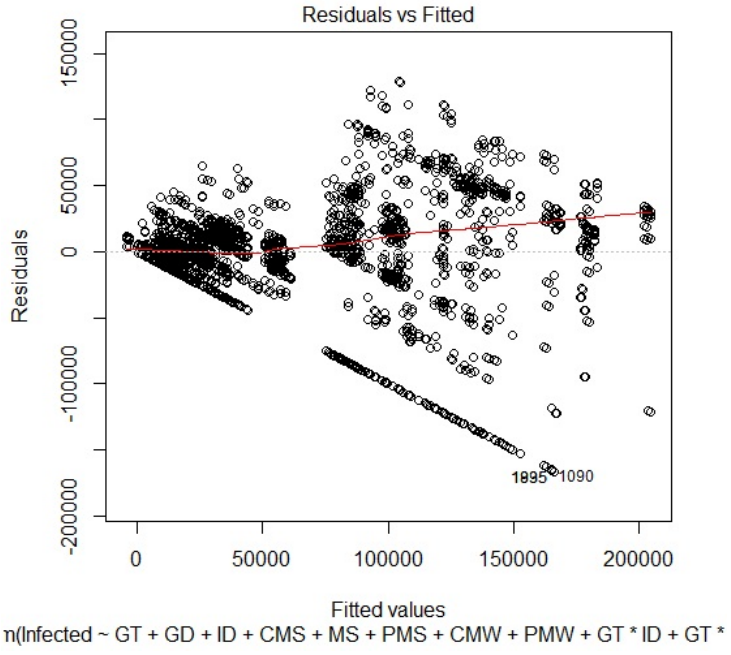


Figure 13: Residuals plot and normal probability plot for the regression analysis for the low transmissibility scenario for the two-level fractional factorial experiment

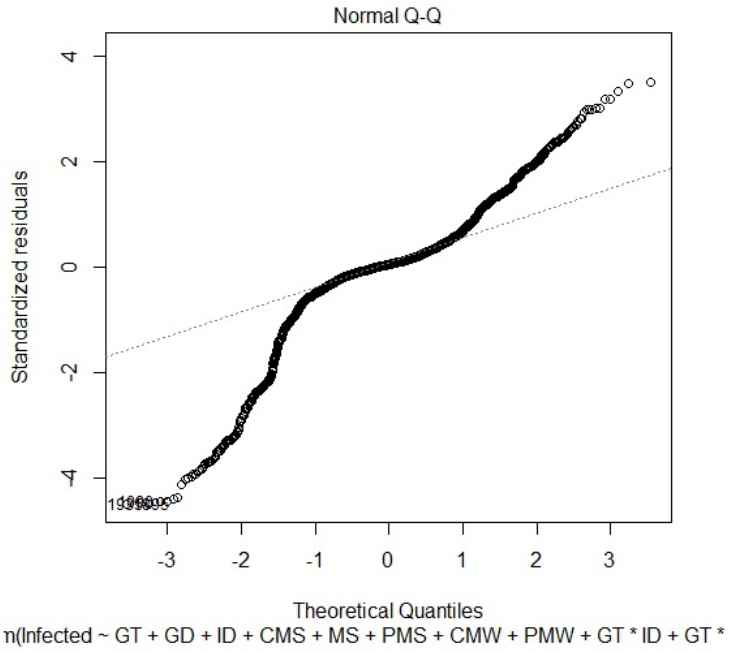


Figure 13: (Continued)

Table 25: Optimal NPI strategy for the low transmissibility scenario based on the two-level fractional factorial experiment

Factor	**Optimal Value**	**Factor**	**Optimal Value**	**Factor**	**Optimal Value**
GT	10	GD	7	ID	1
IP	10	ICW	0.75	ICNW	0.57
HD	1	HP	7	HCW	0.53
HCNW	0.84	CMS	1	MS	3
PMS	21	CMW	3	MW	0.3
PMW	7				

As shown in Table 25 the optimal NPI strategy was able to achieve containment with an IAR of 1.83%. For the low transmissibility scenario, an optimal NPI strategy can also reduce the duration of pandemic. It also reduces infections, deaths, contacts, and CFR.

As shown in Figure 14, an optimal NPI strategy not only reduces IAR but peak attack rates, thus reducing the pressure on hospitals and the health care system in general. Figures 15 through 16 shows baseline vs. optimal NPI strategy daily deaths and contacts, respectively.

Table 26: Regression analysis for the low transmissibility scenario for the two-level fractional factorial experiment

Factor	Estimate	t value	Pr(>|t|)	Signif.
(Intercept)	-5.56E+04	-0.554	0.579527	
GT	9.53E+03	6.008	2.16E-09	***
GD	3.92E+02	0.24	0.810438	
ID	1.12E+05	2.16	0.030891	*
CMS	6.16E+04	10.536	< 2e-16	***
MS	-1.88E+04	-2.482	0.013124	*
PMS	-1.86E+01	-0.029	0.976749	
CMW	4.02E+03	0.845	0.398284	
PMW	-3.06E+04	-4.294	1.82E-05	***
MW	4.61E+04	1.168	0.24287	
HCW	8.79E+04	2.226	0.026082	*
IP	-1.19E+04	-1.193	0.233073	
ICW	5.42E+05	6.347	2.59E-10	***
ICNW	-4.48E+05	-3.963	7.60E-05	***
GT:ID	-6.40E+02	-1.156	0.247711	
GT:MS	-8.47E+01	-0.449	0.653163	
GT:CMW	3.52E+02	3.007	0.002663	**
ID:CMS	-1.14E+04	-7.712	1.78E-14	***
ID:PMS	5.10E+02	3.622	0.000298	***
ID:CMW	-3.93E+03	-2.654	0.008005	**
CMS:MS	3.47E+03	4.687	2.92E-06	***
CMS:PMS	-1.34E+03	-18.995	< 2e-16	***
CMS:CMW	4.33E+03	5.858	5.30E-09	***
CMS:PMW	-4.60E+02	-2.176	0.029644	*
MS:PMS	6.88E+02	5.42	6.53E-08	***
MS:CMW	1.68E+03	2.27	0.023273	*
PMS:CMW	-3.23E+02	-2.543	0.011037	*
PMS:PMW	4.71E+01	2.341	0.019298	*
PMW:MW	-4.05E+03	-1.916	0.05552	.
GT:GD	2.35E+01	0.518	6.05E-01	

Factor	Estimate	t value	Pr(>|t|)	Signif.
GD:ID	-3.43E+03	-2.575	0.01007	*
GT:CMS	1.82E+02	1.83	0.067309	.
GD:CMS	1.63E+03	2.441	0.014733	*
GT:HCW	-3.44E+03	-3.138	0.001724	**
ID:HCW	-2.62E+04	-1.1	0.271431	
GT:MW	-9.51E+02	-1.05	0.293874	
ID:MW	5.64E+04	2.115	0.034563	*
GT:IP	-1.04E+03	-7.273	4.67E-13	***
GT:ICW	-1.39E+04	-7.314	3.47E-13	***
IP:ICW	-5.10E+04	-6.427	1.55E-10	***
GT:PMW	-1.70E+02	-2.763	0.005764	**
PMW:HCW	-7.11E+03	-2.091	0.036636	*
GT:PMS	5.05E+01	3.127	0.001785	**
MS:MW	-2.25E+04	-1.686	0.091989	.
ID:ICW	-1.46E+05	-2.017	0.04381	*
ID:ICNW	-1.24E+05	-1.884	0.059716	.
ICW:ICNW	-1.54E+05	-2.156	0.031193	*
IP:ICNW	6.37E+04	5.329	1.07E-07	***
PMW:IP	4.17E+03	5.384	7.98E-08	***
PMW:ICNW	5.12E+04	5.501	4.17E-08	***
GT:GD:ID	8.19E+01	2.214	0.026905	*
GT:GD:CMS	-4.03E+01	-2.182	0.029179	*
GT:ID:HCW	1.21E+03	1.827	0.067744	.
GT:ID:MW	-1.69E+03	-2.285	0.02242	*
GT:IP:ICW	1.64E+03	7.444	1.33E-13	***
GT:PMW:HCW	2.51E+02	2.658	0.007904	**
GT:MS:PMS	-7.52E+00	-2.135	0.032818	*
GT:MS:MW	9.77E+02	2.643	0.008268	**
GT:PMS:CMW	-8.43E+00	-2.395	0.016705	*
ID:ICW:ICNW	2.05E+05	2.023	0.043145	*
PMW:IP:ICNW	-5.95E+03	-5.512	3.91E-08	***

Table 27: Performance measures for baseline vs. optimal NPI strategy for the low transmissibility scenario based on the two-level fractional factorial experiment

Measure	Baseline	NPI	Measure	Baseline	NPI
IAR	33.06%	1.83%	Infections 0-19 yrs.	225,467	14,345
CFR	0.69%	0.03%	Infections 20-64 yrs.	91,959	3,346
Pandemic Duration (Days)	135	75	Infections 65-99 yrs.	17,645	857
Total Contacts	1,177,393	71,771	Infections Households	37,562	7,470
Contacts 0-19 yrs.	818,912	62,920	Infect. MG Types(1-2)	46,600	535
Contacts 20-64 yrs.	294,046	7,160	Infect. Schools	249,304	10,458
Contacts 65-99 yrs.	64,435	1,691	Infect. MG Types(9-12)	1,605	85
Contacts Households	238,684	40,213	Total Deaths	7,009	303
Contacts MG Types(1-2)	231,051	3,185	Deaths 0-19 yrs.	1,041	67
Contacts Schools	699,427	28,013	Deaths 20-64 yrs.	4,095	156
Contacts MG Types(9-12)	8,231	360	Deaths 65-99 yrs.	1,873	80
Total Infections	335,071	18,548			

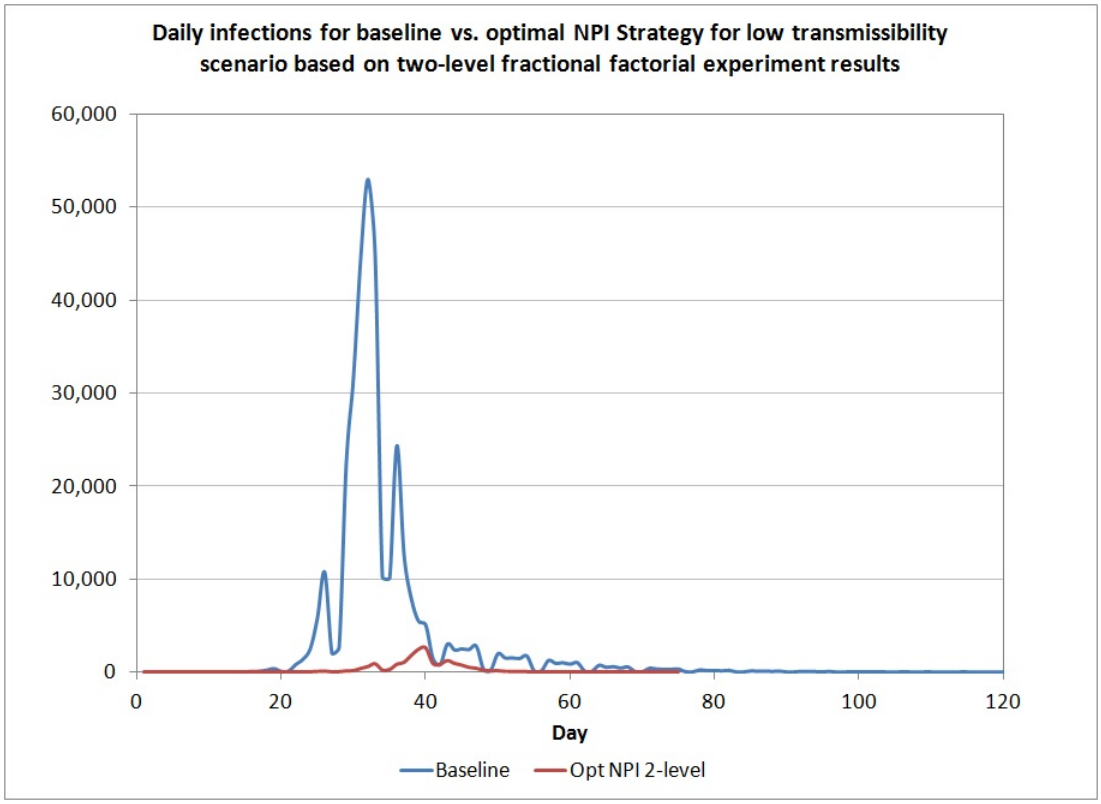


Figure 14: Daily infections for baseline vs. optimal NPI strategy for the low transmissibility scenario based on the two-level fractional factorial experiment

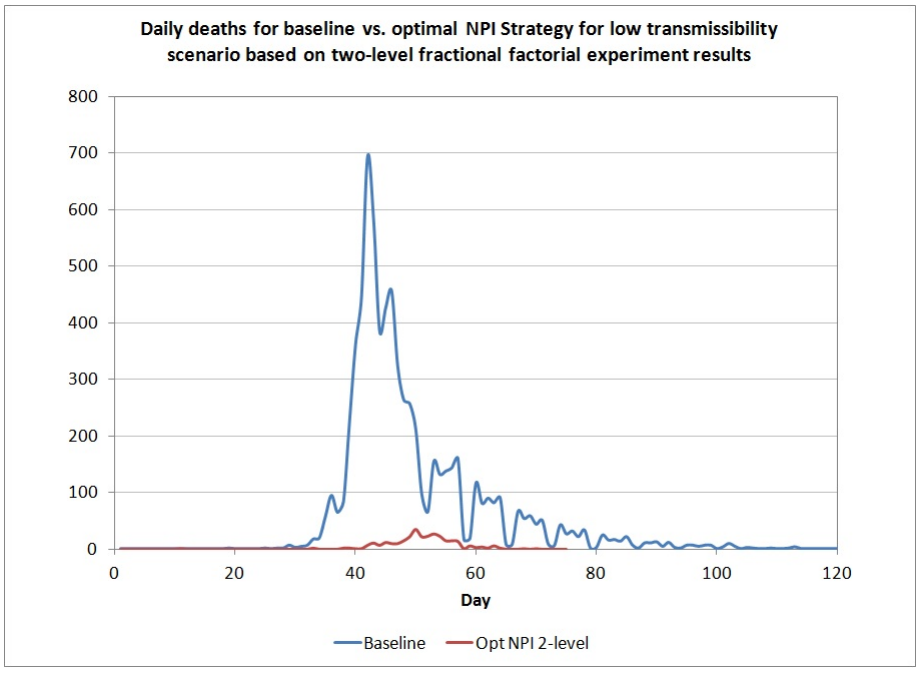


Figure 15: Daily deaths for baseline vs. optimal NPI strategy for the low transmissibility scenario based on the two-level fractional factorial experiment

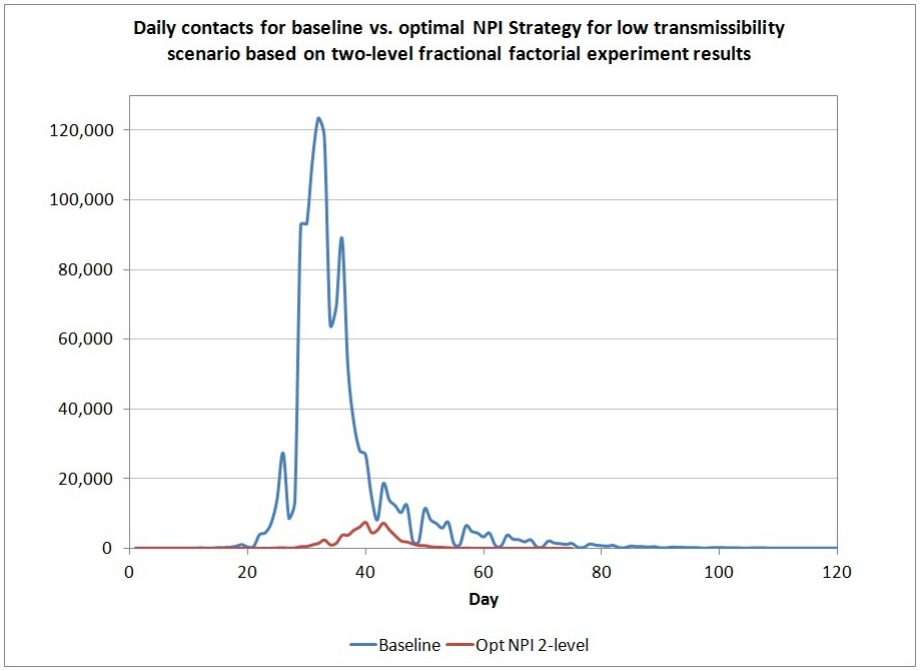


Figure 16: Daily contacts for baseline vs. optimal NPI strategy for the low transmissibility scenario based on the two-level fractional factorial experiment

6.2.2 Medium Transmissibility Scenario

The ANOVA table for the two-level fractional factorial experiment for the medium transmissibility scenario is shown in Table 28. The level of significance that we used to determine significant factors was 0.01, which are the factors marked with two and three stars in the significance level column. Table 29 shows the main effects factors that resulted to be significant. In this table, the mean number of infected at low and high levels are also presented. Figure 17 shows this graphically.

As shown in Figure 17, an increase in the factors global threshold, deployment delay, number of cases to close a department in a workplace, number of classes to close a school, and number of cases to close a classroom result in an increase in the total number of infected. But an increase in the factors of school and workplace closure duration, reduces the total number of infections. The percentage in decrease/increase number of infected is shown in Table 29. In the medium transmissibility scenario we also noted that school closure is perhaps the more significant intervention. With an increase in the number of cases to close a class from one case to three cases, an increase of 15.42% is observed in the total number of infected. Also, an increase from one to three classes to close a school resulted in an increase of 5.35%. Increasing school closure duration from 21 to 42 days, decreased the total number of infected by 5.56%. Workplace closure factors were significant, but the impact in total number of infections is not as notable as with school closure. Even though we observed the same behavior with case isolation threshold as in the low transmissibility scenario, isolating individuals after one day of becoming symptomatic only resulted in a 0.61% reduction in total number of infected.

Table 30 shows all significant interactions for medium transmissibility scenario for the two-level fractional factorial experiment. Figure 18 show the graphs for these significant interactions. The interaction of global threshold with deployment delay shows that for a short deployment delay, an increase in the number of cases to declare pandemic does not have a significant impact on total number of infections. However, as the deployment delay increase to seven days, then an increase in global threshold from 10 to 50 cases results in an increase of 6.10% in total number of infections.

Table 28: ANOVA Table for medium transmissibility scenario two-level fractional factorial experiment using total number of infected as measure of performance

Factor	Df	F value	Pr(>F)	Signif.
GT	1	701.7593	< 2.2e-16	***
GD	1	708.273	< 2.2e-16	***
ID	1	27.9696	1.34E-07	***
CMS	1	17647.6256	< 2.2e-16	***
MS	1	2126.347	< 2.2e-16	***
PMS	1	2295.0783	< 2.2e-16	***
CMW	1	515.009	< 2.2e-16	***
PMW	1	16.0364	6.40E-05	***
MW	1	0.215	0.6428831	
HCNW	1	0.7639	0.3822061	
HCW	1	0.6292	0.4277298	
IP	1	0.2158	0.6423274	
ICW	1	0.3785	0.538452	
ICNW	1	0.8278	0.3629862	
HD	1	0.6	0.4386446	
GT:GD	1	679.8101	< 2.2e-16	***
GT:CMS	1	443.0754	< 2.2e-16	***
GT:MS	1	94.1393	< 2.2e-16	***
GT:PMS	1	25.1911	5.56E-07	***
GT:CMW	1	3.8163	0.0508676	.
GT:MW	1	5.3622	0.0206594	*
GD:HCNW	1	7.9694	0.0047953	**
GD:CMS	1	496.7615	< 2.2e-16	***
GD:MS	1	87.4009	< 2.2e-16	***
GD:PMS	1	20.1081	7.65E-06	***
ID:CMS	1	12.4502	0.0004255	***
ID:PMS	1	5.9268	0.0149826	*
PMW:HCW	1	7.8791	0.0050398	**
CMS:MS	1	340.4819	< 2.2e-16	***
CMS:PMS	1	5.0961	0.0240664	*
CMS:MW	1	5.0676	0.0244639	*
CMS:PMW	1	3.8593	0.049581	*
MS:PMS	1	23.9828	1.03E-06	***
PMS:CMW	1	168.8749	< 2.2e-16	***
PMS:PMW	1	12.3169	0.0004569	***
CMW:MW	1	3.159	0.0756311	.
GT:ID	1	2.7296	0.098628	.

Factor	Df	F value	Pr(>F)	Signif.
GT:IP	1	0.0005	0.9817763	
GT:ICW	1	0.1483	0.7001734	
IP:ICW	1	0.4232	0.5153843	
GT:ICNW	1	0.6509	0.4198612	
GT:HD	1	0.1165	0.7328509	
ICNW:HD	1	0.1965	0.6576226	
GT:PMW	1	1.1719	0.2791242	
PMS:MW	1	0.6422	0.4229761	
CMW:PMW	1	0.0425	0.8367241	
ID:CMW	1	2.8755	0.0900646	.
CMS:CMW	1	33.2767	8.99E-09	***
ICW:HD	1	0.554	0.4567446	
MS:ICW	1	0.6469	0.4213123	
MS:HD	1	0.3688	0.5437369	
CMW:HCW	1	1.4193	0.2336267	
MW:HCW	1	0.4766	0.4900138	
PMW:MW	1	1.8103	0.1785904	
GT:GD:CMS	1	482.2682	< 2.2e-16	***
GT:GD:MS	1	55.2258	1.47E-13	***
GT:GD:PMS	1	14.8429	0.0001198	***
GT:ID:CMS	1	9.7381	0.0018256	**
GT:ID:PMS	1	2.9927	0.0837653	.
GT:ID:MW	1	7.273	0.0070472	**
GT:IP:ICW	1	162.3524	< 2.2e-16	***
GT:ICNW:HD	1	3.223	0.0727317	.
GT:CMS:MS	1	36.0349	2.22E-09	***
GT:CMS:PMW	1	3.318	0.0686467	.
GT:PMS:CMW	1	8.8626	0.0029388	**
GT:PMS:MW	1	6.5399	0.0106072	*
GT:CMW:PMW	1	4.3438	0.0372458	*
GD:CMS:MS	1	37.2893	1.18E-09	***
ID:CMS:CMW	1	6.9004	0.0086706	**
MS:ICW:HD	1	3.7604	0.0525934	.
CMW:PMW:HCW	1	3.5119	0.0610454	.
PMW:MW:HCW	1	10.8332	0.0010109	**
Residuals	2486			

Table 29: Significant main effects observations using infected as the measure of performance for the medium transmissibility scenario for the two-level fractional factorial experiment

Factor	**Low level**	**High level**	**Observation**
GT	259,959.6	291,117.2	An increase in the number of cases to declare pandemic from 10 to 50 cases results in an increase of 3.07% in total number of infected.
GD	259,887.4	291,189.3	An increase in deployment delay from 3 to 7 days results in an increase of 3.09% in total number of infected.
ID	278,648.6	272,428.2	An increase in case isolation threshold from 0 to 1 day results in a decrease of 0.61% in total number of infected.
CMS	197,414.6	353,662.2	An increase in the number of cases to close a school from 1 to 3 cases results in an increase of 15.42% in total number of infected.
MS	248,420.4	302,656.4	An increase in the number of classes to close a school from 1 to 3 classes results in an increase of 5.35% in total number of infected.
PMS	303,711.8	247,365	An increase in school closure duration from 21 to 42 days results in a decrease of 5.56% in total number of infected.
CMW	262,192.5	288,884.3	An increase in the number of cases to close a department from 3 to 5 cases results in an increase of 2.63% in total number of infected.
PMW	277,893.4	273,183.4	An increase in workplace closure duration from 7 to 14 days results in a decrease of 0.46% in total number of infected.

This particular result shows the importance of surveillance and preparedness. When interventions are not prepared to be deployed soon after pandemic declaration in a region, then pandemic declaration should happen with a minimal number of cases to ensure a better NPI effectiveness. Table 30 shows all significant interactions for medium transmissibility scenario for the two-level fractional factorial experiment. Figures 18 show the graphs for these significant interactions.

The interaction of global threshold with deployment delay shows that for a short deployment delay, an increase in the number of cases to declare pandemic does not have a significant impact on total number of infections. However, as the deployment delay increase to seven days, then an increase in global threshold from 10 to 50 cases results in an increase

of 6.10% in total number of infections. This particular result shows the importance of surveillance and preparedness. When interventions are not prepared to be deployed soon after pandemic declaration in a region, then pandemic declaration should happen with a minimal number of cases to ensure a better NPI effectiveness.

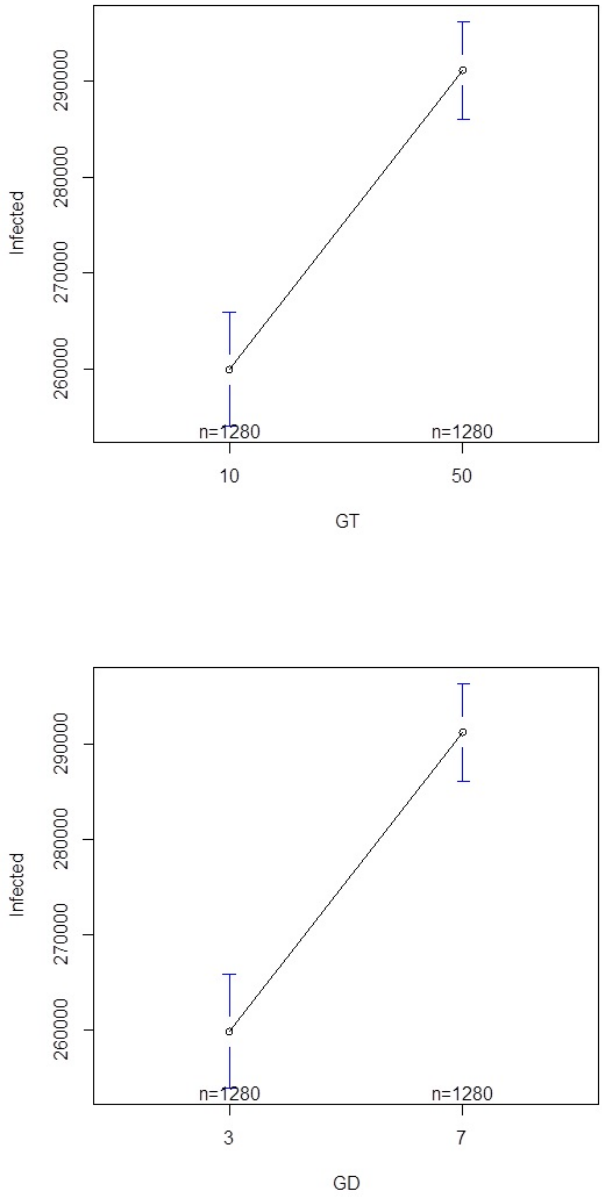
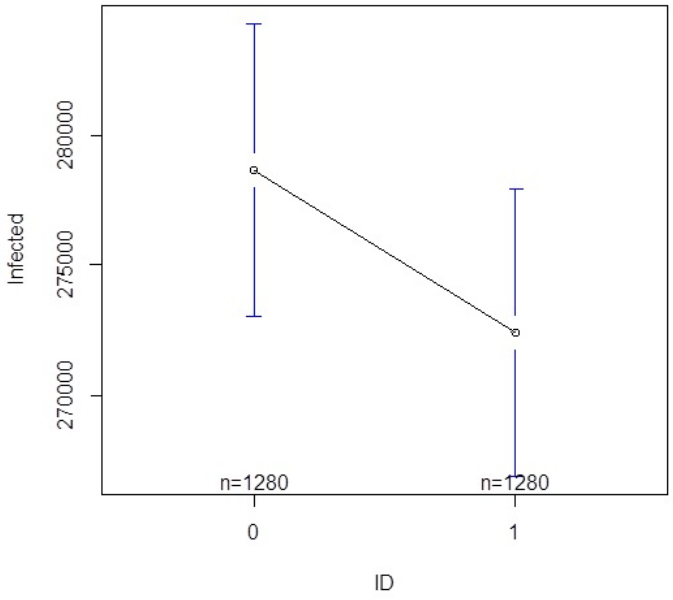


Figure 17: Main factor effects for the medium transmissibility scenario for the two-level fractional factorial experiment



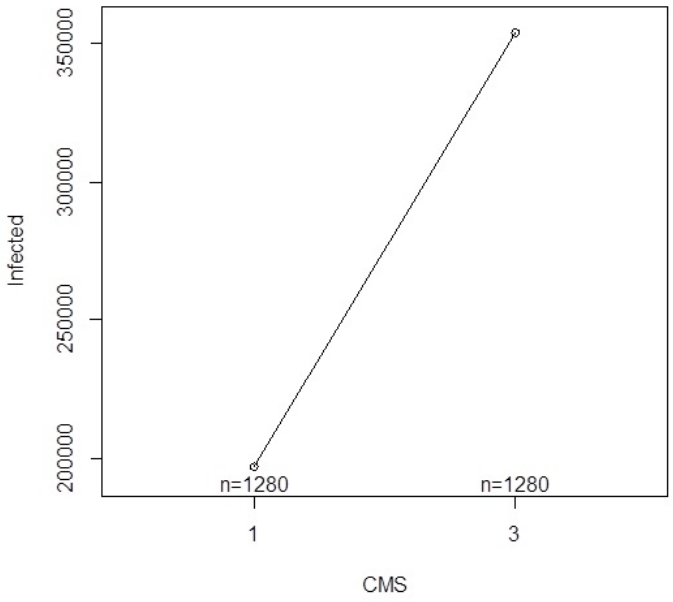
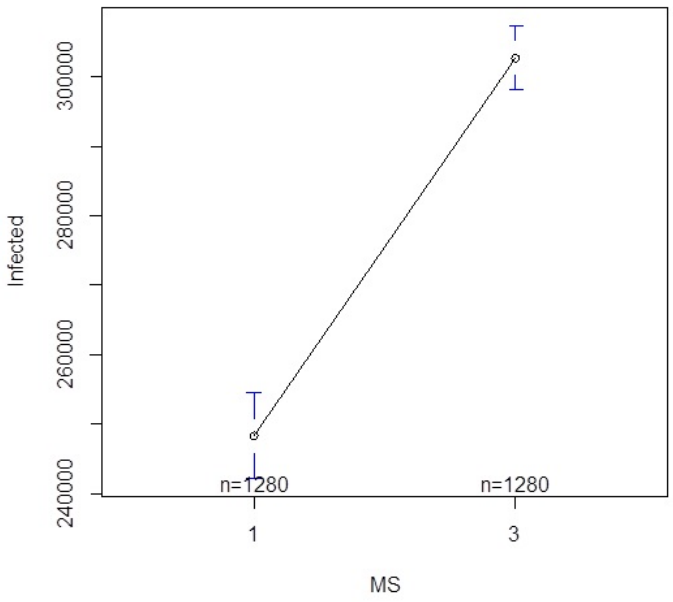


Figure 17: (Continued)



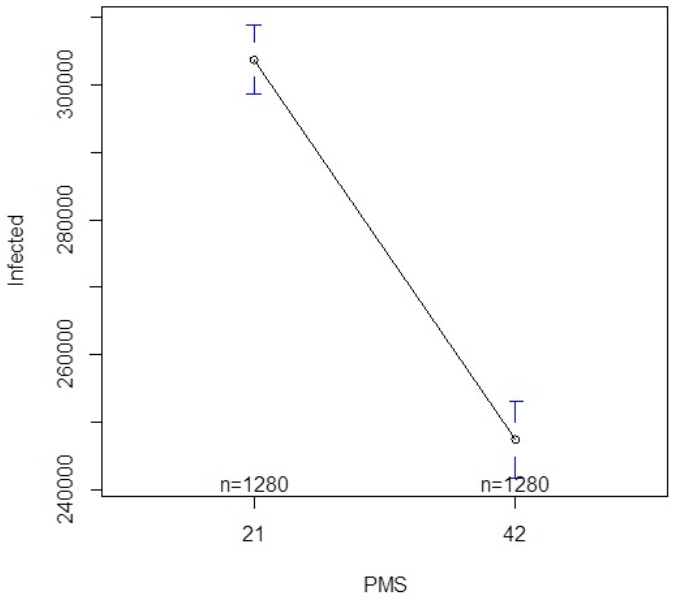
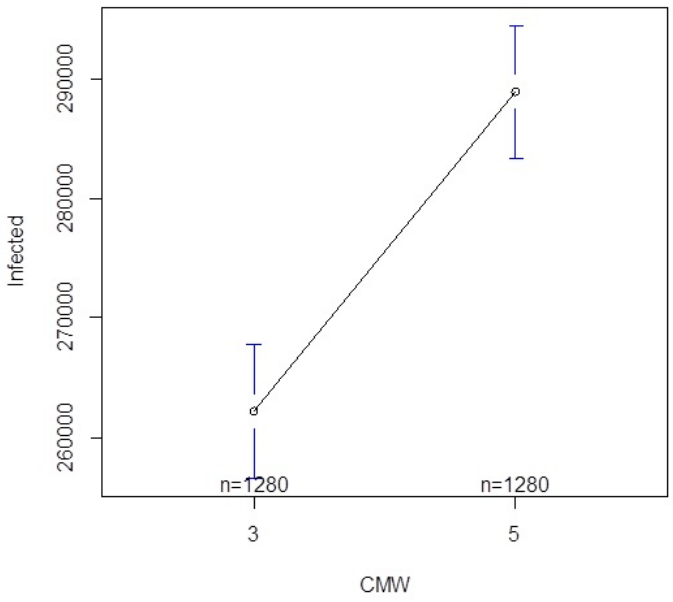


Figure 17: (Continued)



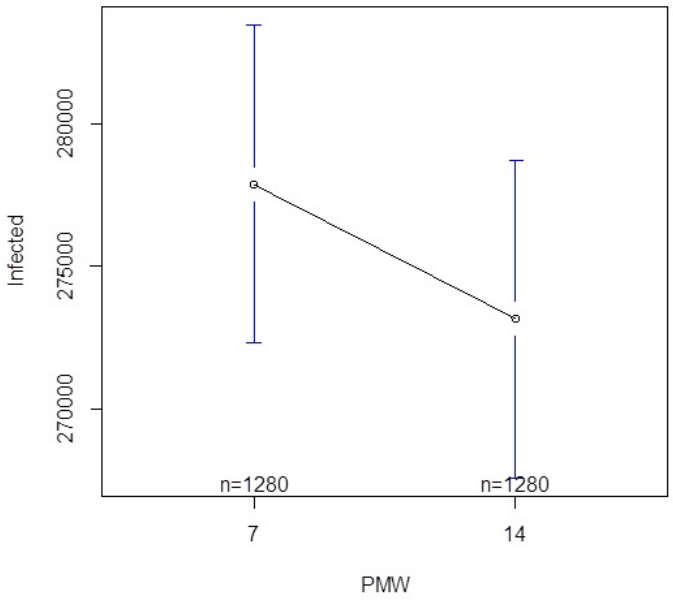


Figure 17: (Continued)

Table 30: Significant interactions observations for the medium transmissibility scenario for the two-level fractional factorial experiment

Interaction	**Low, Low**	**High, Low**	**Low, High**	**High, High**
GT x GD	259,641.9	260,133	260,277.3	322,101.4
GT x CMS	169,456.9	225,372.2	350,462.2	356,862.2
GT x MS	227,135.7	269,705.1	292,783.5	312,529.3
GT x PMS	291,084.6	316,339	228,834.5	265,895.5
GD x HCNW	262,061.6	290,043.1	257,713.3	292,335.5
GD x CMS	168,656.3	226,172.8	351,118.6	356,205.8
GD x MS	227,271.5	269,569.3	292,503.3	312,809.4
GD x PMS	290,697.9	316,725.6	229,077	265,653
ID x CMS	198,449.7	196,379.5	358,847.4	348,477
PMW x HCW	280,010.6	271,999.1	275,776.2	274,367.6
CMS x MS	159,445.1	337,395.7	235,384	369,928.8
MS x PMS	279,473.8	327,949.8	217,367	277,363
PMS x CMW	298,008.2	226,376.8	309,415.4	268,353.2
PMS x PMW	304,002.9	251,783.9	303,420.7	242,946.1
CMS x CMW	187,461.1	336,923.9	207,368	370,400.5

Interaction	**Interpretation**
GT x GD	When deployment delay is three days, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 0.05%. When deployment delay is seven days, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 6.10%.
GT x CMS	When number of cases to close a class is one, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 5.52%. When number of cases to close a class is three, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 0.63%.
GT x MS	When number of classes to close a school is one, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 4.20%. When number of classes to close a school is three, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 1.95%.
GT x PMS	When school closure duration is 21 days, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 2.49%. When school closure duration is 42 days, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 3.66%.
GD x HCNW	When household quarantine compliance for non-workers is 57.5%, an increase in deployment delay from 3 to 7 days results in an increase in total number of infected by 2.76%.

Table 30 (Continued)

	When household quarantine compliance for non-workers is 83.6%, an increase in deployment delay from 3 to 7 days results in an increase in total number of infected by 3.42%.
GD x CMS	When cases to close a class is 1, an increase in deployment delay from 3 to 7 days results in an increase in total number of infected by 5.67%. When cases to close a class is 3, an increase in deployment delay from 3 to 7 days results in an increase in total number of infected by 0.5%.
GD x MS	When number of classes to close a school is 1, an increase in deployment delay from 3 to 7 days results in an increase in total number of infected by 4.17%. When number of classes to close a school is 3, an increase in deployment delay from 3 to 7 days results in an increase in total number of infected by 2%.
GD x PMS	When school closure duration is 21 days, an increase in deployment delay from 3 to 7 days results in an increase in total number of infected by 2.57%. When school closure duration is 42 days, an increase in deployment delay from 3 to 7 days results in an increase in total number of infected by 3.61%.
ID x MS	When number of cases to close a school is one, an increase in case isolation threshold from 0 to 1 day results in a decrease in total number of infected by 0.20%. When number of cases to close a school Is three,an increase in case isolation threshold from 0 to 1 day results in a decrease in total number of infected by 1.02%.
PMW x HCW	When household quarantine compliance for workers is 53%, an increase in workplace closure duration from 7 to 14 days results in a decrease in total number of infected by 0.79%. When household quarantine compliance for workers is 75.4%, an increase in workplace closure duration from 7 to 14 days results in a decrease in total number of infected by 0.14%.
CMS x MS	When total number of classes to close a school is one, an increase in the number of cases to close a school from 1 to 3 cases results in an increase in total number of infected by 17.56%. When total number of classes to close a school is 3, an increase in the total number of cases to close a school from 1 to 3 cases results in an increase in total number of infected by 13.27%.
MS x PMS	When school closure duration is 21 days, an increase in number of classes to close a school from 1 to 3 classes results in an increase in total number of infected by 4.78%. When school closure duration is 42 days, an increase in number of classes to close a school from 1 to 3 classes results in an increase in total number of infected by 5.92%.

Table 30 (Continued)

PMS x CMW	When number of cases to close a workplace is 3 cases, an increase in school closure duration from 21 to 42 days results in a decrease in total number of infected by 7.07%. When number of cases to close a workplace is 5 cases, an increase in school closure duration from 21 to 42 days results in a decrease in total number of infected by 4.05%.
PMS x PMW	When workplace closure duration is 7 days, an increase in school closure duration from 21 to 42 days results in a decrease in total number of infected by 5.15%. When workplace closure duration is 14 days, an increase in school closure duration from 21 to 42 days results in a decrease in total number of infected by 5.97%.
(CMS)(CMW)	When classes to close a school is 3 classes, an increase in cases to close a class from 1 to 3 cases results in an increase in total number of infected by 14.75% When classes to close a school is 5 classes, an increase in cases to close a class from 1 to 3 cases results in an increase in total number of infected by 16.09%

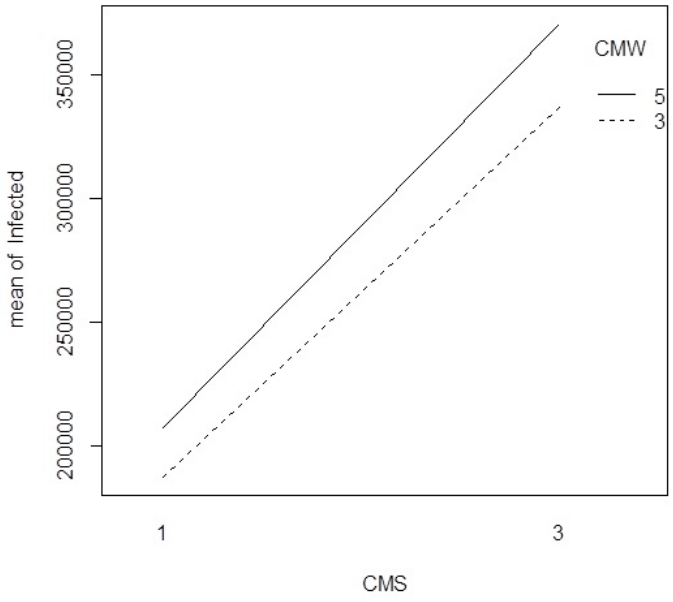
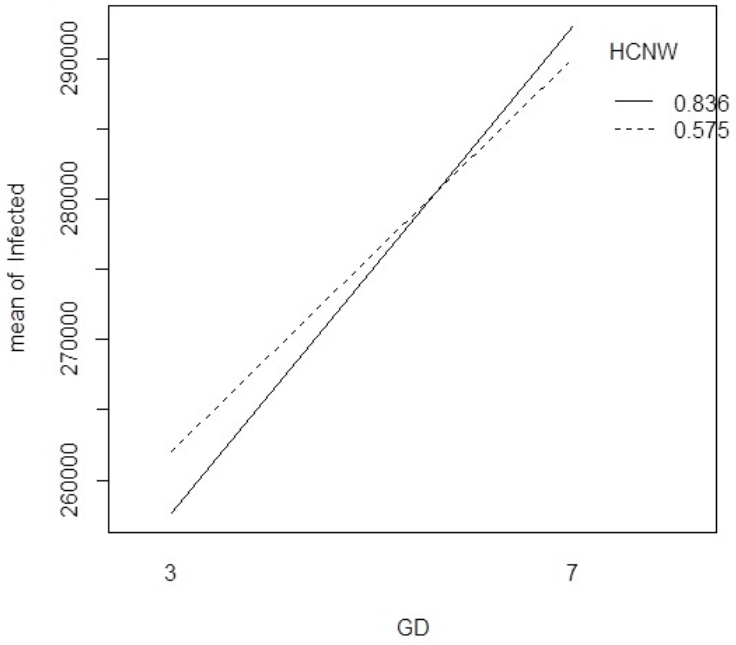


Figure 18: Interaction effects for the medium transmissibility scenario for the two-level fractional factorial experiment



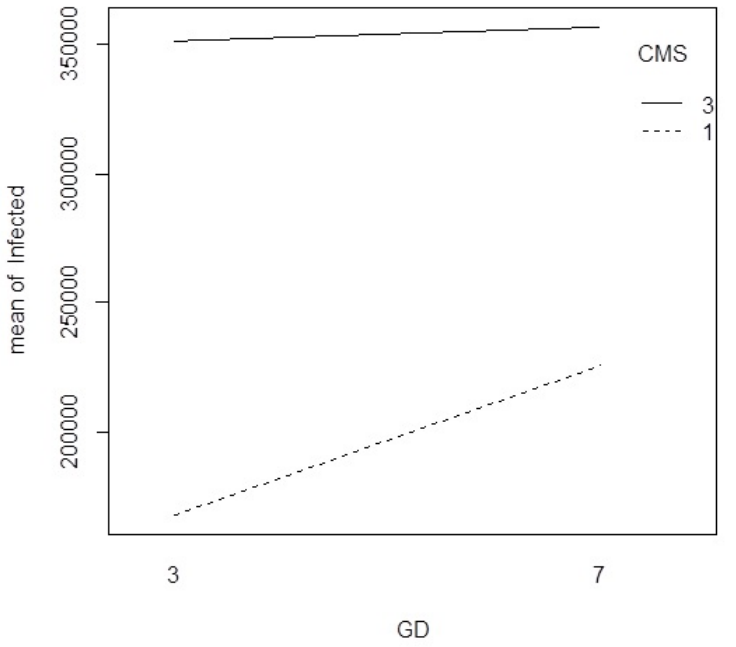
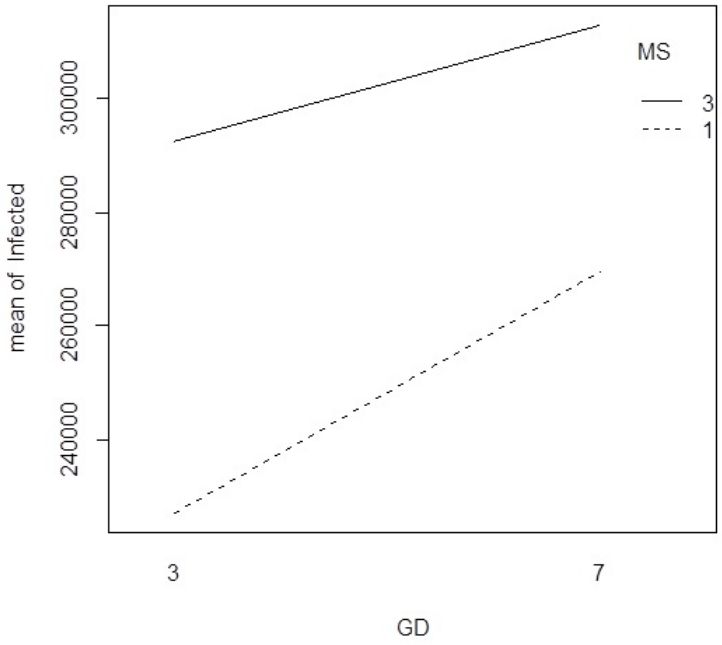


Figure 18: (Continued)



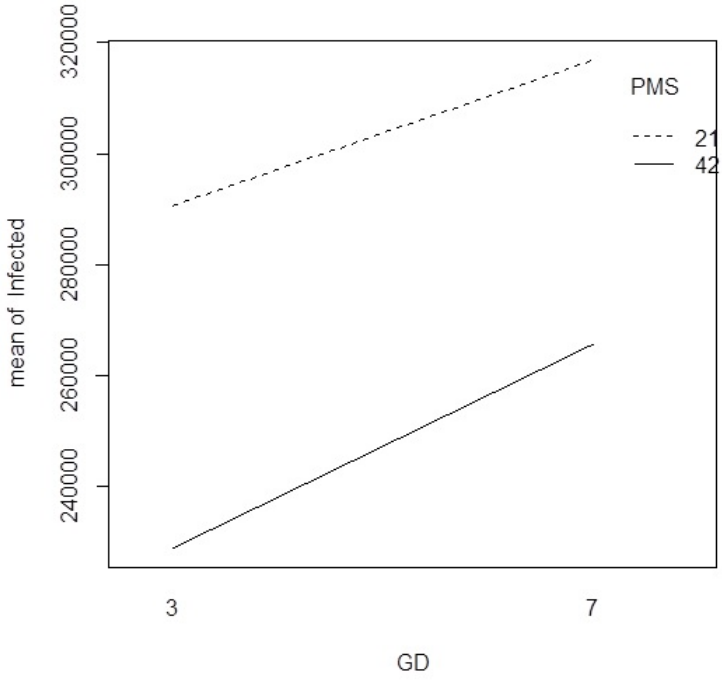
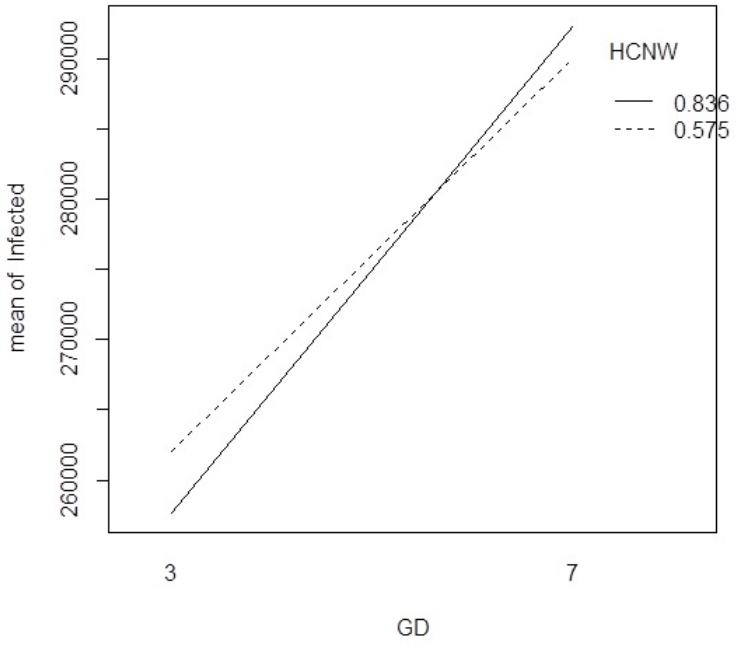


Figure 18: (Continued)



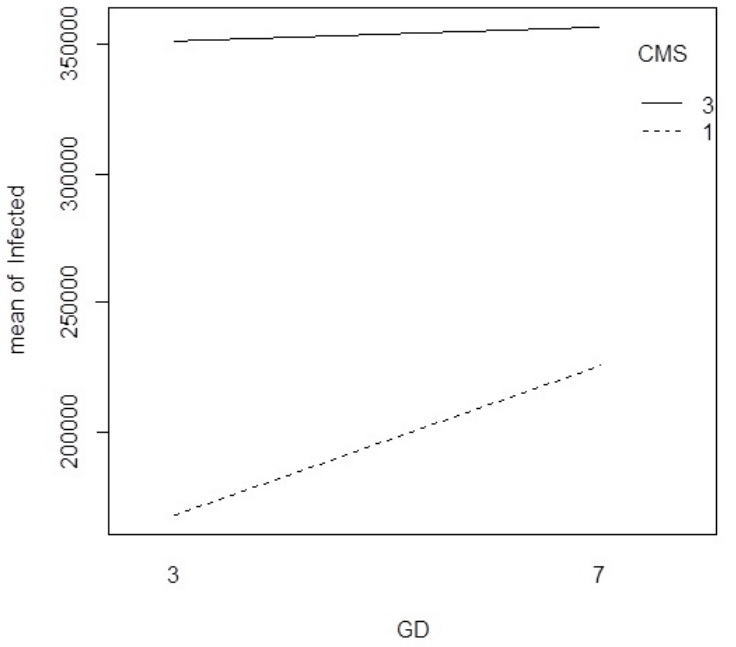
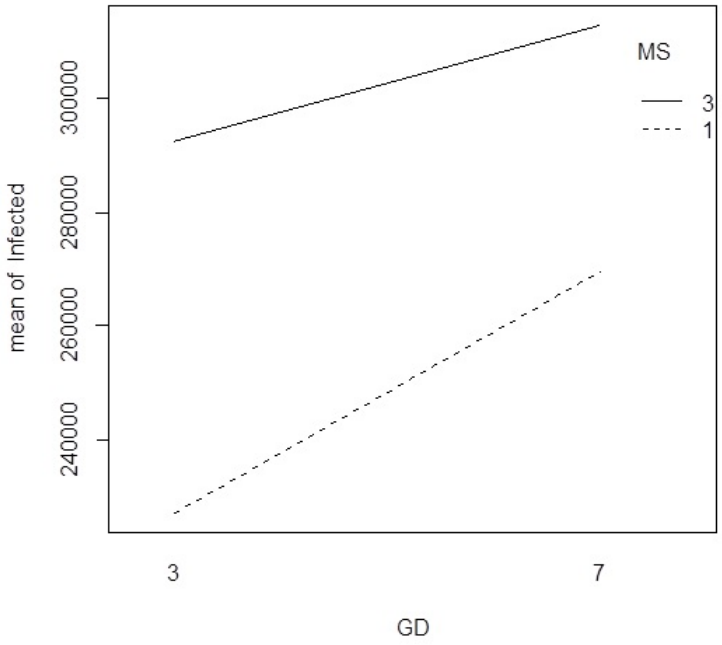


Figure 18: (Continued)



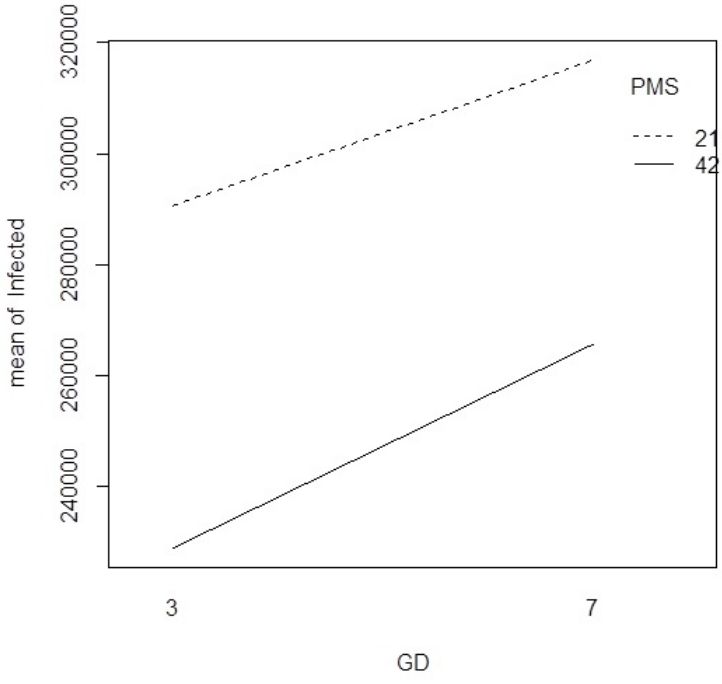
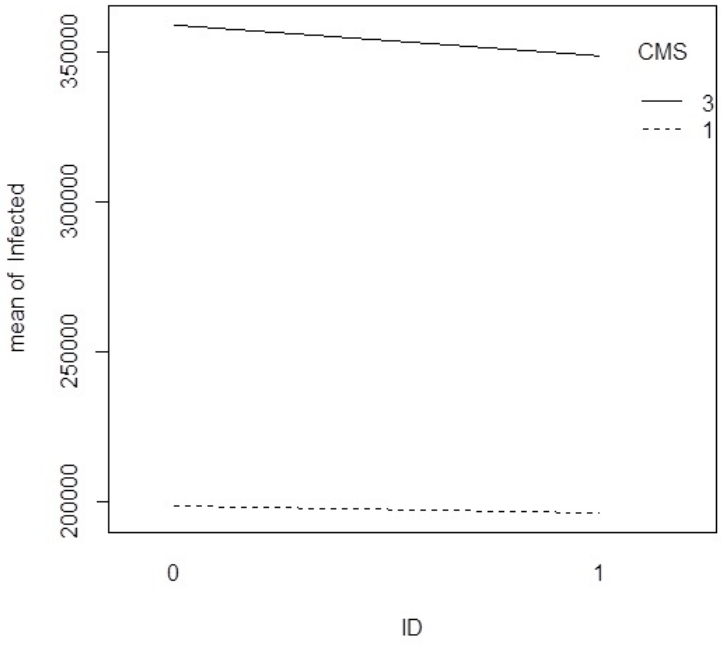


Figure 18: (Continued)



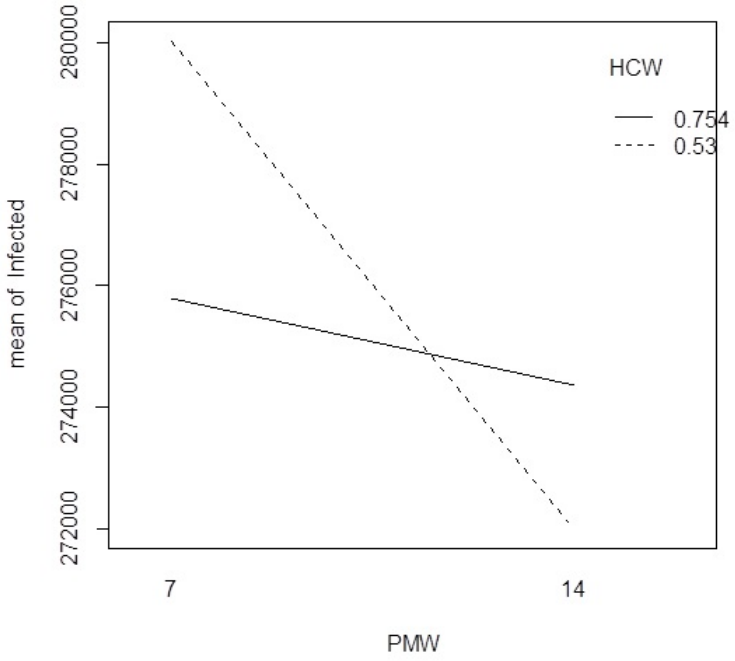
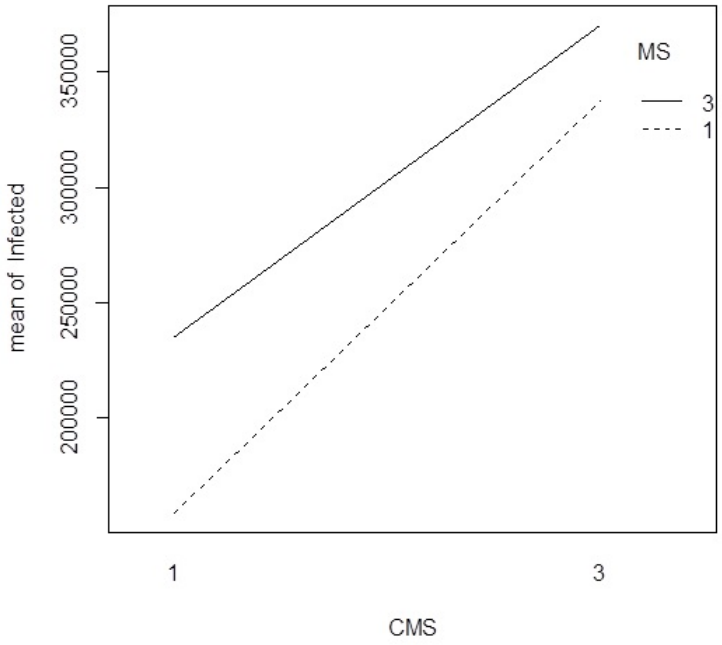


Figure 18: (Continued)



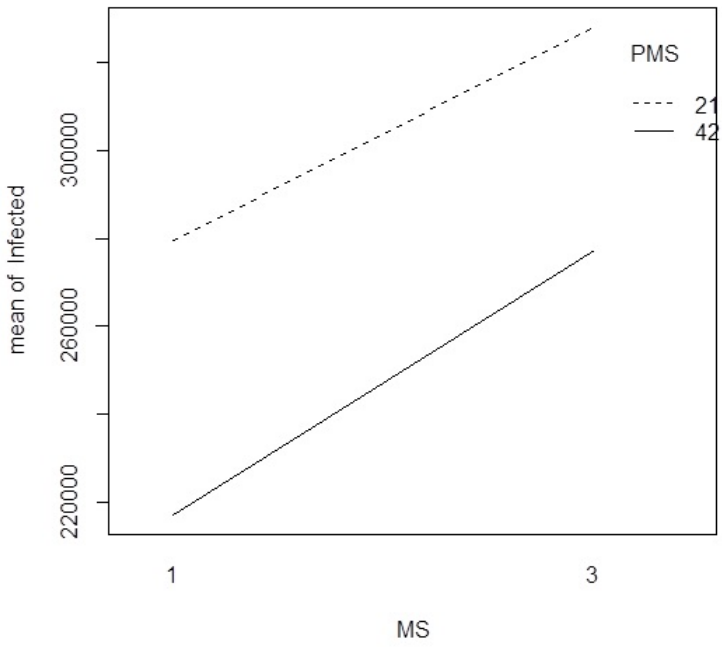
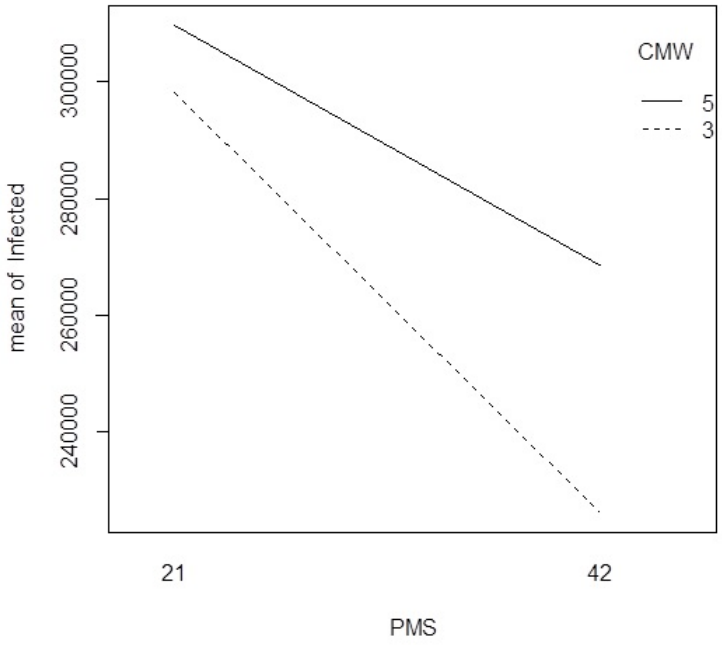
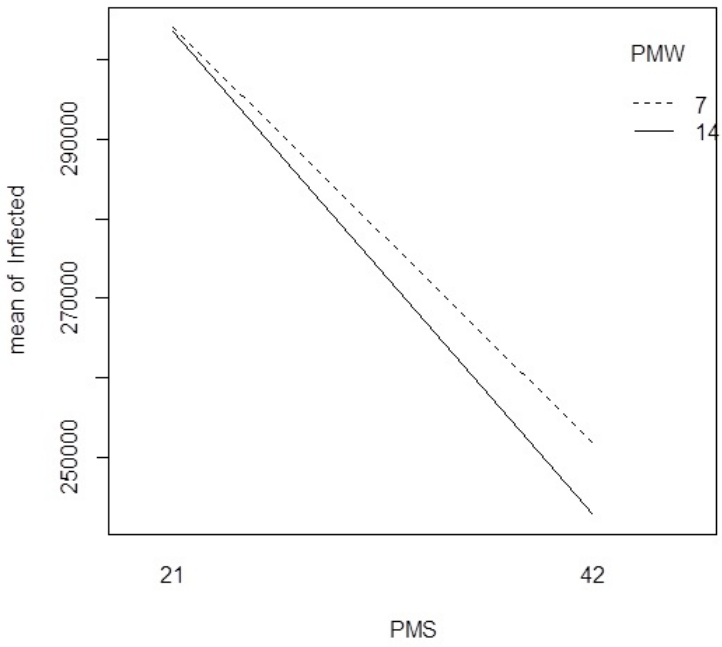


Figure 18: (Continued)





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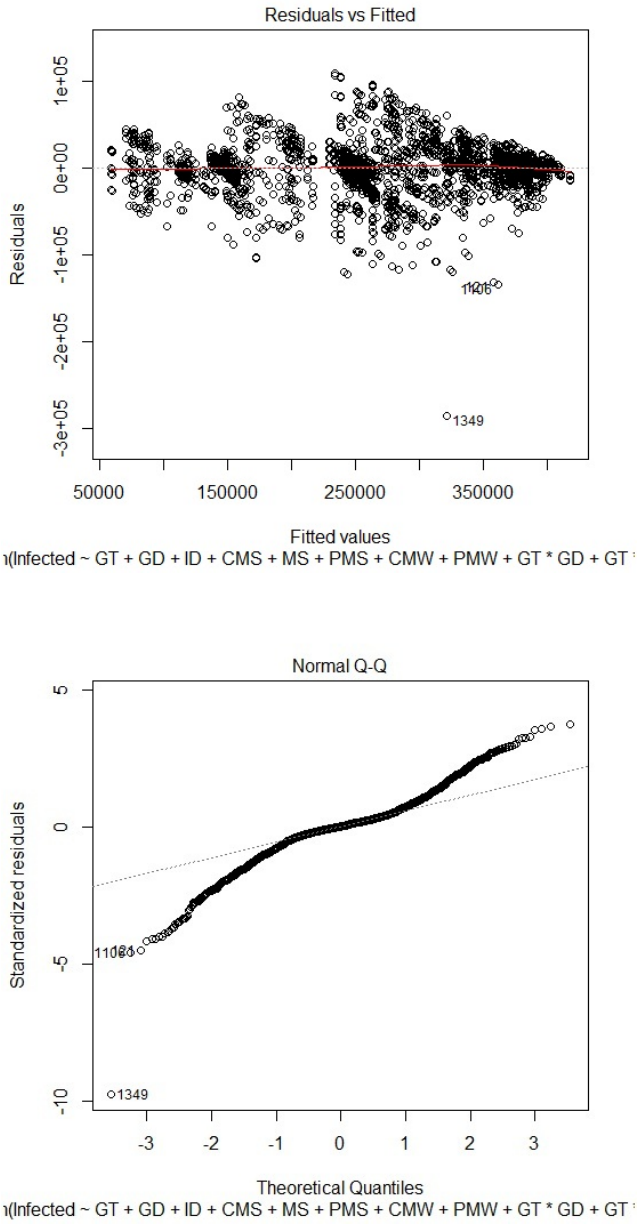


Figure 19: Residuals plot and normal probability plot for the regression analysis for the medium transmissibility scenario for the two-level fractional factorial experiment

Interactions like GT x CMS, GD x MS, GD x CMS, and GT x MS show that for stringent school closure strategies, the most effectiveness is achieved when they start immediately after closing one classroom. When starting closure later with more cases, then an increase in global threshold and deployment delay results in a large increase in the total number of infected.

All these results helps us in understanding the underlying relationships among NPI implementation parameters. It is important to note that is not one or two factors that comprise an optimal strategy but is multiple factors that are embedded in the regression analysis. The regression analysis for the medium transmissibility scenario two-level fractional factorial experiment is shown in Table 31.

Table 31: Regression analysis for the medium transmissibility scenario for the two-level fractional factorial experiment

Factor	Estimate	t value	Pr(>|t|)	Signif.
(Intercept)	-1.26E+05	-1.584	0.11323	
GT	8.60E+03	6.768	1.62E-11	***
GD	-7.16E+03	-2.391	0.016884	*
ID	-3.00E+03	-0.191	0.848263	
CMS	1.14E+05	15.729	< 2e-16	***
MS	7.12E+04	10.33	< 2e-16	***
PMS	-5.22E+03	-7.667	2.51E-14	***
CMW	-1.14E+04	-0.949	0.342628	
PMW	-8.93E+03	-1.549	0.121395	
MW	-2.76E+05	-2.367	0.017985	*
HCNW	-3.57E+04	-2.946	0.003252	**
HCW	-1.77E+05	-1.858	0.063309	.
IP	4.42E+04	10.752	< 2e-16	***
ICW	5.66E+05	9.981	< 2e-16	***
ICNW	2.37E+04	2.062	0.039344	*
HD	-1.13E+04	-0.589	0.555924	
GT:GD	1.08E+03	17.277	< 2e-16	***
GT:CMS	7.11E+02	5.248	1.67E-07	***
GT:MS	-9.20E+01	-0.933	0.350841	
GT:PMS	-1.31E+01	-0.735	0.462349	
GT:CMW	3.89E+02	3.035	0.002429	**
GT:MW	-7.82E+02	-0.802	0.42271	
GD:HCNW	6.36E+03	2.823	0.004795	**
GD:CMS	-4.59E+02	-0.579	0.562333	
GD:MS	-3.06E+03	-3.868	0.000113	***
GD:PMS	-3.63E+01	-0.718	0.472698	
ID:CMS	2.70E+03	0.524	0.600477	
ID:PMS	-5.63E+02	-2.79	0.005314	**
PMW:HCW	1.27E+04	1.476	0.14019	
CMS:MS	-2.51E+04	-13.861	< 2e-16	***
CMS:PMS	-1.26E+02	-2.257	0.024066	*
CMS:MW	1.32E+04	2.251	0.024464	*
CMS:PMW	1.29E+02	0.426	0.67023	
MS:PMS	2.74E+02	4.897	1.03E-06	***
PMS:CMW	9.78E+02	9.685	< 2e-16	***
PMS:PMW	-5.62E+01	-3.51	0.000457	***
CMW:MW	-1.05E+04	-1.777	0.075631	.

Factor	Estimate	t value	Pr(>|t|)	Signif.
GT:ID	5.93E+01	0.184	0.853923	
ID:MW	3.55E+04	1.672	0.094637	.
GT:IP	-1.43E+03	-12.548	< 2e-16	***
GT:ICW	-1.89E+04	-12.481	< 2e-16	***
IP:ICW	-6.92E+04	-10.963	< 2e-16	***
GT:ICNW	-5.86E+02	-1.84	0.065896	.
GT:HD	-5.51E+02	-1.703	0.088649	.
ICNW:HD	-2.83E+04	-1.74	0.082048	.
GT:PMW	1.10E+02	2.85	0.004402	**
PMS:MW	-2.60E+03	-2.572	0.010159	*
CMW:PMW	-1.25E+03	-1.233	0.217648	
ID:CMW	4.19E+03	1.591	0.111694	
CMS:CMW	4.94E+03	5.936	3.32E-09	***
ICW:HD	4.86E+04	2.067	0.038807	*
MS:ICW	5.96E+03	0.802	0.422346	
MS:HD	1.24E+04	1.806	0.071046	.
CMW:HCW	-2.33E+04	-1.401	0.161307	
MW:HCW	5.55E+05	3.341	0.000848	***
PMW:MW	2.94E+04	3.011	0.002629	**
GT:GD:CMS	-3.23E+02	-21.961	< 2e-16	***
GT:GD:MS	-1.09E+02	-7.431	1.47E-13	***
GT:GD:PMS	5.39E+00	3.853	0.00012	***
GT:ID:CMS	1.84E+02	3.121	0.001826	**
GT:ID:PMS	9.69E+00	1.73	0.083765	.
GT:ID:MW	-1.59E+03	-2.697	0.007047	**
GT:IP:ICW	2.23E+03	12.742	< 2e-16	***
GT:ICNW:HD	8.09E+02	1.795	0.072732	.
GT:CMS:MS	1.77E+02	6.003	2.22E-09	***
GT:CMS:PMW	-1.53E+01	-1.822	0.068647	.
GT:PMS:CMW	-8.34E+00	-2.977	0.002939	**
GT:PMS:MW	7.16E+01	2.557	0.010607	*
GT:CMW:PMW	-1.75E+01	-2.084	0.037246	*
GD:CMS:MS	1.80E+03	6.106	1.18E-09	***
ID:CMS:CMW	-3.09E+03	-2.627	0.008671	**
MS:ICW:HD	-2.04E+04	-1.939	0.052593	.
CMW:PMW:HCW	2.81E+03	1.874	0.061045	.
PMW:MW:HCW	-4.94E+04	-3.291	0.001011	**

Table 32: Optimal NPI strategy for the medium transmissibility scenario based on the two-level fractional factorial experiment

Factor	Optimal Value	Factor	Optimal Value	Factor	Optimal Value
GT	10	GD	3	ID	1
IP	7	ICW	0.53	ICNW	0.84
HD	1	HP	7	HCW	0.75
HCNW	0.84	CMS	1	MS	1
PMS	42	CMW	3	MW	0.5
PMW	14				

Table 33: Performance measures for baseline vs. optimal NPI strategy for medium transmissibility scenario based on two-level fractional factorial experiment

Measure	Baseline	NPI	Measure	Baseline	NPI
IAR	50.80%	3.42%	Infections 0-19 yrs.	230,127	17,179
CFR	1.76%	0.11%	Infections 20-64 yrs.	228,753	13,417
Pandemic Duration (Days)	93	84	Infections 65-99 yrs.	55,964	4,065
Total Contacts	1,047,302	67,823	Infections Households	92,217	17,977
Contacts 0-19 yrs.	520,883	40,110	Infect. MG Types(1-2)	168,185	7,588
Contacts 20-64 yrs.	416,307	20,765	Infect. Schools	247,838	8,670
Contacts 65-99 yrs.	110,112	6,948	Infect. MG Types(9-12)	6,604	426
Contacts Households	236,850	39,326	Total Deaths	17,851	1,158
Contacts MG Types(1-2)	392,793	16,587	Deaths 0-19 yrs.	1,090	67
Contacts Schools	403,908	11,134	Deaths 20-64 yrs.	10,681	71
Contacts MG Types(9-12)	13,751	776	Deaths 65-99 yrs.	6,080	656
Total Infections	514,844	34,661			

This model has an R-square value of 91.44%. The graph for residual analysis and the normal probability plot for residuals is shown in Figure 19. As opposed to the low transmissibility scenario, for the medium transmissibility scenario this model does a better job in characterizing the variation in total number of infected across changes in all factors considered. The resulting optimal NPI strategy for a medium transmissibility scenario also improves performance compared to baseline and the non-optimal NPI strategy. The optimal strategy is shown in Table 32. As shown in Table 33 the optimal NPI strategy contains the pandemic achieving an IAR of 3.42%. For this scenario, an optimal NPI strategy can also reduce the duration of pandemic. It also reduces infections, deaths, contacts, and CFR. As shown in Figures 20 through 22 an optimal NPI strategy for a medium transmissibility scenario can reduce infections, deaths, and contacts as well as the peak number of infections, deaths, and contacts. These figures also show that the opening and re-opening of schools and workplaces results in 4 pandemic waves as opposed to one in the baseline.

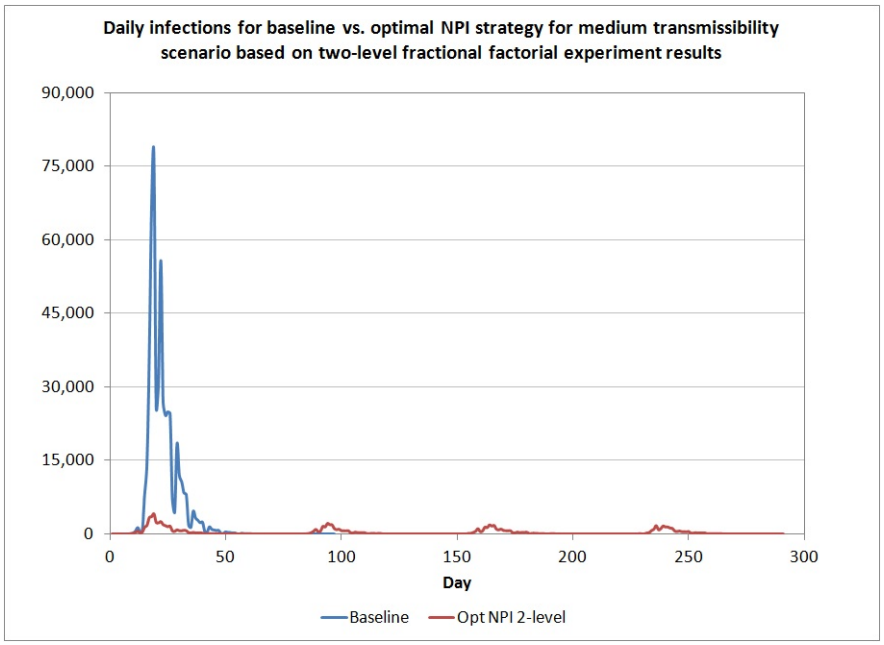


Figure 20: Daily infections for baseline vs. optimal NPI strategy for the medium transmissibility scenario based on the two-level fractional factorial experiment

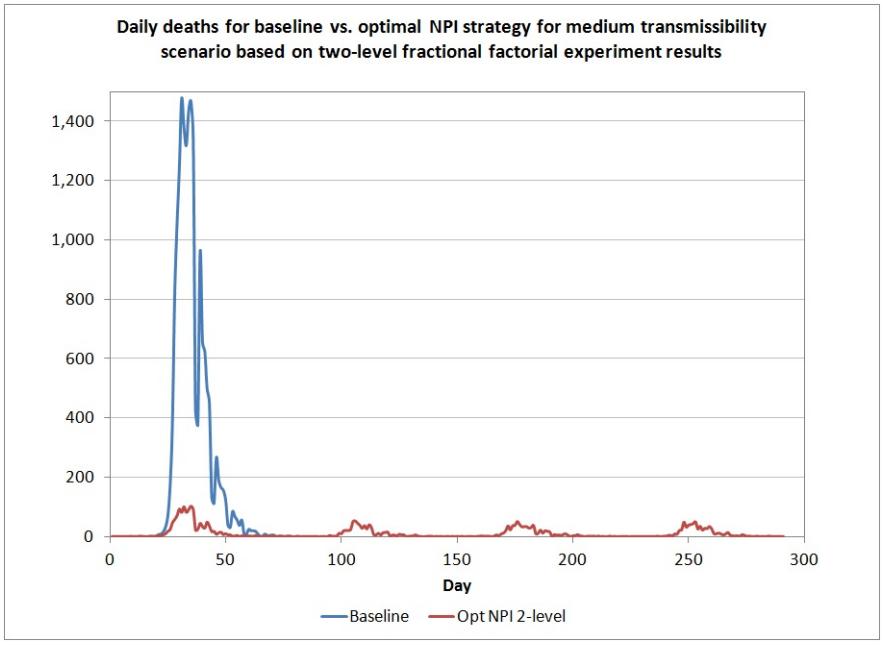


Figure 21: Daily deaths for baseline vs. optimal NPI strategy for the medium transmissibility scenario based on the two-level fractional factorial experiment

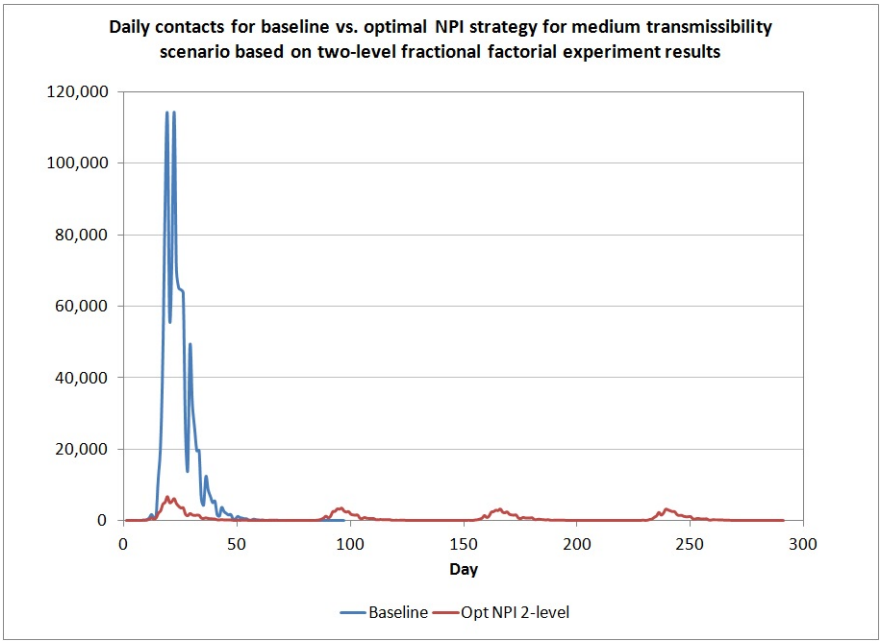


Figure 22: Daily contacts for baseline vs. optimal NPI strategy for the medium transmissibility scenario based on the two-level fractional factorial experiment

6.2.3 High Transmissibility Scenario

The ANOVA table for the two-level fractional factorial experiment for the high transmissibility scenario is shown in Table 34. The level of significance that we used to determine significant factors was 0.01, which are the factors marked with two and three stars in the significance level column. Table 35 shows the main effect factors that resulted to be significant. In this table, the mean number of infected at low and high levels are also presented. Figure 23 shows this graphically.

Table 34: ANOVA table for the high transmissibility scenario for the two-level fractional factorial experiment using total number of infected as the measure of performance

Factor	Df	F value	Pr(>F)	Signif.
GT	1	946.6127	< 2.2e-16	***
GD	1	883.0699	< 2.2e-16	***
ID	1	73.7811	< 2.2e-16	***
CMS	1	34516.8886	< 2.2e-16	***
MS	1	2754.1608	< 2.2e-16	***
PMS	1	842.2516	< 2.2e-16	***
CMW	1	1655.1974	< 2.2e-16	***
MW	1	59.4164	1.83E-14	***
PMW	1	43.5562	5.02E-11	***
HCNW	1	0.133	0.7154135	
IP	1	0.0011	0.973349	
ICW	1	1.0266	0.311057	
HCW	1	0.5622	0.453449	
ICNW	1	0.5654	0.4521614	
HP	1	0.5697	0.4504358	
GT:GD	1	1052.219	< 2.2e-16	***
GT:ID	1	7.1712	0.0074572	**
GT:CMS	1	812.3968	< 2.2e-16	***
GT:MS	1	126.4957	< 2.2e-16	***
GT:PMS	1	11.8848	0.0005754	***
GD:CMS	1	891.6658	< 2.2e-16	***
GD:MS	1	118.4676	< 2.2e-16	***
GD:PMS	1	6.5408	0.0106016	*
GD:CMW	1	5.1854	0.0228626	*
ID:HCNW	1	4.1234	0.0424002	*
ID:CMS	1	10.2784	0.0013631	**
ID:CMW	1	16.4753	5.08E-05	***
IP:ICW	1	5.9649	0.0146629	*
CMS:MS	1	2812.3384	< 2.2e-16	***
CMS:PMS	1	119.3307	< 2.2e-16	***
CMS:CMW	1	14.9355	0.0001141	***
CMS:MW	1	18.7153	1.58E-05	***
MS:PMS	1	53.2201	3.99E-13	***
MS:CMW	1	5.2517	0.0220085	*
MS:MW	1	5.9617	0.0146898	*
MS:PMW	1	5.4621	0.019513	*
PMS:CMW	1	4.9475	0.0262184	*
PMS:PMW	1	5.4952	0.0191475	*
CMW:MW	1	4.1132	0.042657	*
GD:ID	1	6.29	0.0122053	*

Factor	Df	F value	Pr(>F)	Signif.
GT:CMW	1	2.6363	0.1045709	
GT:MW	1	0.9149	0.3389	
GD:MW	1	2.5606	0.1096853	
GT:HCNW	1	0.0805	0.7765846	
ID:MS	1	0.1723	0.6780679	
GT:IP	1	0.0273	0.8687771	
GT:ICW	1	0.0332	0.8553509	
GT:HCW	1	0.0009	0.9759845	
HCNW:HCW	1	1.7132	0.1906965	
IP:ICNW	1	0.3984	0.5279627	
PMS:IP	1	0.1193	0.729853	
PMS:ICNW	1	0.005	0.9438744	
PMW:IP	1	0.0003	0.9854894	
PMW:ICNW	1	0.4016	0.5263379	
HCNW:HP	1	0.5932	0.4412659	
MW:HP	1	0.1786	0.672594	
MW:HCNW	1	0.2255	0.6349356	
CMW:HCW	1	0.0795	0.7780075	
MW:HCW	1	0.3535	0.5522064	
PMW:HCW	1	0.0027	0.9587465	
MW:PMW	1	1.8997	0.1682389	
GT:GD:ID	1	5.3951	0.0202741	*
GT:GD:CMS	1	1152.8086	< 2.2e-16	***
GT:GD:MS	1	107.8217	< 2.2e-16	***
GT:GD:PMS	1	7.9991	0.0047177	**
GT:GD:CMW	1	8.5242	0.0035361	**
GT:GD:MW	1	3.5751	0.0587676	.
GT:ID:HCNW	1	2.9691	0.0849947	.
GT:ID:MS	1	4.8436	0.0278405	*
GT:IP:ICW	1	4.9277	0.0265197	*
GT:HCNW:HCW	1	4.3404	0.0373195	*
GT:CMS:MS	1	118.0914	< 2.2e-16	***
GT:CMS:PMS	1	4.8173	0.0282683	*
GD:CMS:MS	1	126.3484	< 2.2e-16	***
GD:CMS:PMS	1	14.692	0.0001297	***
PMS:IP:ICNW	1	5.038	0.0248853	*
PMW:IP:ICNW	1	3.6827	0.0550956	.
MW:HCNW:HP	1	3.7465	0.0530326	.
CMW:MW:HCW	1	4.3585	0.0369266	*
MW:PMW:HCW	1	18.559	1.71E-05	***
Residuals	2479			

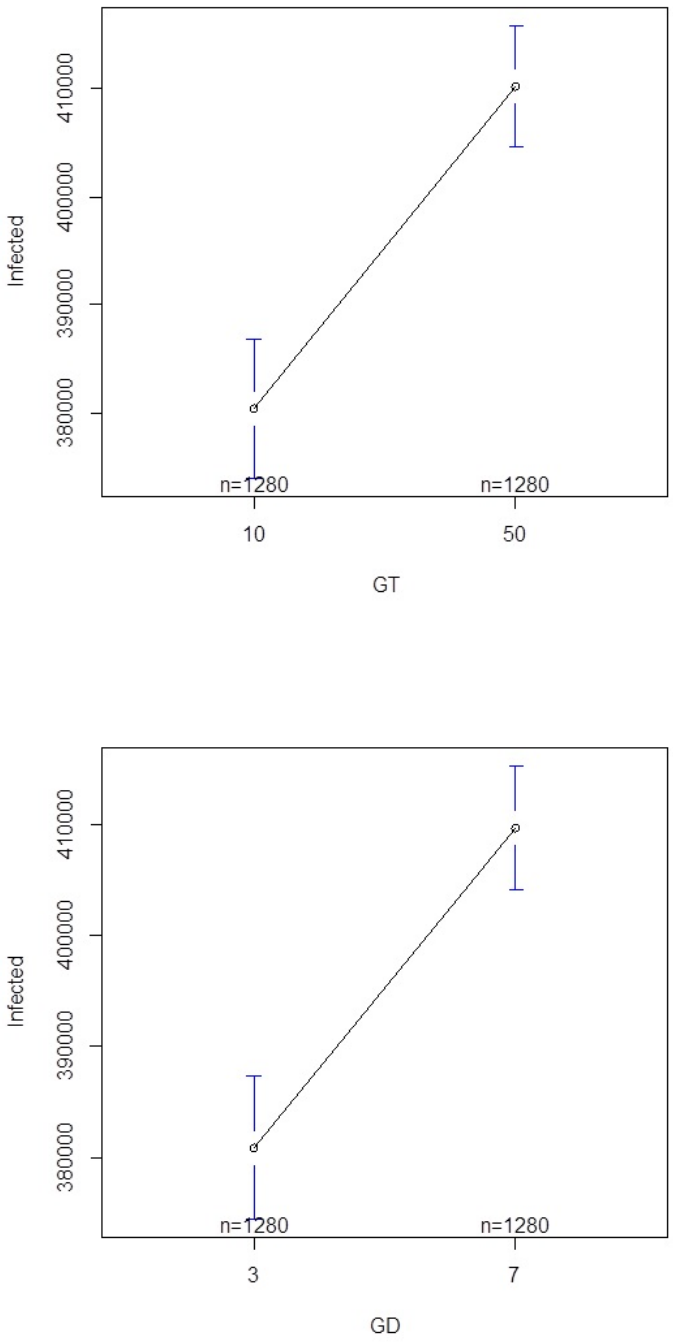
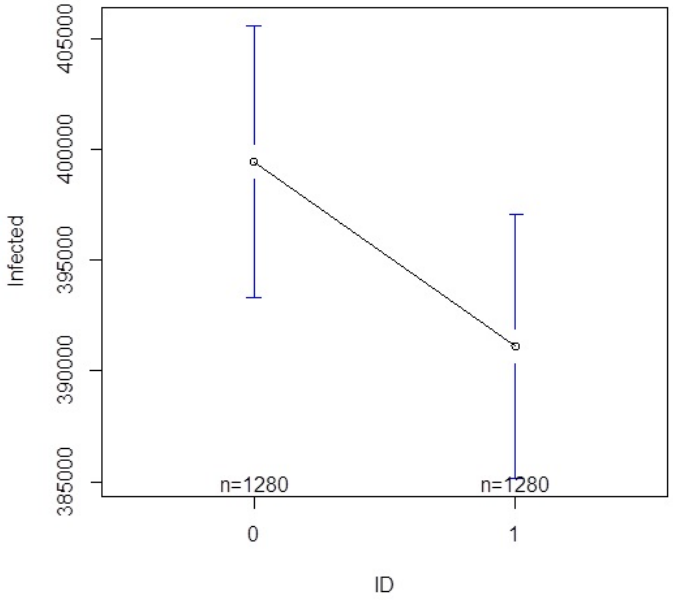


Figure 23: Main factor effects for the high transmissibility scenario for the two-level fractional factorial experiment



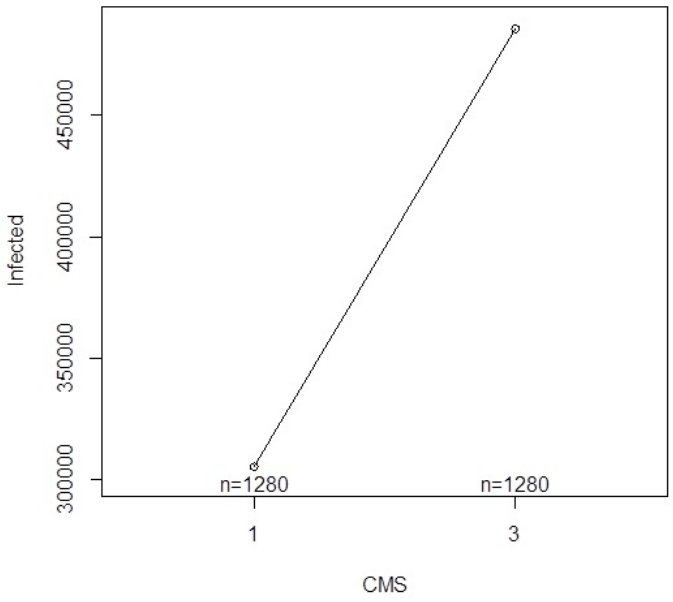
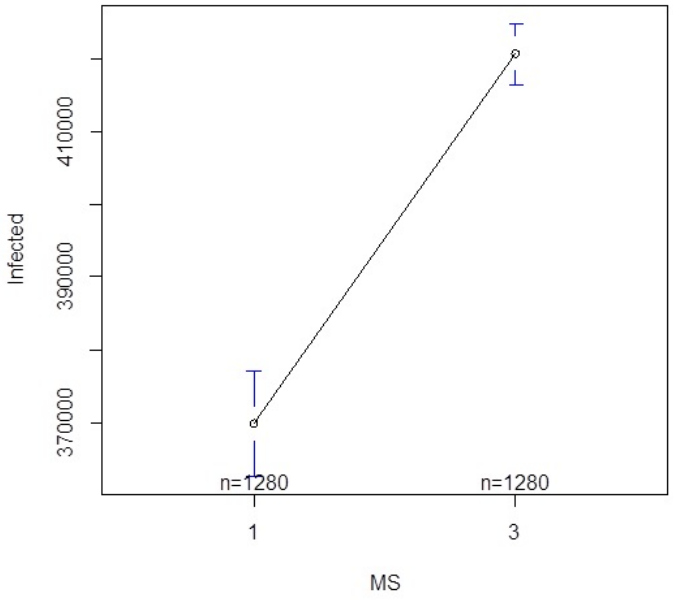
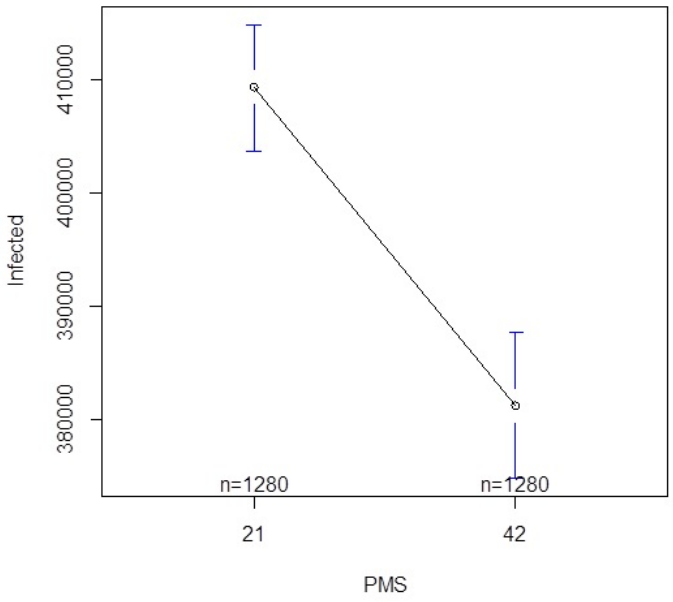


Figure 23: (Continued)





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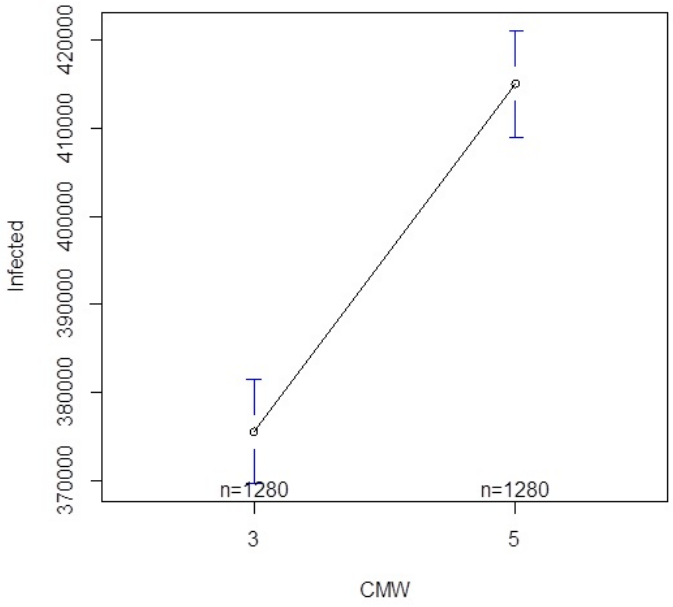

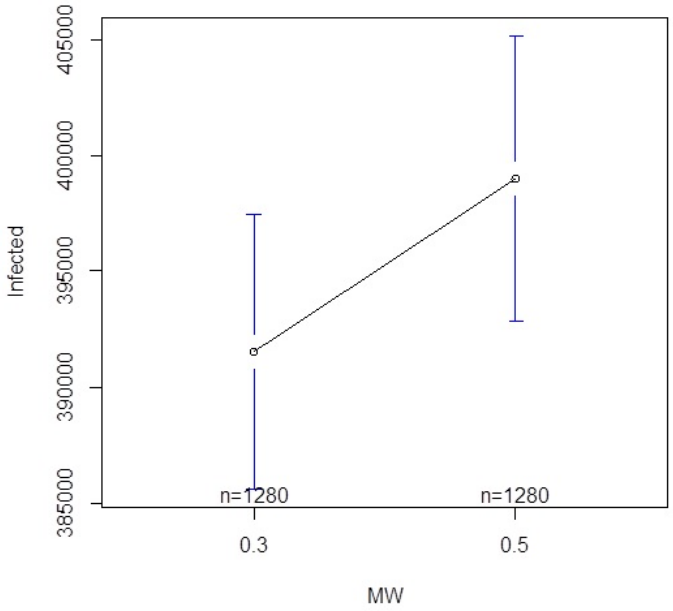

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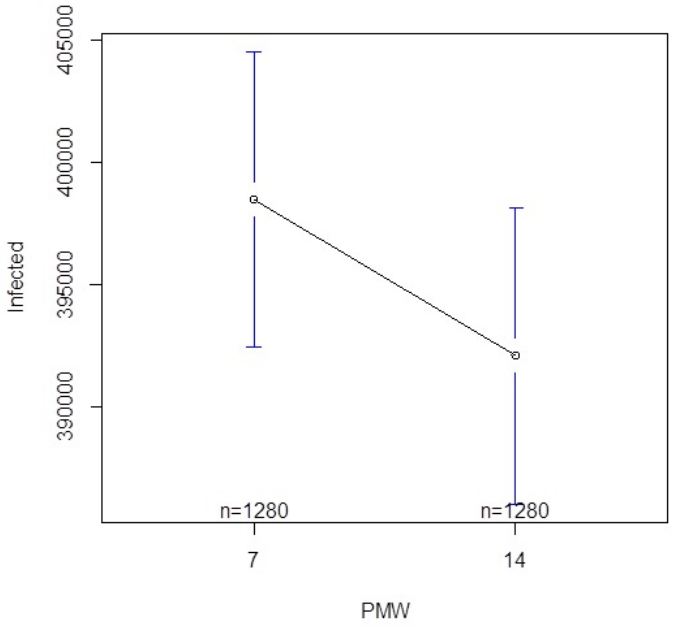


Figure 23: (Continued)

As shown in Figure 23, an increase in the factors global threshold, deployment delay, number of cases to close a department in a workplace, percentage of departments closed to close a workplace, number of classes to close a school, and number of cases to close a classroom result in an increase in the total number of infected. But an increase in the factors of school and workplace closure duration, reduces the total number of infections. The percentage in decrease/increase number of infected is shown in Table 35. In the high transmissibility scenario we also noted that school closure is perhaps the more significant intervention. But the most significant factors of these intervention are the number of cases to close a class. With an increase in the number of cases to close a class from one case to three cases, an increase of 17.7% is observed in the total number of infected. An increase in the number of classes to close a school from 1 to 3 classes results in an increase in the total number of infected by 5%. For the high transmissibility scenario, workplace closure is also a significant factor, an increase in the number of cases to close a department from 3 to 5 cases results in an increase in the total number of infected by 3.87%. This factor was not

as significant for the low and medium transmissibility scenarios. Even though we observed the same behavior with case isolation threshold as in the low and medium transmissibility scenarios, isolating individuals after one day of becoming symptomatic only resulted in a 0.82% reduction in the total number of infected.

Table 35: Significant main effects observations using the number of infected as the measure of performance for the high transmissibility scenario for the two-level fractional factorial experiment

Factor	**Low level**	**High level**	**Observation**
GT	380,431.4	410,133.1	An increase in the number of cases to declare pandemic from 10 to 50 cases results in an increase of 2.93% in total number of infected.
GD	380,938.5	409,626	An increase in deployment delay from 3 to 7 days results in an increase of 2.83% in total number of infected.
ID	399,428.3	391,136.2	An increase in case isolation threshold from 0 to 1 day results in a decrease of 0.82% in total number of infected.
CMS	305,605.2	484,959.3	An increase in the number of cases to close a school from 1 to 3 cases results in an increase of 17.70% in total number of infected.
MS	369,950.8	420,613.7	An increase in the number of classes to close a school from 1 to 3 classes results in an increase of 5% in total number of infected.
PMS	409,290.6	381,273.9	An increase in school closure duration from 21 to 42 days results in a decrease of 2.76% in total number of infected.
CMW	375,644.5	414,919.9	An increase in the number of cases to close a department from 3 to 5 cases results in an increase of 3.87% in total number of infected.
MW	391,561.6	399,002.9	An increase in the percentage of departments to close a workplace from 30% to 50% results in an increase of 0.73% in total number of infected.
PMW	398,467.8	392,096.6	An increase in workplace closure duration from 7 to 14 days results in a decrease of 0.63% in total number of infected.

Table 36: Significant interactions observations for the high transmissibility scenario for the two-level fractional factorial design

Interaction	**Low, Low**	**High, Low**	**Low, High**	**High, High**
GT x GD	381,745	380,132	379,117.8	440,134.2
GT x ID	385,870	412,986.6	374,992.7	407,279.6
GT x CMS	276,996.5	334,213.9	483,866.2	486,052.3
GT x MS	349,671.1	390,230.4	411,191.6	430,035.8
GT x PMS	396,103.7	422,477.4	364,759	397,788.8
GD x CMS	276,848	334,362.4	485,028.9	484,889.6
GD x MS	350,353.3	389,548.2	411,523.6	429,703.7
ID x CMS	308,203.8	303,006.6	490,652.8	479,265.7
ID x CMW	377,831.4	373,457.7	421,025.2	408,814.6
CMS x MS	254,676.1	485,225.4	356,534.2	484,693.1
CMS x PMS	324,886.3	493,694.8	286,324.1	476,223.7
CMS x CMW	287,832.9	463,456.2	323,377.5	506,462.4
CMS x MW	303,972.7	479,150.5	307,237.7	490,768.1
MS x PMS	387,480.4	431,100.7	352,421.2	410,126.7
Interaction	**Interpretation**			
GT x GD	When deployment delay is three days, an increase in cases to declare pandemic from 10 to 50 cases results in a decrease in total number of infected by 0.16%. When deployment delay is seven days, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 6.02%.			
GT x ID	When case isolation threshold is zero, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 2.68%. When case isolation threshold is one, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 3.19%.			
GT x CMS	When number of cases to close a class is one, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 5.65%. When number of cases to close a class is three, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 0.22%.			
GT x MS	When number of classes to close a school is one, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 4%. When number of classes to close a school is three, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 1.86%.			
GT x PMS	When school closure duration is 21 days, an increase in cases to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 2.60%. When school closure duration is 42 days, an increase in cases			

Table 36 (Continued)

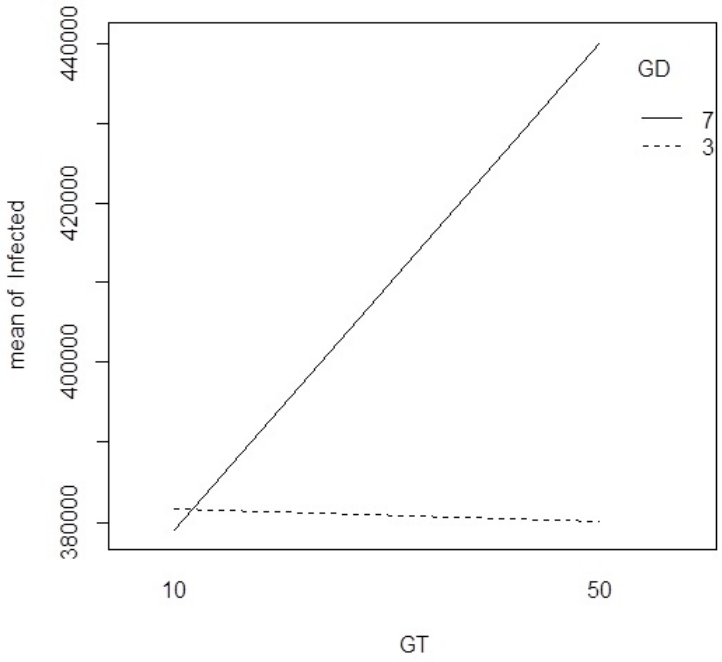
	to declare pandemic from 10 to 50 cases results in an increase in total number of infected by 3.26%.
GD x CMS	When cases to close a class is 1, an increase in deployment delay from 3 to 7 days results in an increase in total number of infected by 5.67%. When cases to close a class is 3, an increase in deployment delay from 3 to 7 days results in a decrease in total number of infected by 0.01%.
GD x MS	When number of classes to close a school is 1, an increase in deployment delay from 3 to 7 days results in an increase in total number of infected by 3.87%. When number of classes to close a school is 3, an increase in deployment delay from 3 to 7 days results in an increase in total number of infected by 1.79%.
ID x CMS	When number of cases to close a school is one, an increase in case isolation threshold from 0 to 1 day results in a decrease in total number of infected by 0.51%. When number of cases to close a school Is three,an increase in case isolation threshold from 0 to 1 day results in a decrease in total number of infected by 1.12%.
ID x CMW	When number of cases to close a department is three, an increase in case isolation threshold from 0 to 1 day results in a decrease in total number of infected by 0.43%. When number of cases to close a department is five, an increase in case isolation threshold from 0 to 1 day results in a decrease in total number of infected by 1.20%.
CMS x MS	When total number of classes to close a school is one, an increase in the number of cases to close a school from 1 to 3 cases results in an increase in total number of infected by 22.75%. When total number of classes to close a school is 3, an increase in the total number of cases to close a school from 1 to 3 cases results in an increase in total number of infected by 12.64%.
CMS x PMS	When school closure duration is 21 days, an increase in cases to close a class from 1 to 3 cases results in an increase in total number of infected by 16.66%. When school closure duration is 42 days, an increase in cases to close a class from 1 to 3 cases results in an increase in total number of infected by 18.74%.
CMS x CMW	When classes to close a school is 3 classes, an increase in cases to close a class from 1 to 3 cases results in an increase in total number of infected by 17.33%. When classes to close a school is 5 classes, an increase in cases to close a class from 1 to 3 cases results in an increase in total number of infected by 18.06%.
CMS x MW	When percentage of departments to close a workplace is 30%, an

Table 36 (Continued)

	increase in number of cases to close a class from 1 to 3 cases results in an increase in total number of infected by 17.28%. When percentage of department to close a workplace is 50%, an increase in number of cases to close a class from 1 to 3 cases results in an increase in total number of infected by 18.11%.
MS x PMS	When school closure duration is 21 days, an increase in number of classes to close a school from 1 to 3 classes results in an increase in total number of infected by 4.30%. When school closure duration is 42 days, an increase in number of classes to close a school from 1 to 3 classes results in an increase in total number of infected by 5.69%.

Table 36 shows all significant interactions for high transmissibility scenario for the two-level fractional factorial experiment. Figure 24 show the graphs for these significant interactions. As with the medium transmissibility scenario the interaction of global threshold with deployment delay shows that for a short deployment delay, an increase in the number of cases to declare pandemic does not have a significant impact on total number of infections. However, as the deployment delay increases to seven days, then an increase in global threshold from 10 to 50 cases results in an increase of 6.02% in total number of infections. This particular result shows the importance of surveillance and preparedness. When interventions are not prepared to be deployed soon after pandemic declaration in a region, then pandemic declaration should happen with a minimal number of cases to ensure a better NPI effectiveness.

Interactions like GT x CMS, GT x MS, GD x CMS, and GD x MS show that for stringent school closure strategies, the most effectiveness is achieved when they start immediately after closing one classroom. When starting closure later with more cases, then an increase in global threshold and deployment delay results in a large increase in the total number of infected. All these results helps us in understanding the underlying relationships among NPI implementation parameters. It is important to note that is not one or two factors that comprise an optimal strategy but is multiple factors that are embedded in the regression analysis.



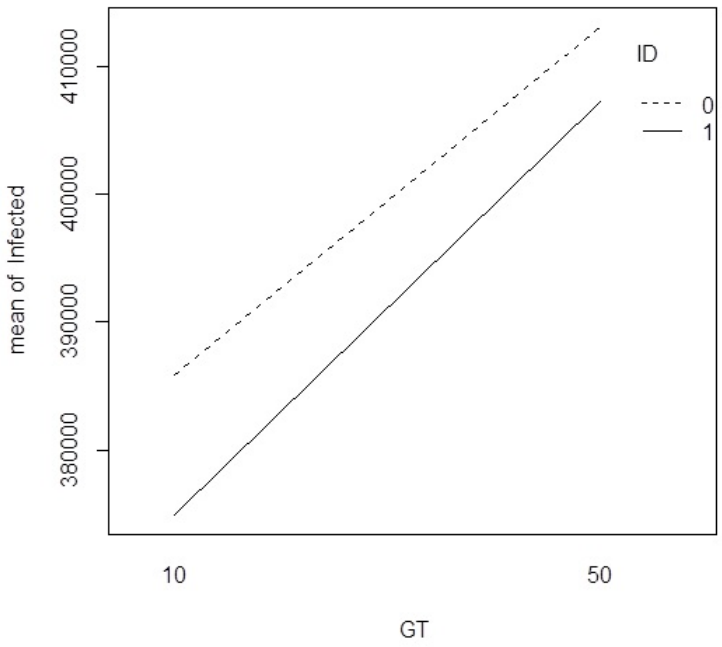
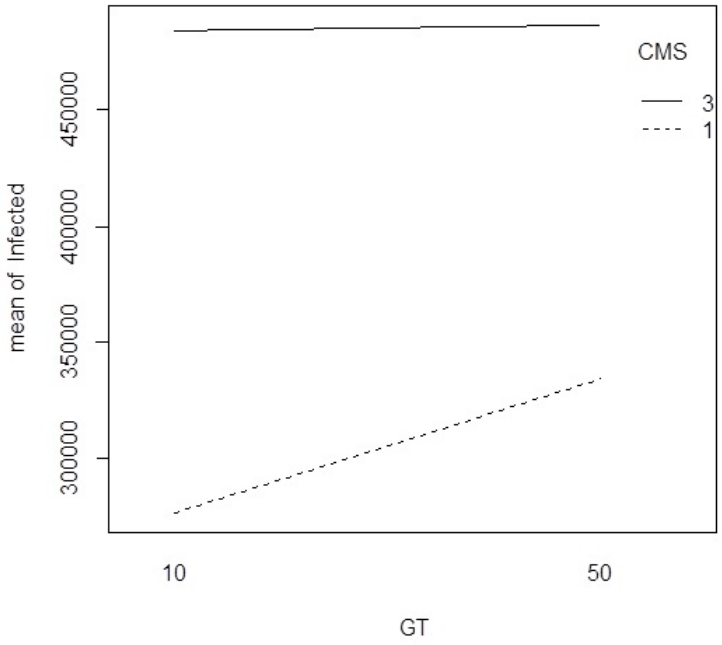
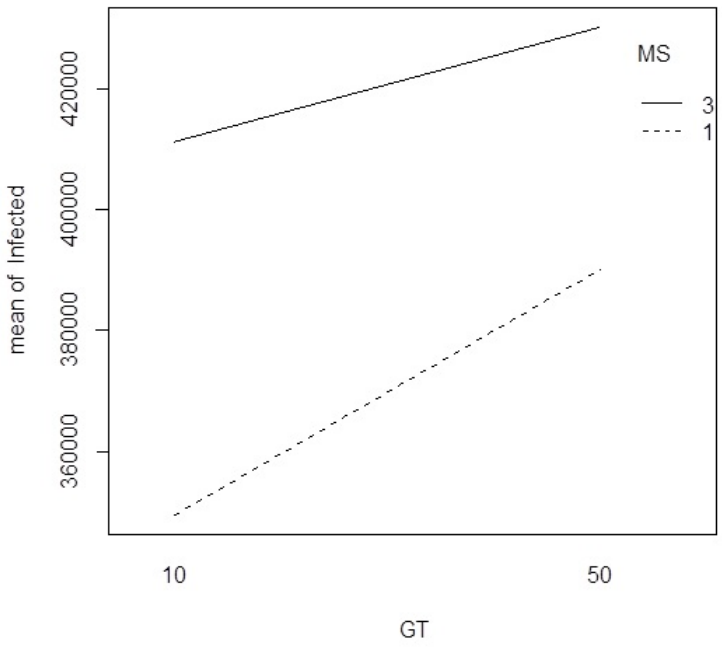


Figure 24: Interaction effects for the high transmissibility scenario for the two-level fractional factorial experiment





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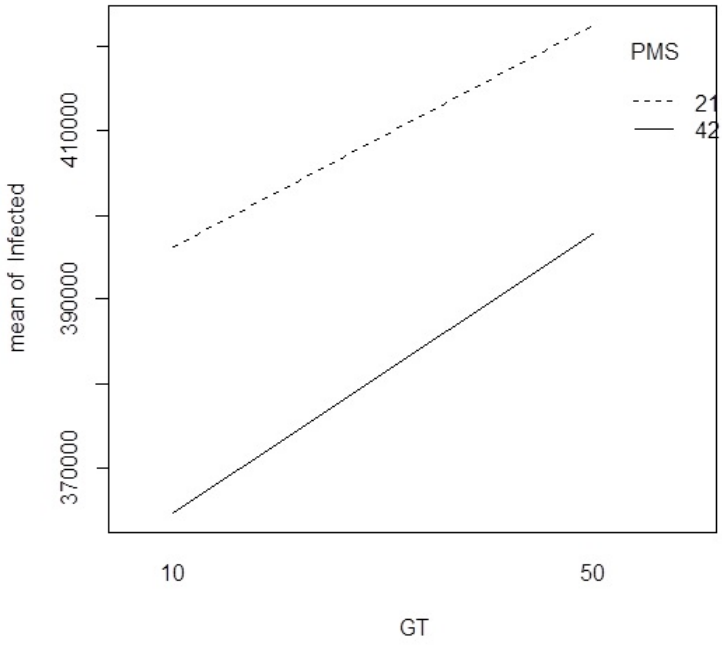

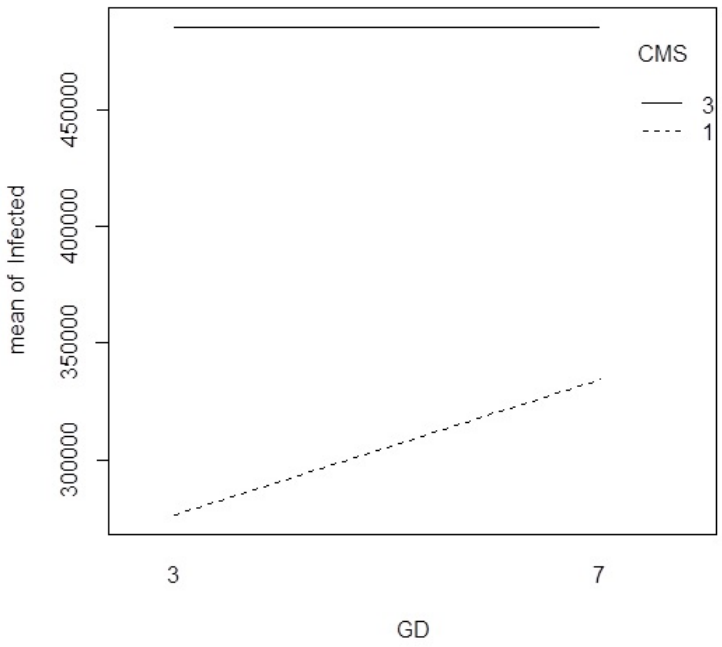

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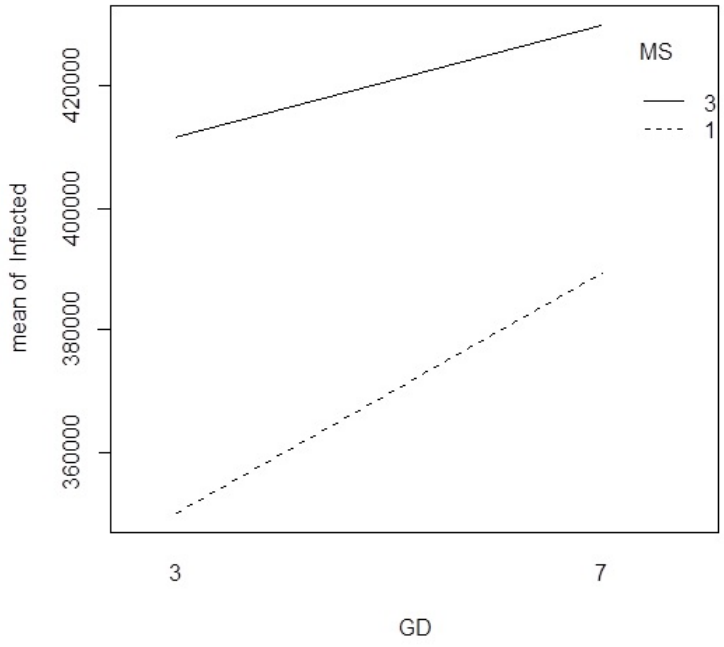

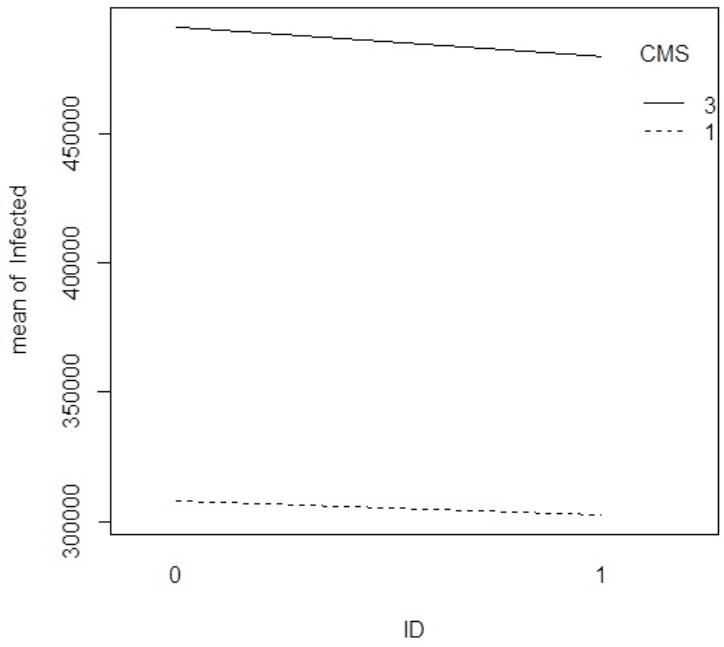

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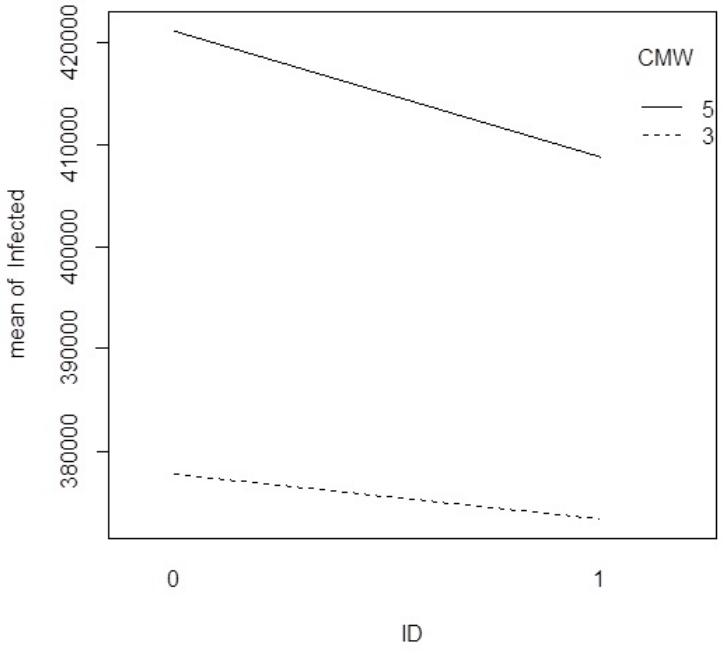


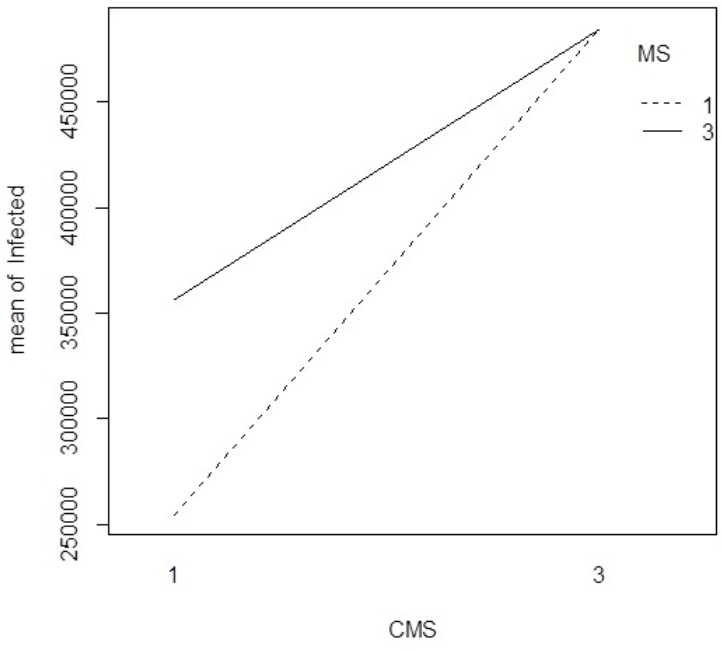
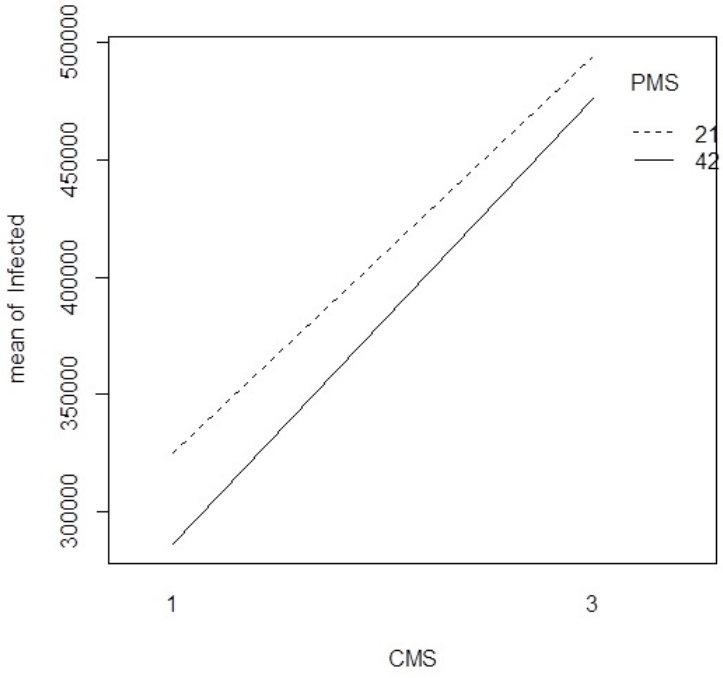


Figure 24: (Continued)



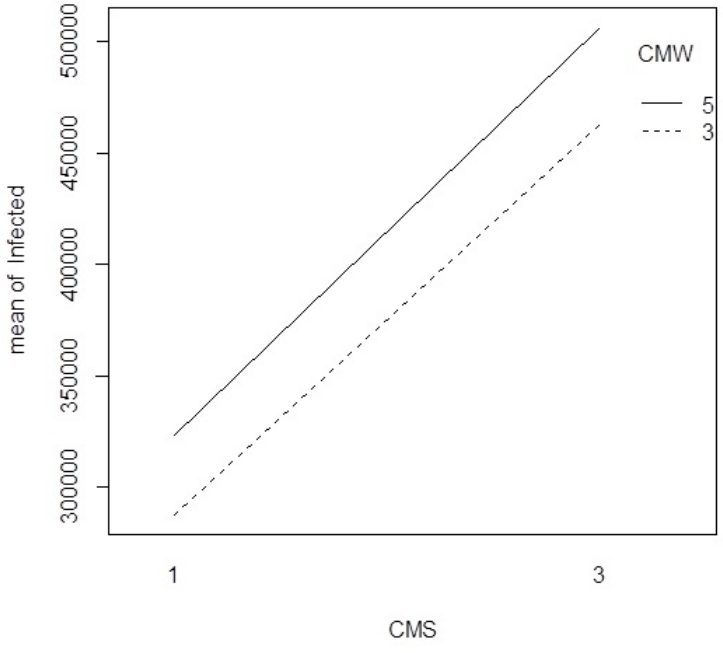
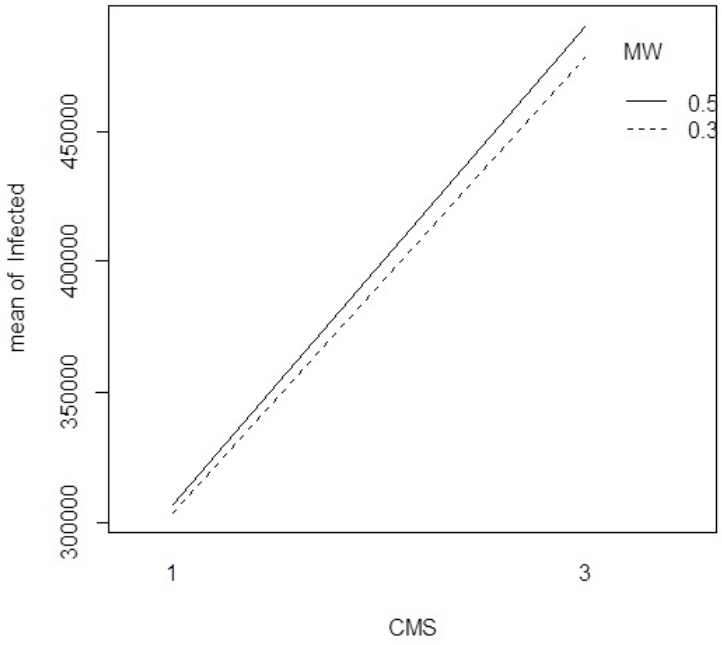


Figure 24: (Continued)



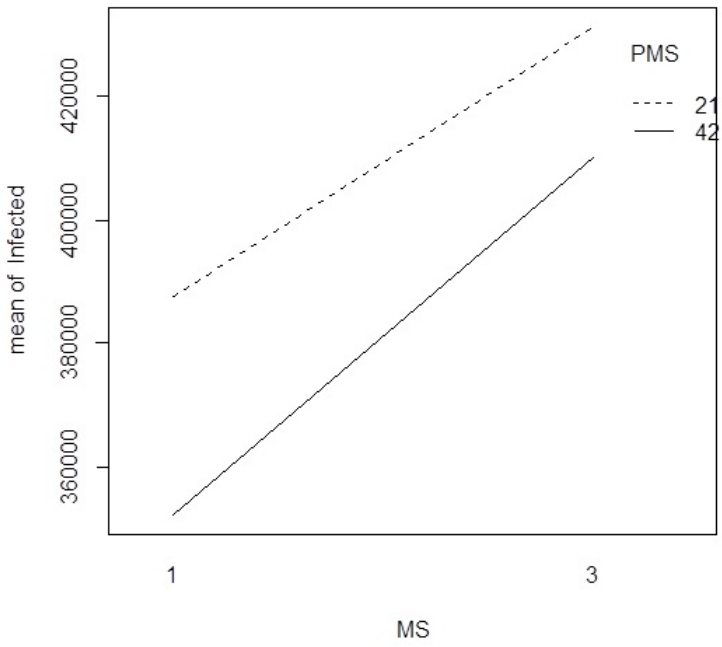


Figure 24: (Continued)

The regression analysis for the high transmissibility scenario for the two-level fractional factorial experiment is shown in Table 37.

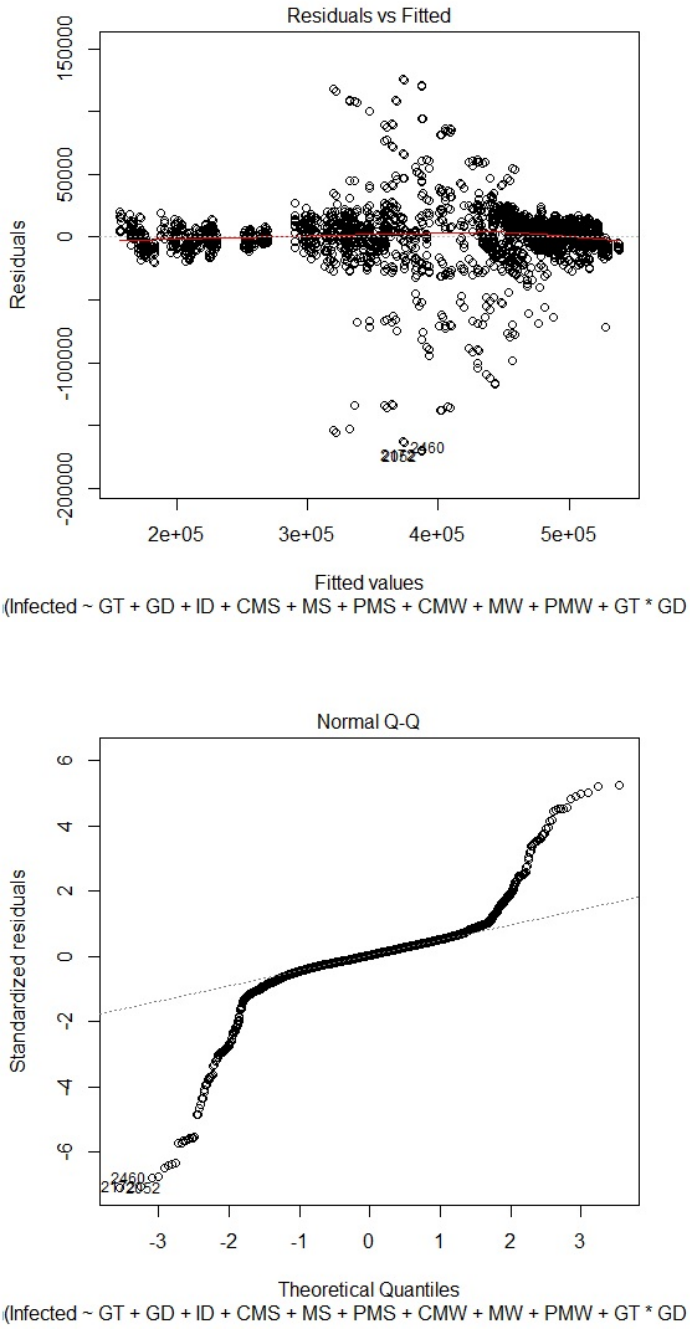


Figure 25: Residuals plot and normal probability plot for the regression analysis of the high transmissibility scenario for the two-level fractional factorial experiment

Table 37: Regression analysis the for high transmissibility scenario for the two-level fractional factorial experiment

Factor	Estimate	t value	Pr(>|t|)	Signif.
(Intercept)	-2.26E+05	-1.911	0.056168	.
GT	-2.77E+03	-2.25	0.02455	*
GD	-7.03E+03	-1.973	0.048619	*
ID	7.77E+03	0.653	0.513536	
CMS	1.30E+05	20.105	< 2e-16	***
MS	1.04E+05	20.062	< 2e-16	***
PMS	-1.23E+03	-0.813	0.416259	
CMW	-4.62E+03	-0.385	0.700117	
MW	3.96E+05	1.878	0.060529	.
PMW	2.22E+04	4.039	5.52E-05	***
HCNW	2.26E+05	2.349	0.018895	*
IP	9.60E+03	1.141	0.253897	
ICW	-1.44E+05	-3.224	0.001279	**
HCW	1.20E+05	1.194	0.232683	
ICNW	2.54E+05	2.734	0.006309	**
HP	1.40E+04	1.922	0.054686	.
GT:GD	1.10E+03	12.751	< 2e-16	***
GT:ID	-3.88E+02	-1.264	0.206298	
GT:CMS	9.95E+02	9.162	< 2e-16	***
GT:MS	-1.16E+02	-1.377	0.168515	
GT:PMS	1.76E+00	0.229	0.819275	
GD:CMS	2.43E+03	2.502	0.012405	*
GD:MS	-4.29E+03	-6.607	4.79E-11	***
GD:PMS	1.38E+02	2.221	0.026418	*
GD:CMW	-5.07E+02	-1.166	0.243668	
ID:HCNW	-4.10E+03	-0.307	0.758623	
ID:CMS	-3.10E+03	-3.206	0.001363	**
ID:CMW	-3.92E+03	-4.059	5.08E-05	***
IP:ICW	1.66E+04	3.202	0.001383	**
CMS:MS	-4.70E+04	-31.611	< 2e-16	***
CMS:PMS	1.09E+03	7.721	1.66E-14	***
CMS:CMW	1.87E+03	3.865	0.000114	***
CMS:MW	2.09E+04	4.326	1.58E-05	***
MS:PMS	3.35E+02	7.295	3.99E-13	***
MS:CMW	1.11E+03	2.292	0.022008	*
MS:MW	1.18E+04	2.442	0.01469	*
MS:PMW	-3.22E+02	-2.337	0.019513	*
PMS:CMW	1.02E+02	2.224	0.026218	*
PMS:PMW	-3.08E+01	-2.344	0.019148	*
CMW:MW	4.80E+04	1.708	0.087744	.
GD:ID	-4.71E+02	-0.541	5.88E-01	

Factor	Estimate	t value	Pr(>|t|)	Signif.
GT:CMW	-1.37E+02	-2.108	0.03515	*
GT:MW	-9.10E+02	-1.4	0.161543	
GD:MW	-2.98E+03	-0.686	0.493018	
GT:HCNW	-2.48E+03	-2.267	0.023506	*
ID:MS	3.59E+03	2.061	0.039361	*
GT:IP	2.07E+02	2.215	0.026836	*
GT:ICW	2.67E+03	2.154	0.031306	*
GT:HCW	-2.42E+03	-2.043	0.041144	*
HCNW:HCW	-6.00E+04	-1.007	0.313824	
IP:ICNW	-2.92E+04	-2.721	0.006559	**
PMS:IP	-3.61E+02	-2.144	0.032107	*
PMS:ICNW	-4.51E+03	-2.223	0.026331	*
PMW:IP	-9.56E+02	-1.89	0.058831	.
PMW:ICNW	-1.22E+04	-2	0.045614	*
HCNW:HP	-2.10E+04	-2.065	0.039066	*
MW:HP	-3.23E+04	-1.826	0.067907	.
MW:HCNW	-4.23E+05	-1.989	0.04685	*
CMW:HCW	3.48E+04	1.957	0.050461	.
MW:HCW	-1.72E+05	-0.78	0.435294	
PMW:HCW	-2.13E+04	-4.192	2.86E-05	***
MW:PMW	-3.22E+04	-4.007	6.33E-05	***
GT:GD:ID	5.61E+01	2.323	0.020274	*
GT:GD:CMS	-4.10E+02	-33.953	< 2e-16	***
GT:GD:MS	-1.25E+02	-10.384	< 2e-16	***
GT:GD:PMS	3.25E+00	2.828	0.004718	**
GT:GD:CMW	3.52E+01	2.92	0.003536	**
GT:GD:MW	2.28E+02	1.891	0.058768	.
GT:ID:HCNW	6.37E+02	1.723	0.084995	.
GT:ID:MS	-1.06E+02	-2.201	0.027841	*
GT:IP:ICW	-3.19E+02	-2.22	0.02652	*
GT:HCNW:HCW	3.44E+03	2.083	0.03732	*
GT:CMS:MS	2.62E+02	10.867	< 2e-16	***
GT:CMS:PMS	-5.05E+00	-2.195	0.028268	*
GD:CMS:MS	2.71E+03	11.24	< 2e-16	***
GD:CMS:PMS	-8.81E+01	-3.833	0.00013	***
PMS:IP:ICNW	5.27E+02	2.245	0.024885	*
PMW:IP:ICNW	1.35E+03	1.919	0.055096	.
MW:HCNW:HP	4.77E+04	1.936	0.053033	.
CMW:MW:HCW	-9.00E+04	-2.088	0.036927	*
MW:PMW:HCW	5.31E+04	4.308	1.71E-05	***

Table 38: Optimal NPI strategy for the high transmissibility scenario based on the two-level fractional factorial experiment

Factor	**Optimal Value**	**Factor**	**Optimal Value**	**Factor**	**Optimal Value**
GT	10	GD	3	ID	1
IP	7	ICW	0.75	ICNW	0.84
HD	1	HP	7	HCW	0.75
HCNW	0.57	CMS	1	MS	1
PMS	42	CMW	3	MW	0.3
PMW	14				

This model has an R-square value of 95.08%. The graph for the residuals analysis and the normal probability plot for residuals is shown in Figure 25. As with the medium transmissibility scenario regression model, this model does a better job than the model obtained for the medium transmissibility scenario in characterizing the variation in total number of infected across changes in all the factors considered. The resulting optimal NPI strategy for a high transmissibility scenario also improves performance compared to baseline and the non-optimal NPI strategy. The optimal strategy is shown in Table 38.

As shown in Table 39, even though the optimal NPI strategy proves effective in reducing infections, deaths and contacts it didn't contain the pandemic. However, a significant reduction from 64.53% to 16.97% IN IAR was achieved with the optimal NPI strategy. Also, for a high transmissibility scenario, NPIs extend pandemic duration. It extended the pandemic from 83 days for baseline to 350 days for the optimal NPI strategy. In such an scenario, a combination of NPIs with PHIs may be the best combination for reducing pandemic duration and further reducing IAR below 10%.

Table 39: Performance measures for baseline vs. optimal NPI strategy for the high transmissibility scenario based on the two-level fractional factorial experiment

Measure	Baseline	NPI	Measure	Baseline	NPI
IAR	64.53%	16.97%	Infections 0-19 yrs.	229,952	59,476
CFR	2.55%	0.67%	Infections 20-64 yrs.	344,381	88,524
Pandemic Duration (Days)	83	350	Infections 65-99 yrs.	79,718	24,017
Total Contacts	1,063,751	254,011	Infections Households	136,127	86,210
Contacts 0-19 yrs.	482,881	95,796	Infect. MG Types(1-2)	249,929	62,104
Contacts 20-64 yrs.	468,013	122,215	Infect. Schools	256,796	20,891
Contacts 65-99 yrs.	112,857	36,000	Infect. MG Types(9-12)	11,199	2,812
Contacts Households	234,411	125,456	Total Deaths	25,858	6,837
Contacts MG Types(1-2)	439,368	100,155	Deaths 0-19 yrs.	1,077	294
Contacts Schools	372,678	24,311	Deaths 20-64 yrs.	16,018	4,061
Contacts MG Types(9-12)	17,294	4,089	Deaths 65-99 yrs.	8,763	2,482
Total Infections	654,051	172,017			

As shown in Figures 26 through 28, even though an optimal NPI strategy could not achieve containment, it can significantly reduce infections, deaths, and contacts as well as the peak number of infections and deaths. These figures also show that the opening and re-opening of schools and workplaces results in the emergence of new pandemic waves.

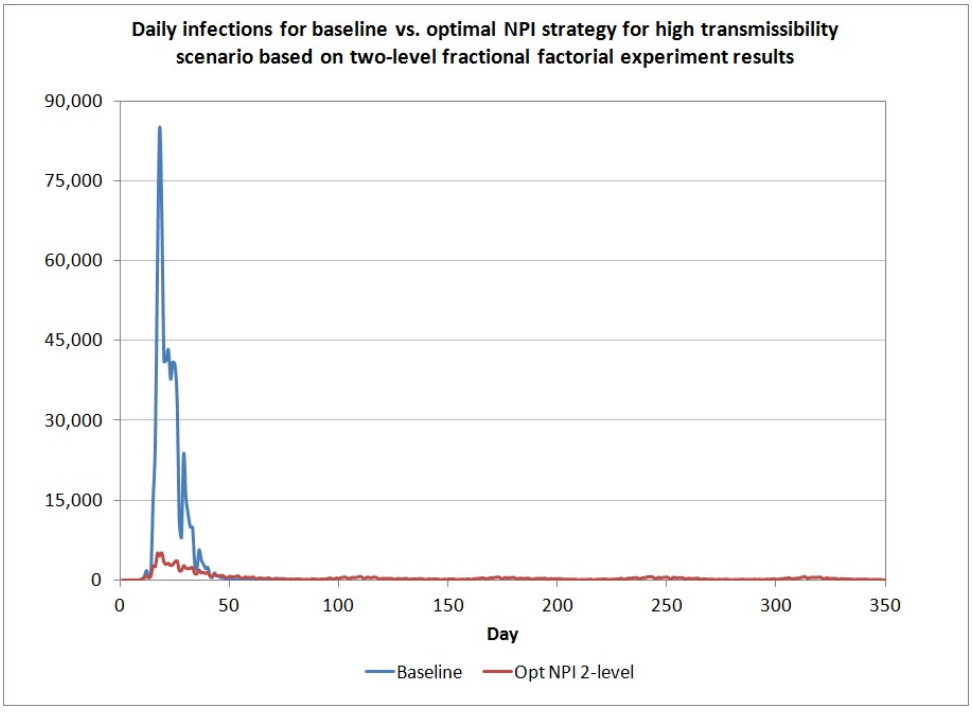


Figure 26: Daily infections for baseline vs. optimal NPI strategy for the high transmissibility scenario based on the two-level fractional factorial experiment

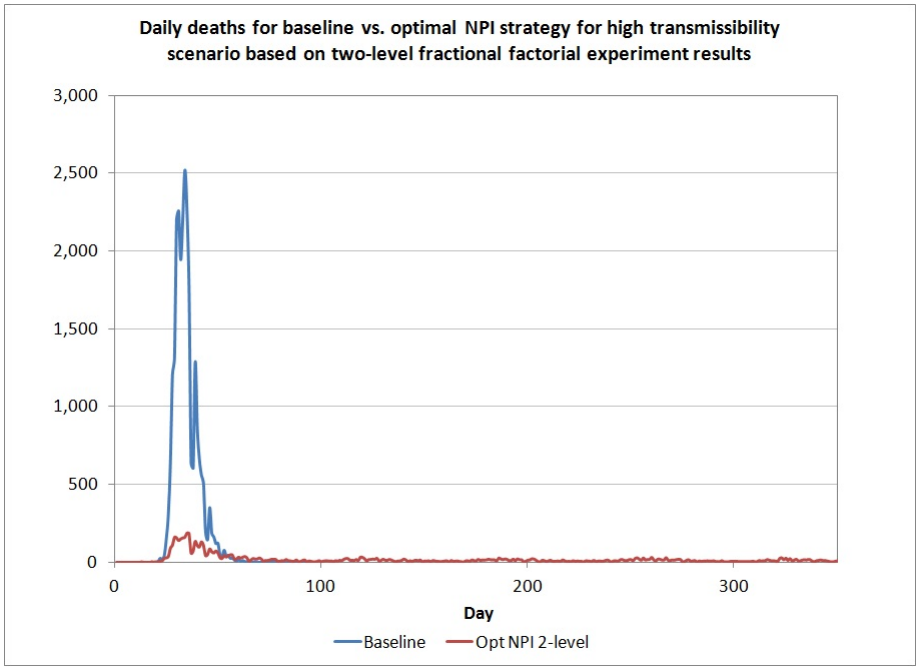


Figure 27: Daily deaths for baseline vs. optimal NPI strategy for the high transmissibility scenario based on the two-level fractional factorial experiment

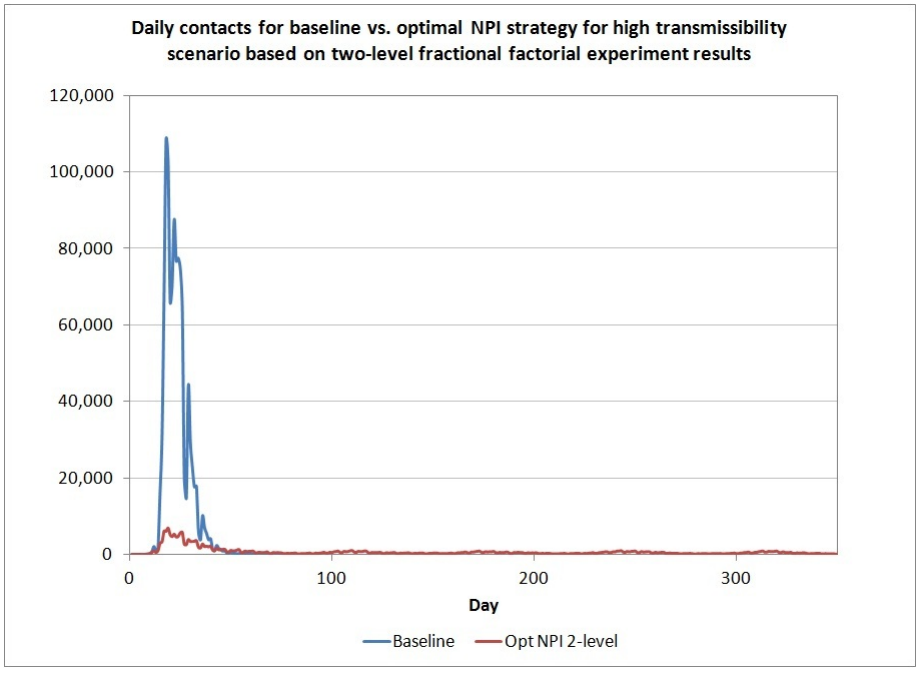


Figure 28: Daily contacts for baseline vs. optimal NPI strategy for the high transmissibility scenario based on the two-level fractional factorial experiment

6.3 Three-Level Experiment Results

In this section we present the results for the three-level experiment for the three transmissibility scenarios considered.

6.3.1 Low Transmissibility Scenario

Table 40 shows the ANOVA table for the low transmissibility scenario for the three-level fractional factorial experiment. Table 41 show the significant factors. Interactions are discussed later on.

Table 40: ANOVA table for the low transmissibility scenario for the three-level fractional factorial experiment using total number of infected as the measure of performance

Factor	Df	Sum Sq	Mean Sq	F value	Pr(>F)	Signif.
GD	2	1.02E+10	5.08E+09	4.7082	0.009581	**
ID	2	4.00E+10	2.00E+10	18.5292	2.18E-08	***
CMS	2	4.35E+11	2.17E+11	201.4023	< 2.2e-16	***
MS	2	4.74E+10	2.37E+10	21.9696	9.88E-10	***
PMS	2	1.22E+11	6.11E+10	56.647	< 2.2e-16	***
CMW	2	1.84E+10	9.22E+09	8.5414	0.000237	***
PMW	2	4.17E+09	2.09E+09	1.9319	0.146363	
GD_ID2	2	8.00E+09	4.00E+09	3.7064	0.025503	*
GD_CMS2	2	4.37E+09	2.19E+09	2.025	0.133486	
GD_PMW2	2	4.38E+09	2.19E+09	2.0279	0.133105	
ID_MS2	2	2.22E+10	1.11E+10	10.2718	4.58E-05	***
ID_PMW	2	1.38E+09	6.89E+08	0.6383	0.528784	
CMS_MS	2	9.75E+09	4.88E+09	4.518	0.011534	*
CMS_PMW2	2	1.56E+08	7.78E+07	0.072	0.93051	
MS_PMW	2	1.04E+10	5.19E+09	4.8048	8.72E-03	**
PMS_PMW2	2	6.07E+08	3.04E+08	0.2813	7.55E-01	
CMW_PMW	2	9.25E+09	4.63E+09	4.2856	0.014471	*
GD_CMW	2	1.73E+09	8.66E+08	0.802	4.49E-01	
CMS_PMS	2	1.61E+10	8.07E+09	7.4747	0.000659	***
MS_CMW	2	1.41E+09	7.06E+08	0.654	0.520567	
PMS_CMW	2	8.05E+09	4.02E+09	3.7271	2.50E-02	*
Residuals	362	3.91E+11	1.08E+09			

As shown in Figure 29, most of these factors relationship with the response (total number of infected) is not linear. In what follows we discuss each one of these factors.

Table 41: Significant main effects and mean number of infected for the low, medium and high levels for the low transmissibility scenario for the three-level fractional factorial experiment

Factor	**Low level**	**Medium level**	**High level**
GD	49,377.67	59,917.12	60,089.93
ID	62,256.9	42,475.24	64,652.58
CMS	15,142.99	58,958.73	95,283.01
MS	42,773.41	57,378.54	69,232.77
PMS	80,767.13	47,446.08	41,171.5
CMW	48,136.3	56,585.76	64,662.66

An increase in deployment delay from 3 to 5 days results in an increase by 1.04% in total number of infections. An increase in deployment delay from 5 to 7 days results in an increase by 0.02% in total number of infections.

Increasing deployment delay from 5 to 7 days does not have a significant impact on total number of infected. However, a change in deployment delay from 3 to 5 days results in an increase in the total number of infected. When considering to deploy interventions between 3 and 5 days, releasing them at three days results in the least number of infections.

An increase in case isolation threshold from 0 to 1 day results in a decrease by 1.95% in total number of infections. An increase in case isolation threshold from 1 to 2 days results in an increase by 2.19% in total number of infections. As expected, increasing case isolation threshold from one to two days, results in an increase in total number of infected and not in a further decrease. When an individual is already in their second day in the infectiousness profile, keeping the infected individual at home is better than letting the individual keep contacting others at school, work, and/or community.

An increase in cases to close a classroom from 1 to 2 cases results in an increase by 4.32% in total number of infections. An increase in cases to close a classroom from 2 to 3 cases, results in an increase by 3.58% in total number of infected. Cases to close a classroom does appear to have more of a linear relationship with the response (total number of infected). This parameter of school closure is one of the most significant parameters in this study. Increasing one case to close a class, results in a significant linear increase in the total number of infected.

An increase in the number of classes to close a school from 1 to 2 classes, results in an increase by 1.44% in total number of infections. An increase in the number of classes to close a school from 2 to 3 classes, results in an increase by 1.17% in total number of infections.

Just as with the number of cases to close a classroom, the number of classes to close a school also have a linear relationship with the response. A small increase in one of the two school closure thresholds result in a significant increase in the total number of infections.

An increase in school closure duration from 21 to 30 days, results in a decrease by 3.29% in total number of infections. An increase in school closure duration from 30 to 42 days, results in a decrease by 0.62% in total number of infections.

School closure duration impact is more notable between 21 and 30 days, as school closure duration increase from 30 to 42 days is still decreases the total number of infected but the percentage of decrease is only 0.62% versus 3.29% when closing between 21 and 30 days.

An increase in cases to close a workplace from 3 to 4 cases, results in an increase by 0.83% in total number of infections. An increase in cases to close a workplace from 4 to 5 cases, results in an increase by 0.80% in total number of infections.

Workplace closure reduces the total number of infections, but when compared to school closure, the impact of this intervention is not as significant. The number of cases to close a workplace also have a linear relationship with the response.

For the low transmissibility scenario, the significant interactions for the three-level experiment are ID x MS, MS x PMW, and CMS x PMS. We now discuss each one of them individually.

Table 42: Mean infected values for the interaction between case isolation threshold and number of classes to close a school for low transmissibility scenario

ID $\downarrow$ \ MS $\rightarrow$	Low level	Medium level	High level
Low level	31,556.58	68,900.73	86,313.38
Medium level	33,455.56	39,537	54,433.18
High level	63,308.09	63,697.89	66,951.76

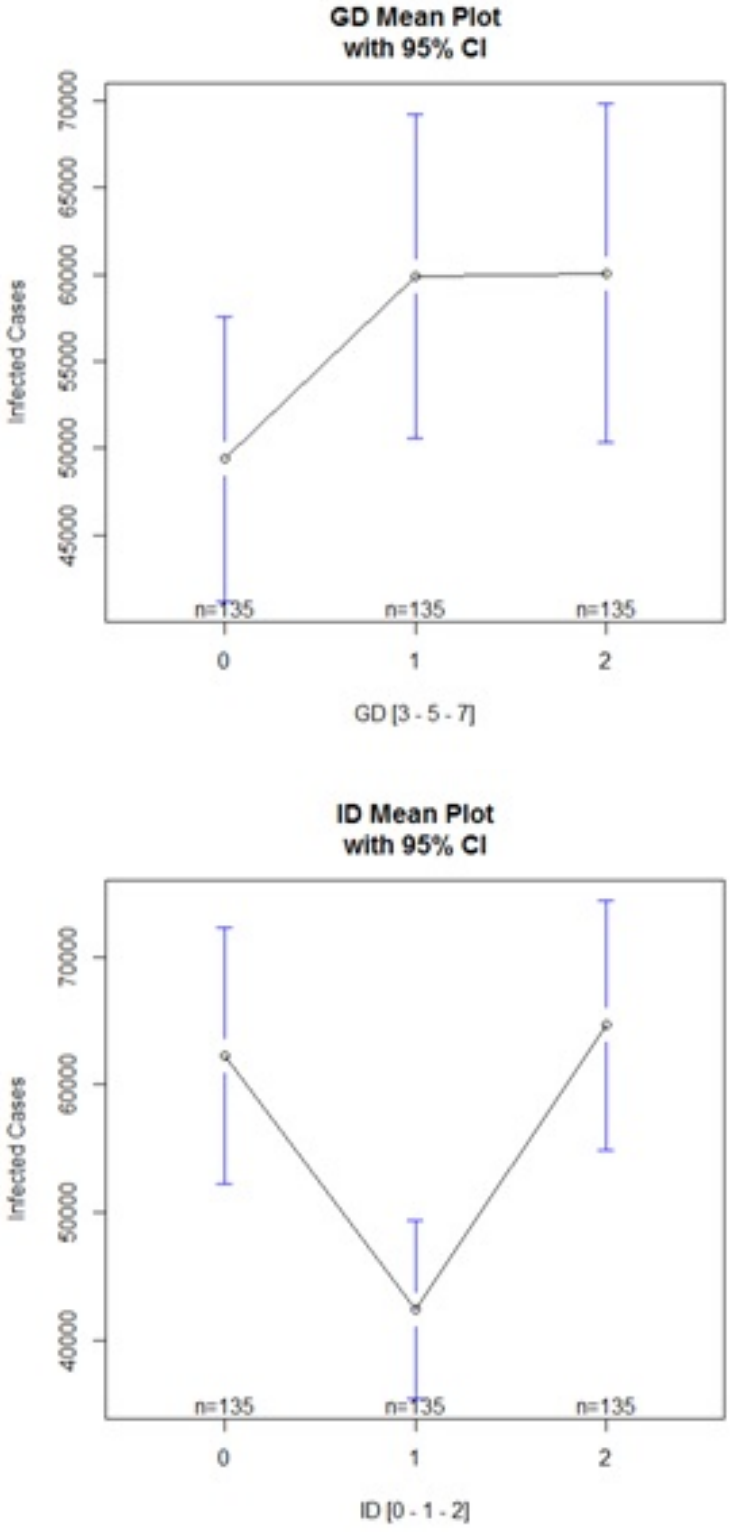
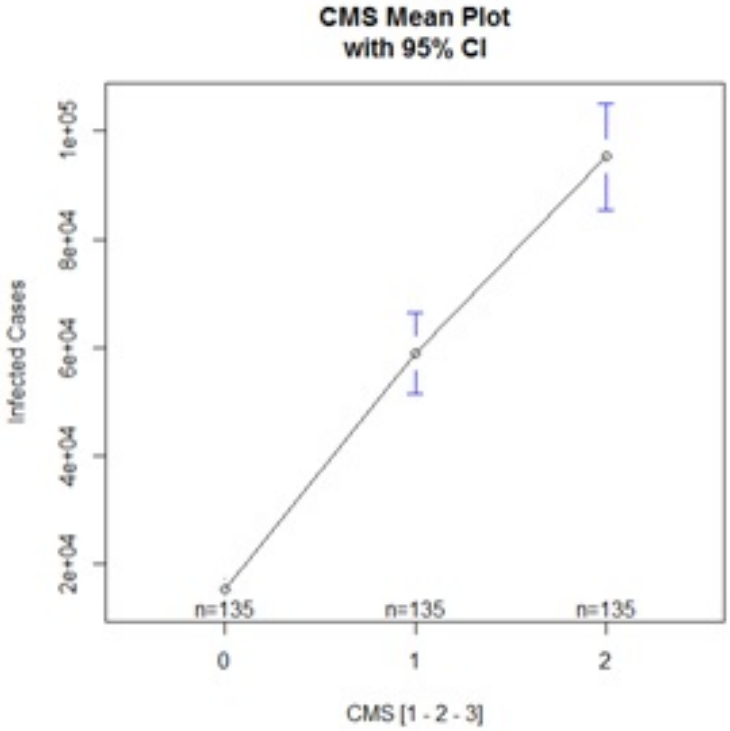


Figure 29: Main factor effects for the low transmissibility scenario for the three-level fractional factorial experiment



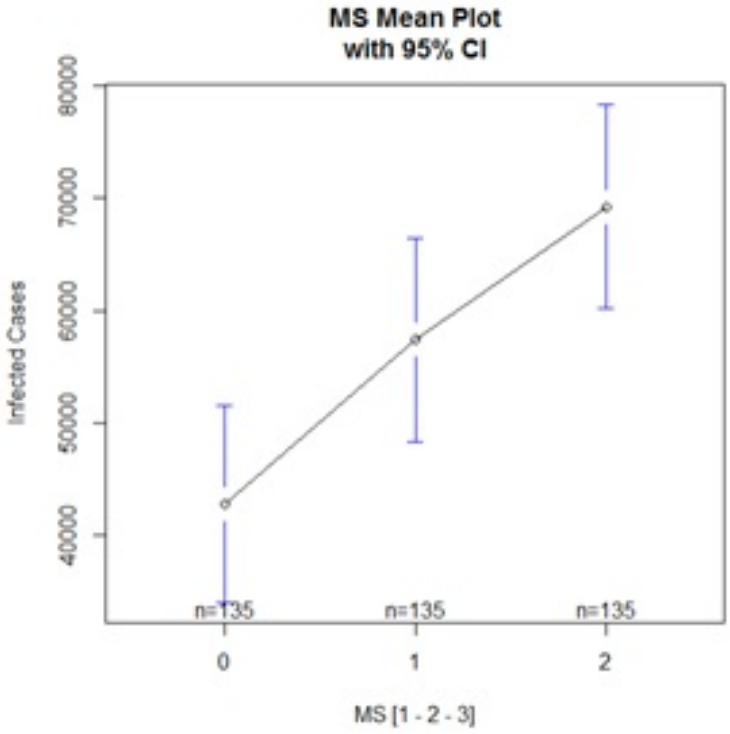
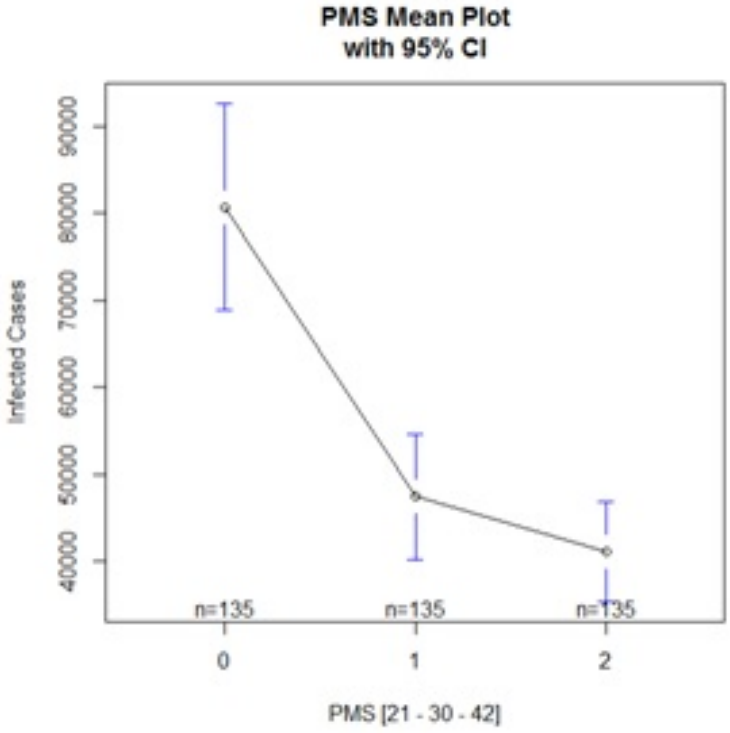


Figure 29: (Continued)



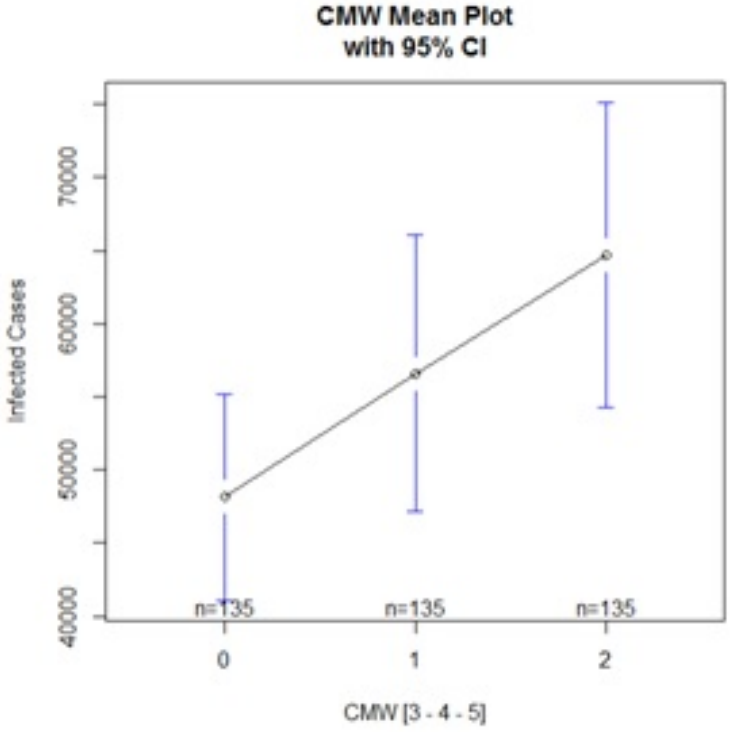


Figure 29: (Continued)

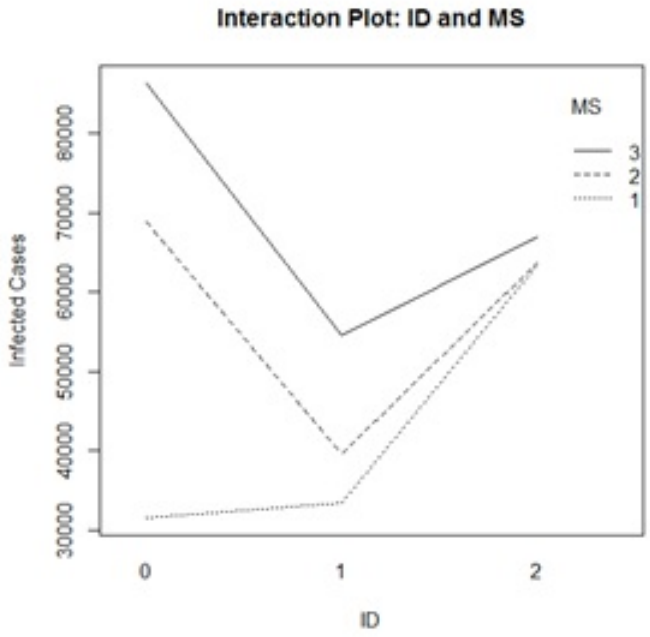


Figure 30: Interaction between case isolation threshold and number of cases to close a school for the low transmissibility scenario

Table 30 shows the mean infected values for the interaction between case isolation threshold and number of classes to close a school for the three-level low transmissibility scenario experiment. Figure 30 shows this interaction graphically. From this information we can observe that when the number of classrooms to close a school is one, an increase in case isolation threshold from 0 to 1, results in an increase by 0.19% in total number of infections. And an increase in case isolation threshold from 1 to 2, results in an increase y 2.95% in total number of infections.

When the number of classrooms to close a school is two, an increase in case isolation threshold from 0 to 1, results in a decrease by 2.90% in total number of infections. And an increase in case isolation threshold from 1 to 2, results in an increase y 2.38% in total number of infections.

When the number of classrooms to close a school is three, an increase in case isolation threshold from 0 to 1, results in a decrease by 3.15% in total number of infections. And an increase in case isolation threshold from 1 to 2, results in an increase y 1.24% in total number of infections.

From this interaction we can conclude that independent of the number of classes to close a classroom the best strategy is to start isolation one day after the individual shows symptoms. Put perhaps, the best is to close a school after one class has been closed and start isolation immediately upon showing symptoms (combination that resulted in the least number of infections).

Table 43: Mean infected values for the interaction between number of classes to close a school and workplace closure duration for the low transmissibility scenario

MS ↓ \ PMW →	Low level	Medium level	High level
Low level	45,309.71	40,585.11	42,425.40
Medium level	60,913.60	62,727.51	48,494.51
High level	76,517.02	57,105.84	74,075.44

Table 43 shows the mean infected values for the interaction between number of classes to close a school and workplace closure duration for the three-level for the low transmissibility scenario experiment. Figure 31 shows this interaction graphically. From this information we can observe that when workplace closure duration is seven days, an increase in the number of classes to close a school from 1 to 2 classes, results in an increase by 1.54% in the total number of infections. And an increase in the number of classes to close a school from 2 to 3 classes also results in an increase y 1.54% in the total number of infections. This relationship is linear.

When workplace closure duration is 10 days, an increase in the number of classes to close a school from 1 to 2 classes, results in an increase by 2.18% in the total number of infections. And an increase in the number of classes to close a school from 2 to 3 classes results in a decrease by 0.55% in the total number of infections.

When workplace closure duration is 14 days, an increase in the number of classes to close a school from 1 to 2 classes, results in an increase by 0.60% in the total number of infections. And an increase in the number of classes to close a school from 2 to 3 classes results in an increase y 2.52% in the total number of infections.

This interaction shows that when workplace closure duration is 7 days, the relationship between an increase in the number of classes to close a school with the response is linear. As workplace closure duration increases to 10 days, increasing the number of

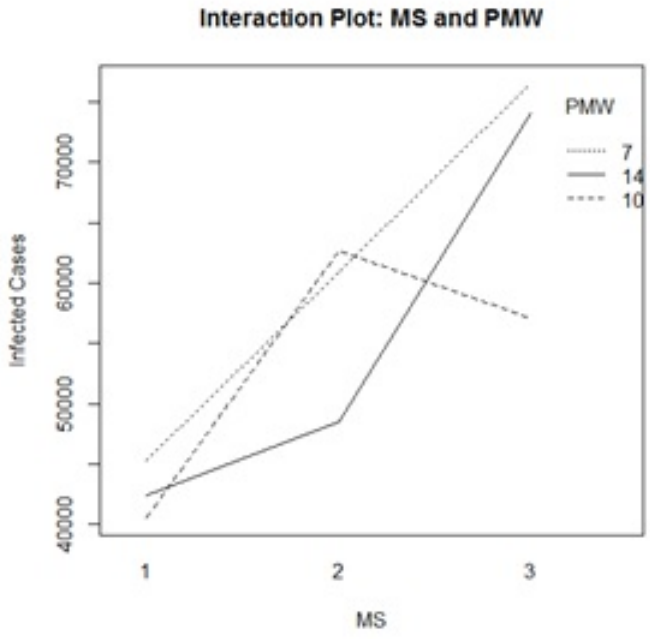


Figure 31: Interaction between number of classes to close a school and workplace closure duration for the low transmissibility scenario

Table 44: Mean infected values for the interaction between number of cases to close a classroom and school closure duration for the low transmissibility scenario

CMS ↓ \ PMS →	Low level	Medium level	High level
Low level	21,150.69	12,127.38	12,150.89
Medium level	88,205.78	47,100.71	41,569.69
High level	132,944.93	83,110.16	69,793.93

classes to close a school from 1 to 3 classes also results in an increase in the total number of infected. A major increase is observed when increasing the number of classes to close a school from 2 to 3 classes. However, when workplace closure duration is 14 days, increasing the number of classes to close a school results in a decrease and not an increase as with the other cases.

Table 44 shows the mean infected values for the interaction between number of cases to close a classroom and school closure duration for the three-level low transmissibility scenario experiment. Figure 32 shows this interaction graphically. From this information we can observe that when school closure duration is 21 days, an increase in the number of cases to close a class from 1 to 2, results in an increase by 6.62% in total number of

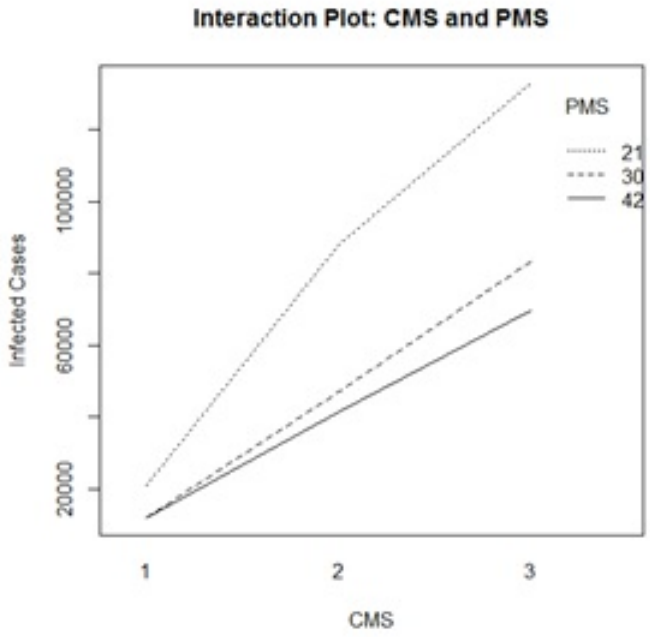


Figure 32: Interaction between number of cases to close a classroom and school closure duration for the low transmissibility scenario

infections. And an increase in cases to close a class from 2 to 3, results in an increase by 4.41% in total number of infections.

When school closure duration is 30 days, an increase in the number of cases to close a class from 1 to 2, results in an increase by 3.45% in total number of infections. And an increase in cases to close a class from 2 to 3, results in an increase by 3.55% in total number of infections.

When school closure duration is 42 days, an increase in the number of cases to close a class from 1 to 2, results in an increase by 2.90% in total number of infections. And an increase in cases to close a class from 2 to 3, results in an increase by 2.78% in total number of infections.

When school closure duration is 21 and 30 days, an increase in the number of classes to close a school, increases the number of infected linearly. However, when school closure duration is 42 days, a major impact in total number of infected is observed when increasing the number of cases to close a class from 1 to 2 cases. A change from 2 to 3 cases also increases the number of infected, but the percentage increase is lower.

The regression analysis for the low transmissibility scenario for the three-level fractional factorial experiment is shown in Table 45.

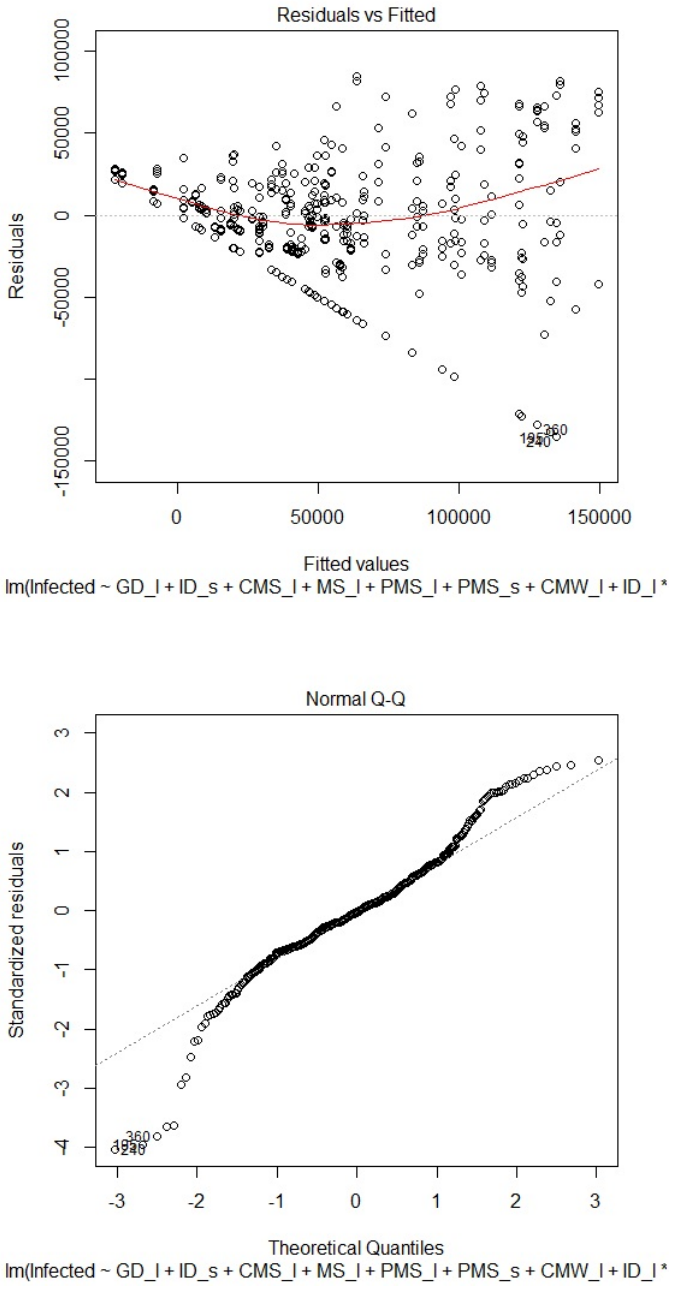


Figure 33: Residuals plot and normal probability plot for the regression analysis of the low transmissibility scenario for the three-level fractional factorial experiment

Table 45: Regression analysis for the low transmissibility scenario for the two-level fractional factorial experiment

Factor	Estimate	Std. Error	t value	Pr(>|t|)	Signif.
(Intercept)	40453.6	6089.8	6.643	1.04E-10	***
GD_l	5356.1	2068.6	2.589	0.00998	**
GD_s	-5183.3	3582.9	-1.447	0.148794	
ID_l	1197.8	2068.6	0.579	0.562884	
ID_s	20979.5	3582.9	5.855	1.01E-08	***
CMS_l	40070	2068.6	19.371	< 2e-16	***
CMS_s	-3745.7	3582.9	-1.045	0.296468	
MS_l	13229.7	2068.6	6.396	4.61E-10	***
MS_s	-1375.5	3582.9	-0.384	0.701268	
PMS_l	-19797.8	2068.6	-9.571	< 2e-16	***
PMS_s	13523.2	3582.9	3.774	0.000185	***
CMW_l	8263.2	2068.6	3.995	7.75E-05	***
CMW_s	-186.3	3582.9	-0.052	0.958561	
PMW_l	-2957.5	2068.6	-1.43	0.153603	
ID_l:MS_l	-8516.7	3055.5	-2.787	0.005576	**
CMW_l:PMW_l	-1512.5	2646.2	-0.572	0.567941	
CMS_l:PMS_l	-9279.5	2958.5	-3.137	0.00184	**

This model has an R-square value of 59.96%. The analysis of residuals and normal probability plot of residuals is shown in Figure 33. As with the two-level experiment, for low transmissibility scenario, our model leaves a lot of the variability unaddressed. However, the optimization of the resulting regression equation resulted in a significantly better strategy than the typical NPI strategy shown before. In this scenario it also performed significantly better than the two-level optimal strategy.

Table 46: Optimal NPI strategy for the low transmissibility scenario based on the three-level fractional factorial experiment

Factor	**Optimal Value**	**Factor**	**Optimal Value**	**Factor**	**Optimal Value**
GT	10	GD	3	ID	1
IP	10	ICW	0.75	ICNW	0.57
HD	1	HP	7	HCW	0.53
HCNW	0.84	CMS	1	MS	1
PMS	35	CMW	3	MW	0.3
PMW	7				

The resulting optimal strategy is shown in Table 46 and the results comparing the performance of this strategy with the baseline scenario is shown in Table 47. As shown in this table, the optimal NPI strategy was successful in containing the epidemic. It also reduced overall number of infections, contacts and deaths. Figures 34 through 36 shows

this information graphically. From these graphs we can see that the optimal strategy not only reduces significantly the total number of infected, but also peak attack rates and peak death rates. For this optimal NPI strategy the pandemic duration was also reduced and no new pandemic waves emerged.

Table 47: Performance measures for baseline vs. optimal NPI strategy for the low transmissibility scenario based on the three-level fractional factorial experiment

Measure	**Baseline**	**NPI**	**Measure**	**Baseline**	**NPI**
IAR	33.06%	0.55%	Infections 0-19 yrs.	225,467	4,315
CFR	0.69%	0.01%	Infections 20-64 yrs.	91,959	961
Pandemic Duration (Days)	135	76	Infections 65-99 yrs.	17,645	272
Total Contacts	1,177,393	21,440	Infections Households	37,562	2,292
Contacts 0-19 yrs.	818,912	19,066	Infect. MG Types(1-2)	46,600	153
Contacts 20-64 yrs.	294,046	1,887	Infect. Schools	249,304	3,080
Contacts 65-99 yrs.	64,435	487	Infect. MG Types(9-12)	1,605	23
Contacts Households	238,684	11,904	Total Deaths	7,009	99
Contacts MG Types(1-2)	231,051	891	Deaths 0-19 yrs.	1,041	17
Contacts Schools	699,427	8,544	Deaths 20-64 yrs.	4,095	54
Contacts MG Types(9-12)	8,231	101	Deaths 65-99 yrs.	1,873	28
Total Infections	335,071	5,548			

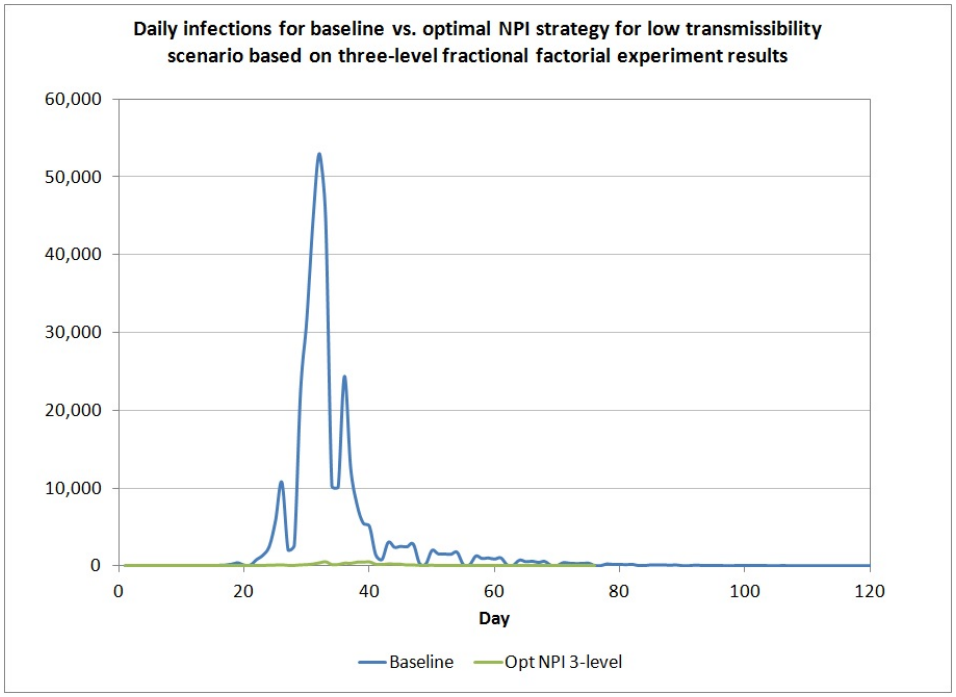


Figure 34: Daily infections for baseline vs. optimal NPI strategy for the low transmissibility scenario based on the three-level fractional factorial experiment

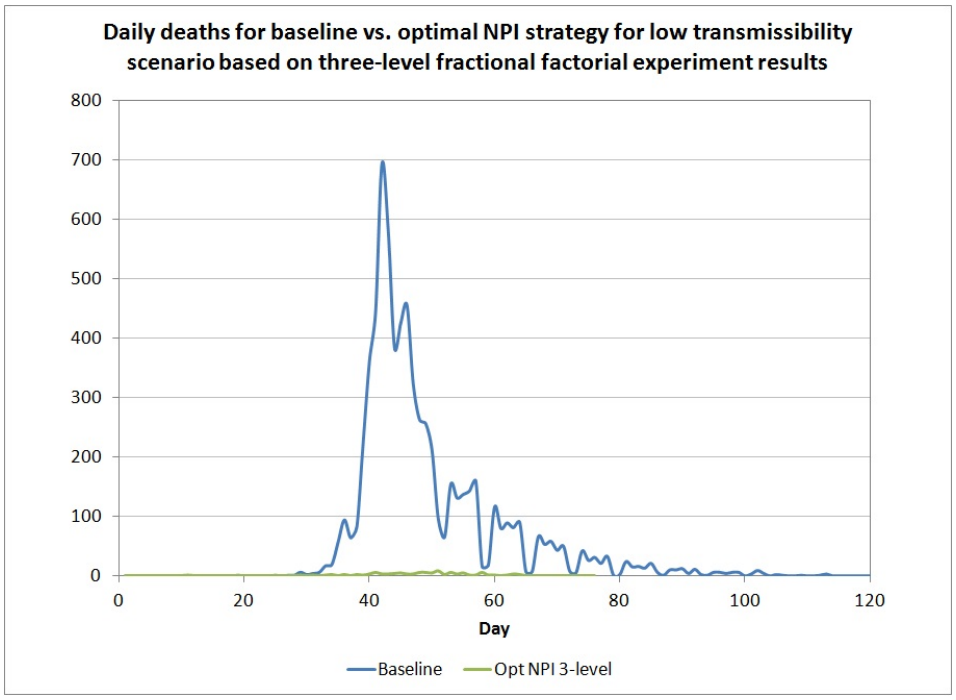


Figure 35: Daily deaths for baseline vs. optimal NPI strategy for the low transmissibility scenario based on the three-level fractional factorial experiment

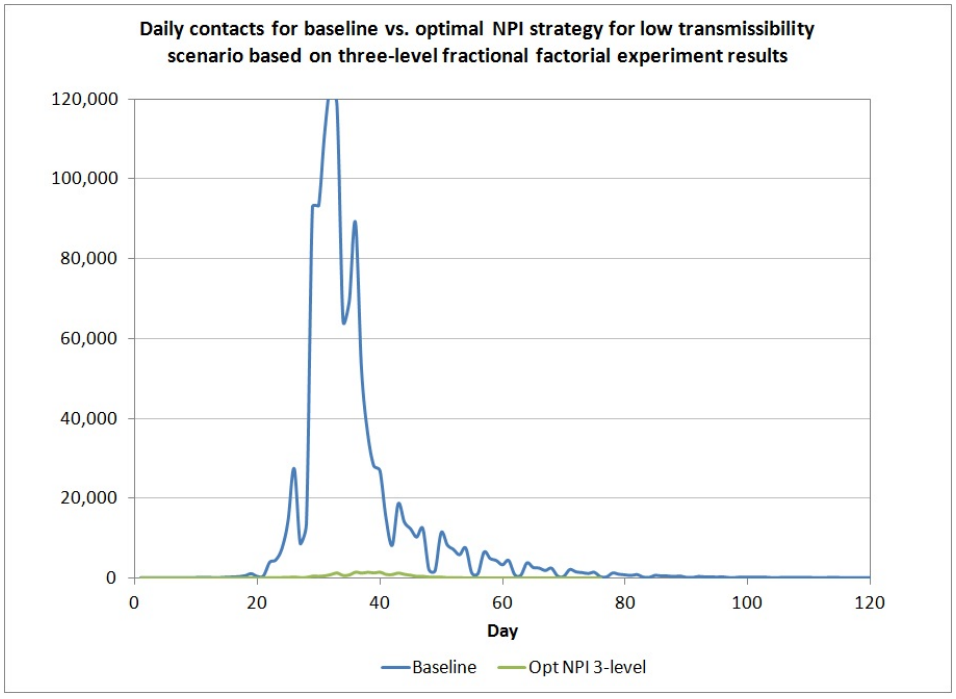


Figure 36: Daily contacts for baseline vs. optimal NPI strategy for the low transmissibility scenario based on the three-level fractional factorial experiment

6.3.2 Medium Transmissibility Scenario

Table 48 shows the ANOVA table for the low transmissibility scenario for the three-level fractional factorial experiment. Tables 49 show the significant factors. Interactions are discussed later on.

Table 48: ANOVA table for the medium transmissibility scenario for the three-level fractional factorial experiment using the total number of infected as the measure of performance

Factor	Df	Sum Sq	Mean Sq	F value	Pr(>F)	Signif.
GT	2	3.16E+10	1.58E+10	18.3194	2.65E-08	***
GD	2	5.47E+10	2.73E+10	31.7021	2.08E-13	***
ID	2	9.83E+09	4.91E+09	5.6975	0.003664	**
CMS	2	1.99E+12	9.93E+11	1151.6213	< 2.2e-16	***
MS	2	2.32E+11	1.16E+11	134.3312	< 2.2e-16	***
PMS	2	3.35E+11	1.68E+11	194.4685	< 2.2e-16	***
CMW	2	7.18E+10	3.59E+10	41.6224	< 2.2e-16	***
GT_GD2	2	2.04E+10	1.02E+10	11.8047	1.08E-05	***
GT_ID2	2	4.46E+09	2.23E+09	2.5884	0.076539	.
GT_CMW2	2	2.64E+08	1.32E+08	0.1531	0.858136	
GD_CMS2	2	8.84E+09	4.42E+09	5.1234	0.006397	**
GD_CMW	2	5.94E+08	2.97E+08	0.3444	0.708876	
ID_CMS	2	4.59E+09	2.30E+09	2.6628	0.071129	.
ID_CMW2	2	5.48E+09	2.74E+09	3.179	0.042797	*
CMS_CMW	2	4.20E+09	2.10E+09	2.4366	0.088897	.
MS_CMW2	2	9.29E+08	4.65E+08	0.5387	0.584004	
PMS_CMW	2	8.38E+09	4.19E+09	4.8587	0.008277	**
GT_PMS	2	6.98E+09	3.49E+09	4.0467	0.01828	*
GD_MS	2	4.60E+09	2.30E+09	2.6694	0.070665	.
ID_MS	2	3.98E+08	1.99E+08	0.2307	0.794065	
CMS_PMS	2	6.16E+09	3.08E+09	3.574	0.029042	*
MS_PMS	2	1.24E+09	6.21E+08	0.7205	0.487222	
Residuals	360	3.10E+11	8.62E+08			

As shown in Figure 37, most of these factors relationship with the response (total number of infected) is not linear. In what follows we discuss each one of these factors.

An increase in global threshold from 10 to 30 cases, results in an increase by 0.20% in the total number of infections. And an increase in global threshold from 30 to 50 cases, results in an increase by 1.74% in the total number of infections.

Changing the number of cases to declare pandemic from 10 to 30 does not have a significant increase impact in the total number of infected.

Table 49: Significant main effects and mean number of infected for the low, medium and high levels for the medium transmissibility scenario for the three-level fractional factorial experiment

Factor	**Low level**	**Medium level**	**High level**
GT	286,568.3	288,581	306,231.1
GD	284,562.7	286,635	310,182.8
ID	293,921.3	287,697.5	299,761.7
CMS	197,419.1	322,202.9	361,758.5
MS	261,636.1	300,783.5	318,960.9
PMS	319,240.2	308,578.7	253,561.6
CMW	275,220.8	300,397	305,762.7

However, when increasing the global threshold from 30 to 50, there is a more significant increase in total number of infected compared to the increase of changing global threshold from 10 to 30 cases.

An increase in deployment delay from 3 to 5 days results in an increase by 0.20% in total number of infections. And an increase in deployment delay from 5 to 7 days, results in an increase by 2.32% in total number of infections.

Increasing deployment delay from 5 to 7 days does not have a significant impact on total number of infected. However, a change in deployment delay from 3 to 5 days results in a major increase in the total number of infected. When considering to deploy interventions between 3 and 5 days, releasing them at three days results in the least number of infections.

An increase in case isolation threshold from 0 to 1 day results in a decrease by 0.61% in total number of infections. An increase in case isolation threshold from 1 to 2 days results in an increase by 1.19% in total number of infections.

As expected, increasing case isolation threshold from one to two days results in an increase in total number of infected and not in a further decrease. When an individual is already in their second day in the infectiousness profile, keeping the infected individual at home is better than letting the individual keep contacting others at school, work, and/or community.

An increase in cases to close a classroom from 1 to 2 cases results in an increase by 12.31% in total number of infections. An increase in cases to close a classroom from 2 to 3, results in an increase by 3.90% in total number of infected.

The relationship between the number of cases to close a classroom and the response in a medium transmissibility pandemic scenario is not longer linear. Increasing the number of cases to close a class from 1 to 2, increases the total number of infections by 12.31% which is a significant increase. As we keep increasing the number of cases from 2 to 3, we can still see an increase in the response, but not as significant.

An increase in the number of classes to close a school from 1 to 2 classes, results in an increase by 3.86% in total number of infections. An increase in the number of classes to close a school from 2 to 3 classes, results in an increase by 1.79% in total number of infections.

The relationship between number of classes to close a school and the response in a medium transmissibility pandemic scenario is not longer linear. Increasing the number of classes to close a school from 1 to 2, increases the total number of infections by 3.86% but as we keep increasing the number of classes from 2 to 3, we can still see an increase in the response, but not as significant.

An increase in school closure duration from 21 to 30 days, results in a decrease by 1.05% in total number of infections. An increase in school closure duration from 30 to 42 days, results in a decrease by 5.43% in total number of infections.

As opposed to the findings about this factor in the low transmissibility scenario, school closure duration impact is more notable between 30 and 42 days, as school closure duration increases from 10 to 30 days is still decreases the total number of infected but the percentage of decrease is only 1.05% versus 5.43% when closing between 30 and 42 days.

An increase in cases to close a workplace from 3 to 4 cases, results in an increase by 2.48% in total number of infections. An increase in cases to close a workplace from 4 to 5 cases, results in an increase by 0.53% in total number of infections.

Workplace closure reduces the total number of infections, but when compared to school closure, the impact of this intervention is not as significant. The number of cases to close a workplace in a medium scenario does not longer shows a linear relationship with the total number of infected. The percentage increase in the response is higher when increasing the number of cases to close a department from 3 to 5 cases, and when increasing from 5

Table 50: Mean infected values for the interaction between global threshold and global delay for the medium transmissibility scenario

GT ↓ \ GD →	Low level	Medium level	High level
Low level	287,394.8	283,262.4	289,047.8
Medium level	276,018.9	284,799	304,925
High level	290,274.4	291,843.5	336,575.5

Table 51: Mean infected values for the interaction between deployment delay and number of classes to close a school for the medium transmissibility scenario

GD ↓ \ CMS →	Low level	Medium level	High level
Low level	178,509.2	311,863.5	363,315.4
Medium level	187,242	317,016.8	355,646.1
High level	226,506	337,728.4	366,313.9

to 7 cases it is almost a straight horizontal line (no impact in the response).

For medium transmissibility scenario, the significant interactions for the three-level experiment are GT x GD, GD x CMS, and PMS x CMW. We now discuss each one of them individually.

Table 50 shows the mean infected values for the interaction between global threshold and deployment delay for the three-level low transmissibility scenario experiment. Figure 38 shows this interaction graphically. From this information we can observe that when the deployment delay is 3 days, an increase in global threshold from 10 to 30 cases, results in a decrease by 1.12% in total number of infections. An increase in global threshold from 30 to 50 cases, results in an increase by 1.41% in total number of infections.

When the deployment delay is 5 days, an increase in global threshold from 10 to 30 cases, results in an increase by 0.15% in total number of infections. An increase in global threshold from 30 to 50 cases, results in an increase by 0.70% in total number of infections.

When the deployment delay is 7 days, an increase in global threshold from 10 to 30 cases, results in an increase by 1.57% in total number of infections. An increase in global threshold from 30 to 50 cases, results in an increase by 3.12% in total number of infections.

Table 51 shows the mean infected values for the interaction between deployment delay and the number of cases to close a classroom for the three-level low transmissibility scenario experiment. Figure 39 shows this interaction graphically. From this information we

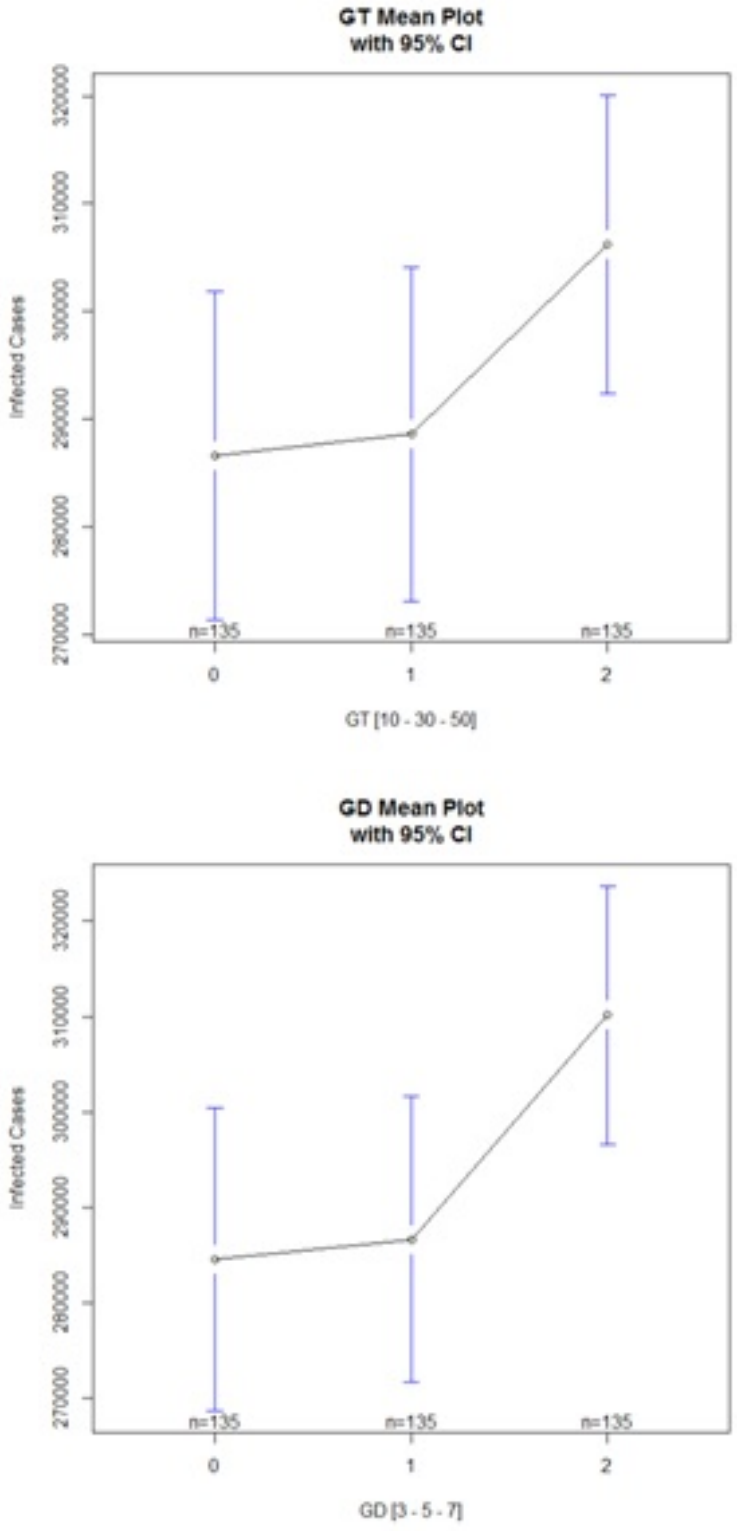
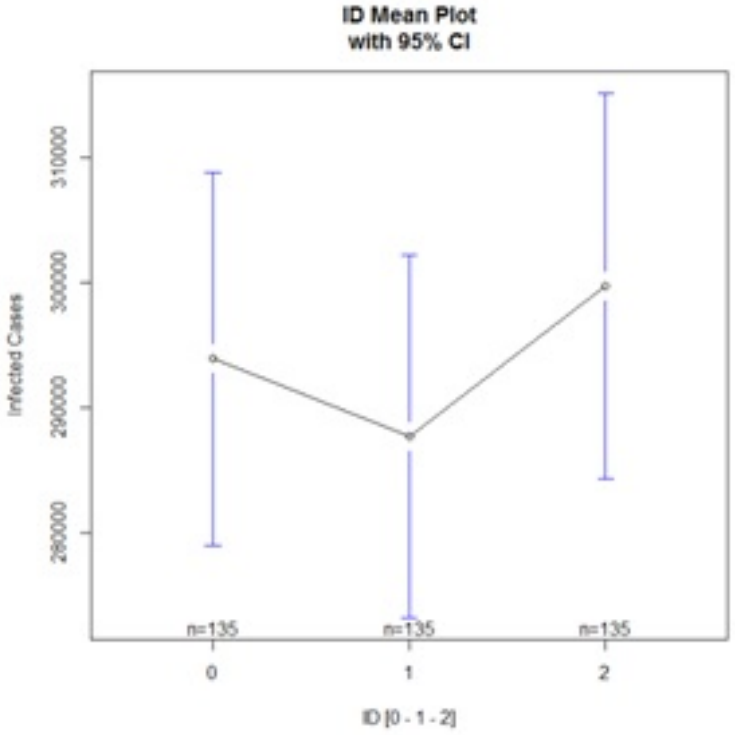


Figure 37: Main factor effects for the medium transmissibility scenario for the three-level fractional factorial experiment



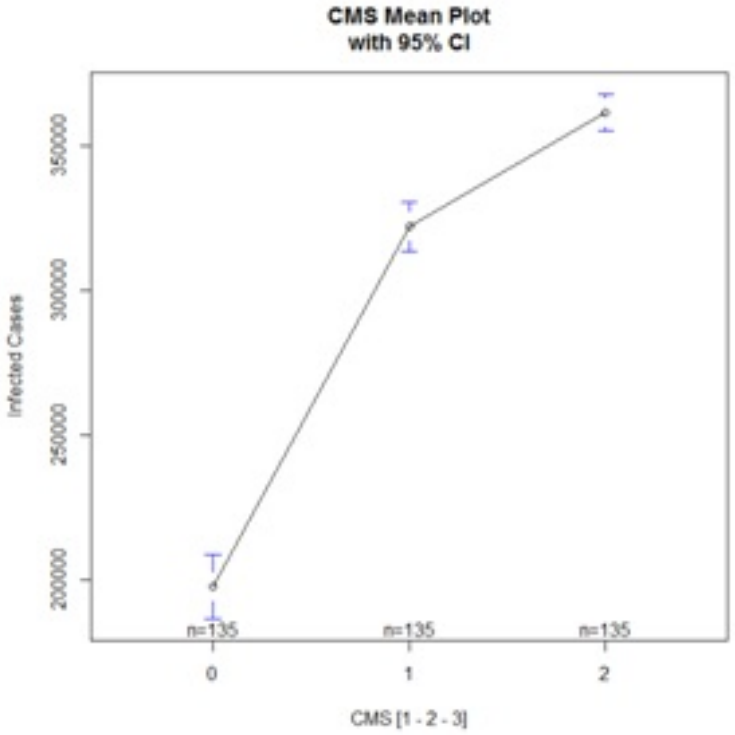
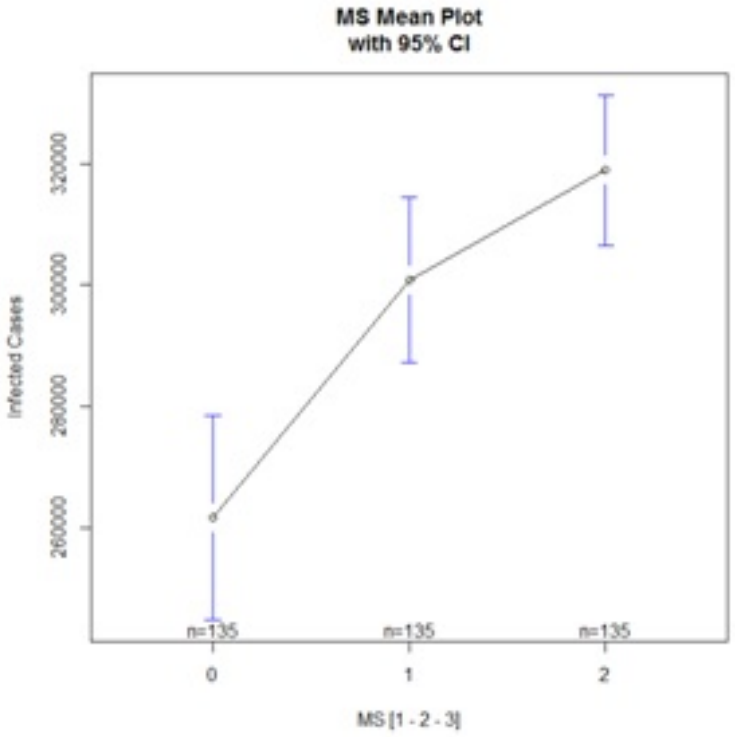


Figure 37: (Continued)



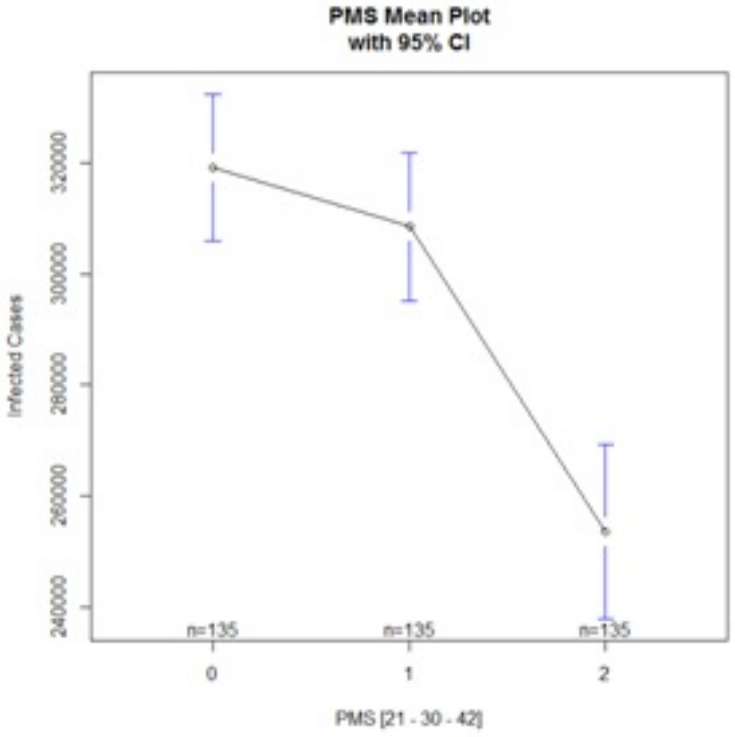


Figure 37: (Continued)

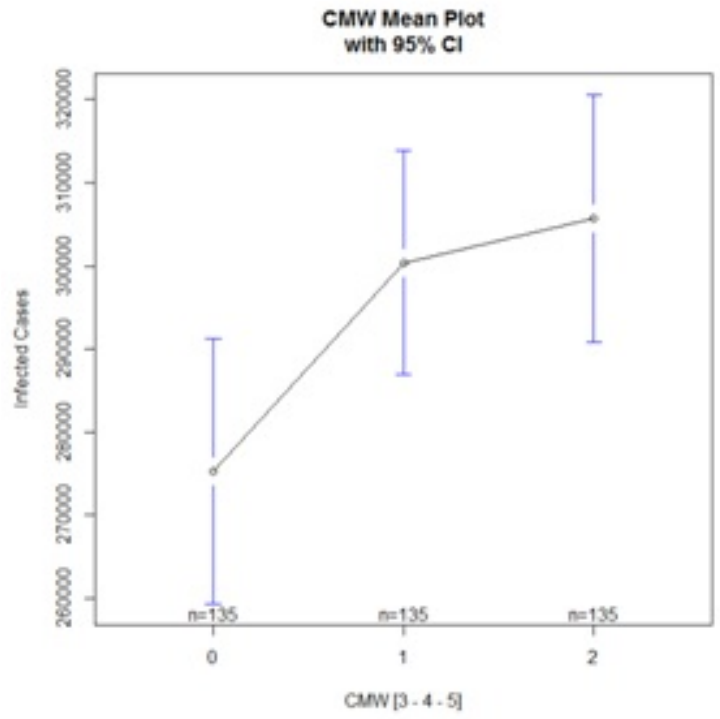


Figure 37: (Continued)

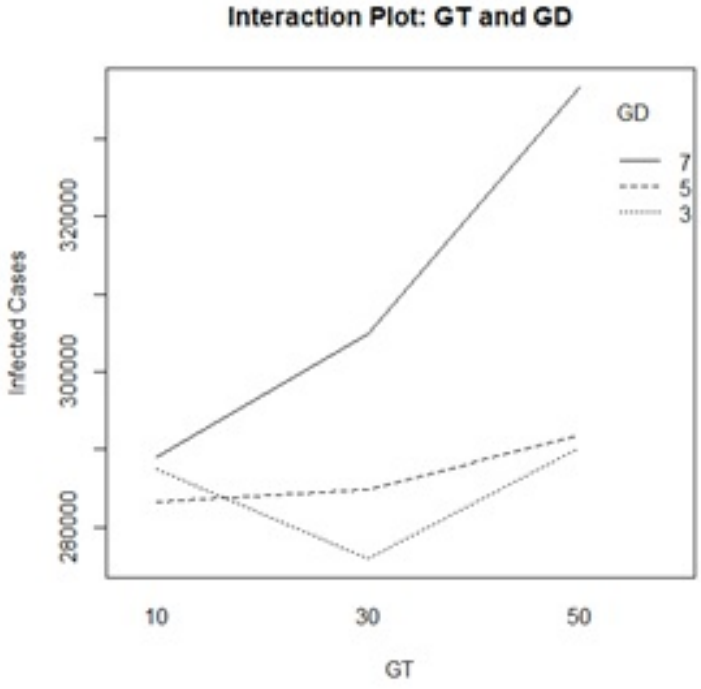


Figure 38: Interaction between global threshold and global delay for the medium transmissibility scenario

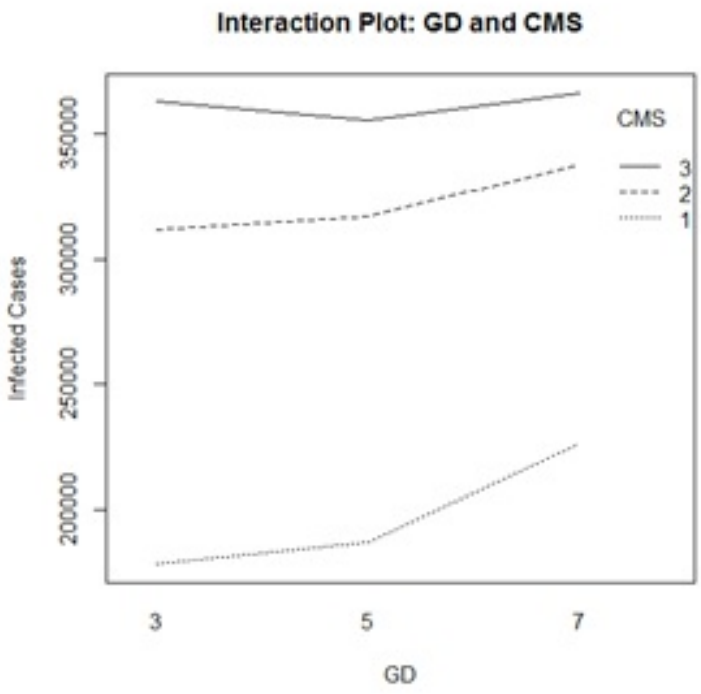


Figure 39: Interaction between deployment delay and number of classes to close a school for the medium transmissibility scenario

can observe that when the number of cases to close a class is one, an increase in deployment delay from 3 to 5 days results in an increase by 0.86% in the total number of infections. And an increase in deployment delay from 5 to 7 days results in an increase by 3.87% in the total number of infected.

When the number of cases to close a class is two, an increase in deployment delay from 3 to 5 days results in an increase by 0.51% in the total number of infections. And an increase in deployment delay from 5 to 7 days results in an increase by 2.04% in the total number of infected.

When the number of cases to close a class is three, an increase in deployment delay from 3 to 5 days results in a decrease by 0.76% in the total number of infections. And an increase in deployment delay from 5 to 7 days results in an increase by 1.05% in the total number of infected.

Table 52: Mean infected values for the interaction between school closure duration and cases to close a workplace for the medium transmissibility scenario

PMS ↓ \ CMW →	Low level	Medium level	High level
Low level	312,382.5	320,974.7	324,363.4
Medium level	293,221.8	317,720.2	314,794.1
High level	220,058.1	262,496.1	278,130.6

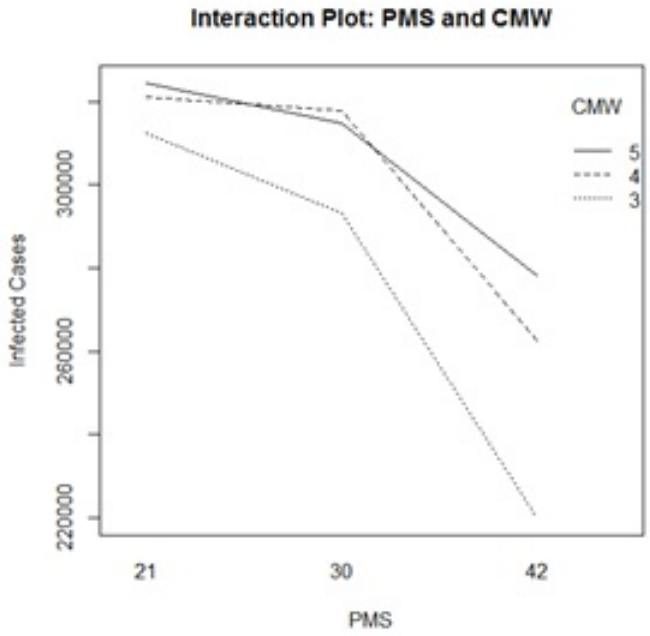
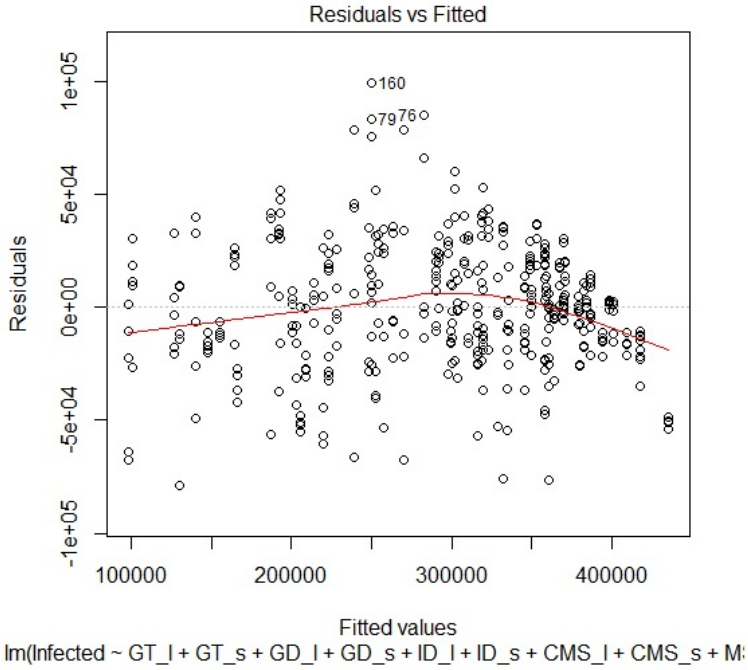


Figure 40: Interaction between school closure duration and cases to close a workplace for the medium transmissibility scenario

Table 52 shows the mean infected values for the interaction between school closure duration and the number of cases to close a department in a workplace for the three-level low transmissibility scenario experiment. Figure 40 shows this interaction graphically. From this information we can observe that when cases to close a department in a workplace is 3, an increase in school closure duration from 21 to 30 days results in a decrease by % in the total number of infections. And an increase in school closure duration from 30 to 42 days results in a decrease by % in the total number of infections.



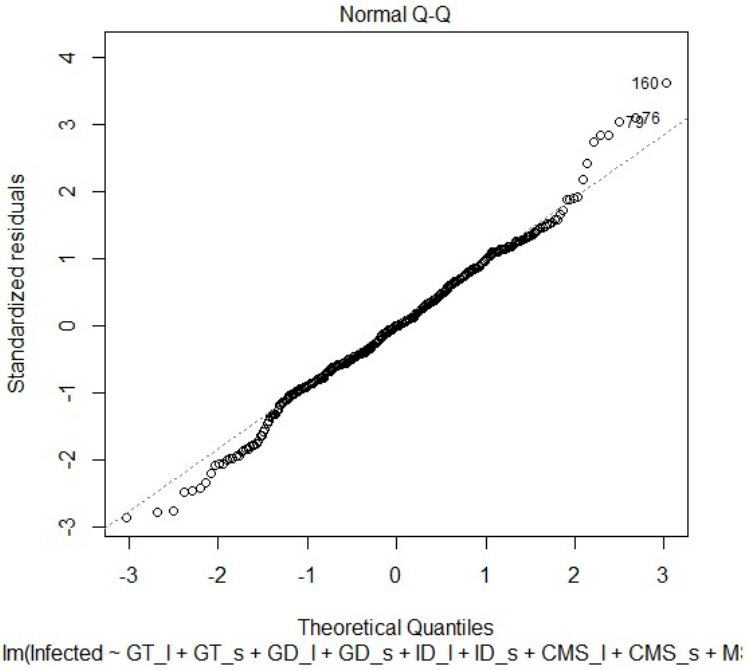


Figure 41: Residuals plot and normal probability plot for the regression analysis of the medium transmissibility scenario for the three-level fractional factorial experiment

When cases to close a department in a workplace is 4, an increase in school closure duration from 21 to 30 days results in a decrease by % in the total number of infections. And an increase in school closure duration from 30 to 42 days results in a decrease by % in the total number of infections. When cases to close a department in a workplace is 5, an increase in school closure duration from 21 to 30 days results in a decrease by % in the total number of infections. And an increase in school closure duration from 30 to 42 days results in a decrease by % in the total number of infections. The regression analysis for the medium transmissibility scenario for the three-level fractional factorial experiment is shown in Table 53.

This model has an R-square value of 89.29%. The regression analysis is shown in Table 53 and the analysis of residuals and normal probability plot of residuals is shown in Figure 41. The optimization of the resulting regression equation resulted in a significantly better strategy than the typical NPI strategy shown before. The strategy resulting from the three-level experiment performs better than the strategy resulting from the two-level experiment. However the difference between the two is not as notable as with the low transmissibility scenario.

The resulting optimal strategy is shown in Table 54 and the results comparing the performance of this strategy with the baseline scenario is shown in Table 54. As shown in this table, the optimal NPI strategy was successful in containing the pandemic. It also reduced overall number of infections, contacts and deaths. Figures 42 through 44 shows this information graphically. From these graphs we can see that the optimal strategy not only reduces significantly the total number of infected, but also peak attack rates and peak death rates. For this optimal NPI strategy the pandemic duration was also reduced and no new pandemic waves emerged.

Table 53: Regression analysis for the medium transmissibility scenario for the three-level fractional factorial experiment

Factor	Estimate	Std. Error	t value	Pr(>|t|)	Signif.
(Intercept)	332115	5524	60.119	< 2e-16	***
GT_l	9831	1747	5.628	3.51E-08	***
GT_s	7819	3026	2.584	1.01E-02	*
GD_l	12810	1747	7.333	1.33E-12	***
GD_s	10738	3026	3.549	4.35E-04	***
ID_l	2920	1747	1.672	9.54E-02	.
ID_s	9144	3026	3.022	2.68E-03	**
CMS_l	82170	1747	47.037	< 2e-16	***
CMS_s	-42614	3026	-14.084	< 2e-16	***
MS_l	28662	1747	16.407	< 2e-16	***
MS_s	-10485	3026	-3.465	5.89E-04	***
PMS_l	-32839	1747	-18.798	< 2e-16	***
PMS_s	-22178	3026	-7.33	1.36E-12	***
CMW_l	15271	1747	8.742	< 2e-16	***
CMW_s	-9905	3026	-3.274	1.16E-03	**
GT_l:GD_l	11162	2140	5.217	2.97E-07	***
GD_l:CMS_l	-11250	2140	-5.258	2.42E-07	***
PMS_l:CMW_l	11523	2140	5.386	1.26E-07	***

Table 54: Optimal NPI strategy for the medium transmissibility scenario based on the three-level fractional factorial experiment

Factor	**Optimal Value**	**Factor**	**Optimal Value**	**Factor**	**Optimal Value**
GT	32	GD	3	ID	1
IP	7	ICW	0.53	ICNW	0.84
HD	1	HP	7	HCW	0.75
HCNW	0.84	CMS	1	MS	1
PMS	42	CMW	3	MW	0.5
PMW	14				

Table 55: Performance measures for baseline vs. optimal NPI strategy for the medium transmissibility scenario based on the three-level fractional factorial experiment

Measure	Baseline	NPI	Measure	Baseline	NPI
IAR	50.80%	3.07%	Infections 0-19 yrs.	230,127	15,219
CFR	1.76%	0.10%	Infections 20-64 yrs.	228,753	12,275
Pandemic Duration (Days)	93	60	Infections 65-99 yrs.	55,964	3,615
Total Contacts	1,047,302	60,964	Infections Households	92,217	16,339
Contacts 0-19 yrs.	520,883	35,465	Infect. MG Types(1-2)	168,185	6,848
Contacts 20-64 yrs.	416,307	19,255	Infect. Schools	247,838	7,573
Contacts 65-99 yrs.	110,112	6,244	Infect. MG Types(9-12)	6,604	349
Contacts Households	236,850	35,176	Total Deaths	17,851	992
Contacts MG Types(1-2)	392,793	15,118	Deaths 0-19 yrs.	1,090	79
Contacts Schools	403908	9,999	Deaths 20-64 yrs.	10,681	498
Contacts MG Types(9-12)	13,751	671	Deaths 65-99 yrs.	6,080	415
Total Infections	514,844	31,109			

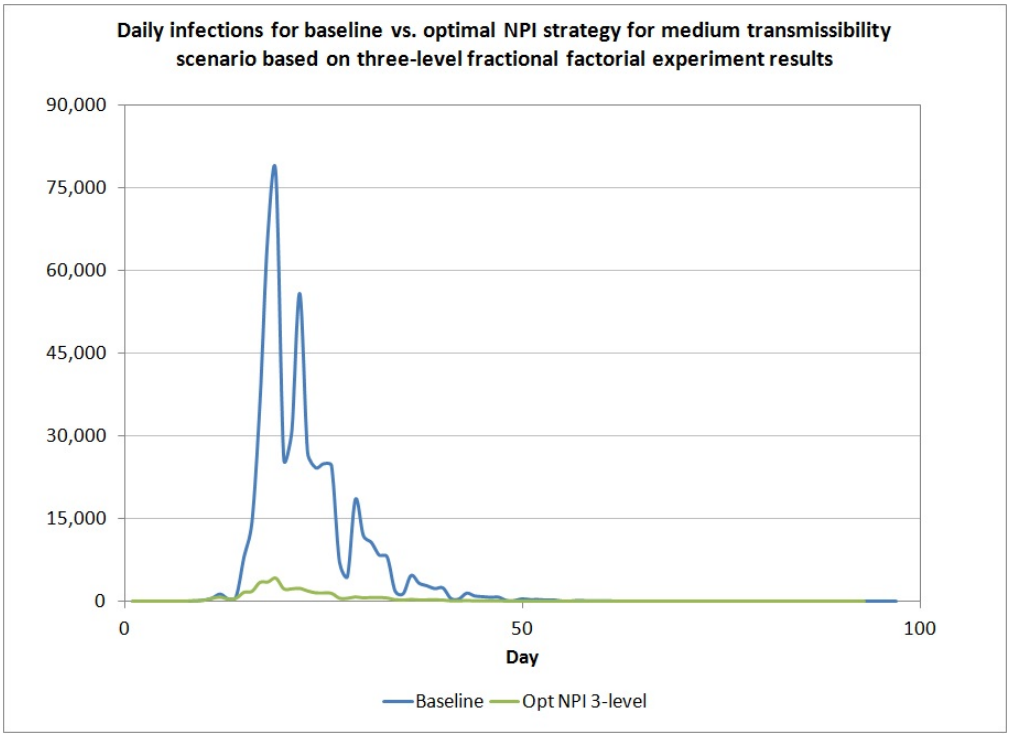


Figure 42: Daily infections for baseline vs. optimal NPI strategy for the medium transmissibility scenario based on the three-level fractional factorial experiment

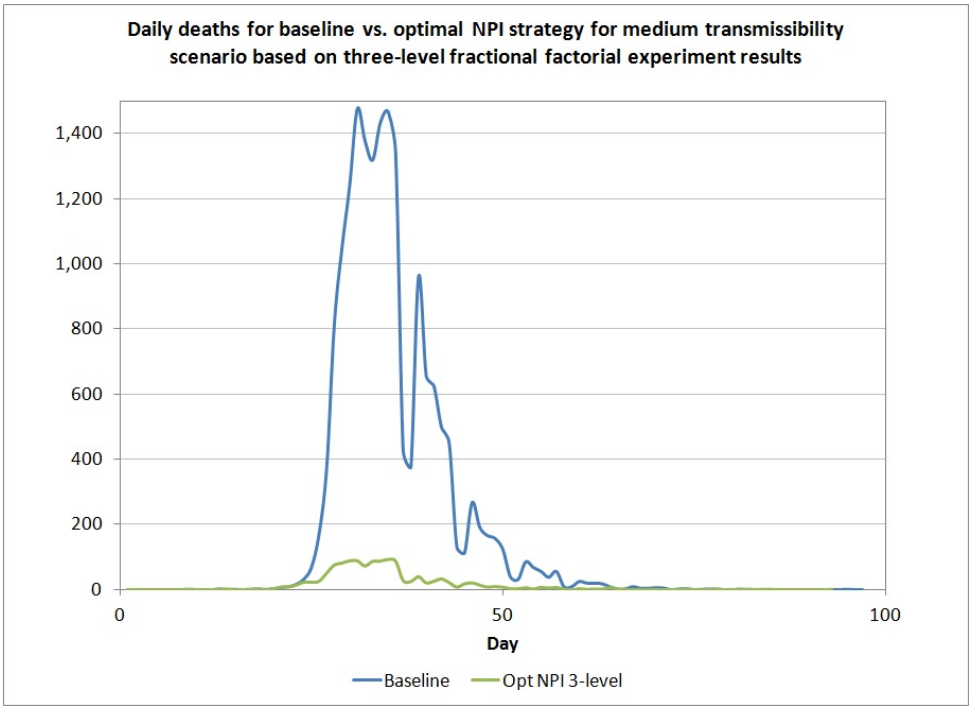


Figure 43: Daily deaths for baseline vs. optimal NPI strategy for the medium transmissibility scenario based on the three-level fractional factorial experiment

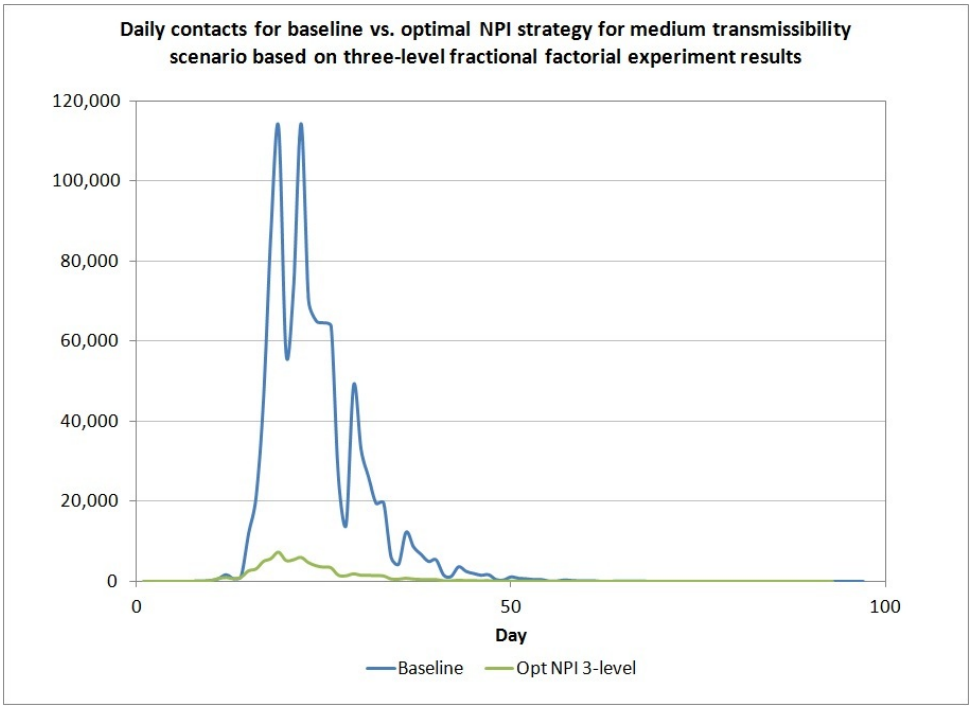


Figure 44: Daily contacts for baseline vs. optimal NPI strategy for the medium transmissibility scenario based on the three-level fractional factorial experiment

6.3.3 High Transmissibility Scenario

Table 56 shows the ANOVA table for the high transmissibility scenario for the three-level fractional factorial experiment. Table 57 show the significant factors. Interactions are discussed later on.

Table 56: ANOVA Table for the high transmissibility scenario for the three-level fractional factorial experiment using total number of infected as measure of performance

Factor	Df	Sum Sq	Mean Sq	F value	Pr(>F)	Signif.
GT	2	3.29E+10	1.64E+10	15.0342	5.36E-07	***
GD	2	3.01E+10	1.50E+10	13.7673	1.73E-06	***
ID	2	1.67E+10	8.33E+09	7.6183	0.000575	***
CMS	2	2.72E+12	1.36E+12	1245.793	< 2.2e-16	***
MS	2	2.98E+11	1.49E+11	136.1606	< 2.2e-16	***
PMS	2	1.02E+11	5.11E+10	46.7786	< 2.2e-16	***
CMW	2	1.11E+11	5.55E+10	50.7726	< 2.2e-16	***
GT_GD2	2	1.55E+10	7.77E+09	7.113	9.34E-04	***
GT_ID2	2	9.61E+08	4.80E+08	0.4396	0.644632	
GT_CMW2	2	1.87E+09	9.33E+08	0.8541	0.426531	
GD_CMS2	2	1.47E+10	7.35E+09	6.7292	0.001352	**
GD_CMW	2	3.39E+08	1.70E+08	0.1551	0.856379	
ID_CMS	2	1.00E+09	5.01E+08	0.4586	0.632568	
ID_CMW2	2	3.61E+09	1.81E+09	1.6526	0.193006	
CMS_CMW	2	1.27E+09	6.34E+08	0.5805	0.560126	
MS_CMW	2	1.46E+08	7.30E+07	0.0668	0.935394	
PMS_CMW	2	1.27E+09	6.36E+08	0.5815	0.559556	
GT_PMS	2	9.03E+09	4.52E+09	4.1322	0.016815	*
GD_MS	2	4.57E+08	2.28E+08	0.209	0.81149	
ID_MS	2	2.81E+09	1.40E+09	1.2841	0.278167	
CMS_PMS	2	2.45E+10	1.23E+10	11.2264	1.86E-05	***
MS_PMS	2	5.01E+08	2.51E+08	0.2292	0.795249	
Residuals	360	3.93E+11	1.09E+09			

As shown in Figure 45, most of these factor's relationship with the response (total number of infected) is not linear. In what follows we discuss each one of these factors.

An increase in global threshold from 10 to 30 cases, results in an increase by 0.56% in the total number of infections. And an increase in global threshold from 30 to 50 cases, results in an increase by 1.54% in the total number of infections. Changing the number of cases to declare pandemic from 10 to 30 does not have a significant increase impact in

Table 57: Significant main effects and mean number of infected for the low, medium and high levels for the high transmissibility scenario for the three-level fractional factorial experiment

Factor	**Low level**	**Medium level**	**High level**
GT	406,313.3	412,010.1	427,621.8
GD	407,716.1	410,859.9	427,369.3
ID	419,191.3	406,277.4	420,476.5
CMS	301,269.1	454,169.7	490,506.5
MS	378,309.2	425,147.9	442,488.2
PMS	429,185.2	423,690.1	393,070
CMW	394,368.1	416,737	434,840.2

the total number of infected. However, when increasing the global threshold from 30 to 50, there is a more significant increase in total number of infected compared to the increase of changing global threshold from 10 to 30 cases.

An increase in deployment delay from 3 to 5 days results in an increase by 0.31% in total number of infections. And an increase in deployment delay from 5 to 7 days, results in an increase by 1.63% in total number of infections. Increasing deployment delay from 3 to 5 days does not have a significant impact on total number of infected. However, a change in deployment delay from 5 to 7 days results in a major increase in the total number of infected. When considering to deploy interventions between 5 and 7 days, releasing them at five days results in the least number of infections.

An increase in case isolation threshold from 0 to 1 day results in a decrease by 1.27% in total number of infections. An increase in case isolation threshold from 1 to 2 days results in an increase by 1.40% in total number of infections. As expected, increasing case isolation threshold from one to two days results in an increase in total number of infected and not in a further decrease. When an individual is already in their second day in the infectiousness profile, keeping the infected individual at home is better than letting the individual keep contacting others at school, work, and/or community.

An increase in cases to close a classroom from 1 to 2 cases results in an increase by 15.09% in total number of infections. An increase in cases to close a classroom from 2 to 3 cases, results in an increase by 3.59% in total number of infected.

The relationship between the number of cases to close a classroom and the response in a high transmissibility pandemic scenario is not longer linear. Increasing the number of cases to close a class from 1 to 2, increases the total number of infections by 15.09% which is a significant increase. As we keep increasing the number of cases from 2 to 3, we can still see an increase in the response, but not as significant.

An increase in the number of classes to close a school from 1 to 2 classes, results in an increase by 4.62% in total number of infections. An increase in the number of classes to close a school from 2 to 3 classes, results in an increase by 1.71% in total number of infections.

The relationship between number of classes to close a school and the response in a high transmissibility pandemic scenario is not longer linear. Increasing the number of classes to close a school from 1 to 2, increases the total number of infections by 4.62% but as we keep increasing the number of classes from 2 to 3, we can still see an increase in the response, but with a lower percentage increase.

An increase in school closure duration from 21 to 30 days, results in a decrease by 0.54% in total number of infections. An increase in school closure duration from 30 to 42 days, results in a decrease by 3.02% in total number of infections.

As opposed to the findings about this factor in the low transmissibility scenario, school closure duration impact is more notable between 30 and 42 days, as school closure duration increases from 10 to 30 days is still decreases the total number of infected but the percentage of decrease is only 0.54% versus 3.02% when closing between 30 and 42 days.

An increase in cases to close a workplace from 3 to 4 cases, results in an increase by 2.21% in total number of infections. An increase in cases to close a workplace from 4 to 5 cases, results in an increase by 1.79% in total number of infections. Workplace closure reduces the total number of infections, but when compared to school closure, the impact of this intervention is not as significant. The number of cases to close a workplace in a high scenario does not longer shows a linear relationship with the total number of infected. But the difference in slope between both sections of the graph is small.

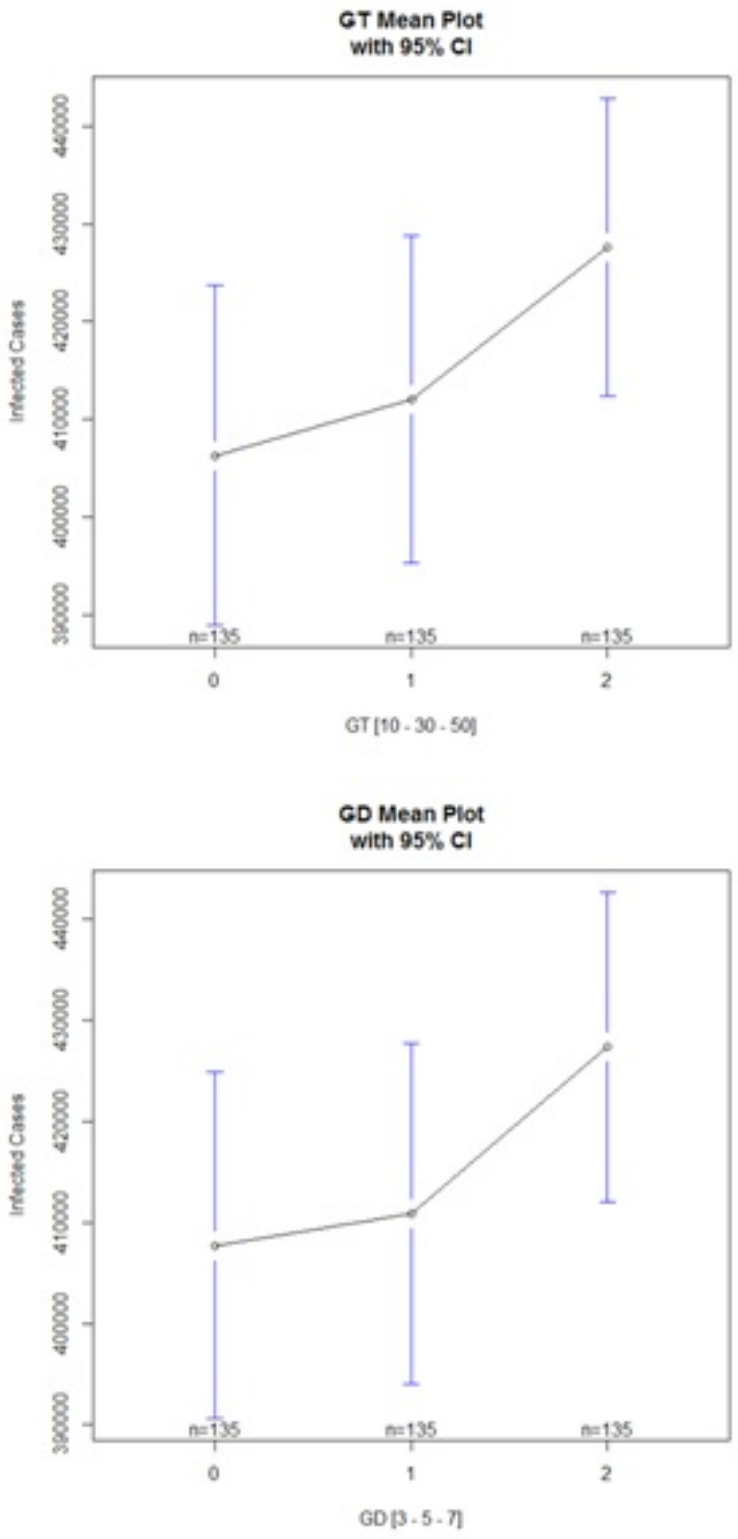
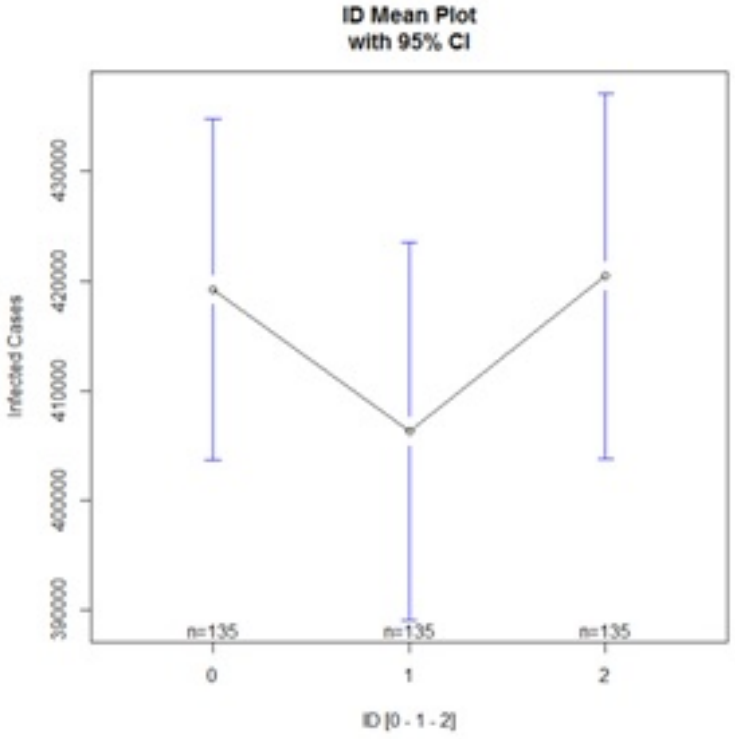


Figure 45: Main factor effects for the high transmissibility scenario for the three-level fractional factorial experiment



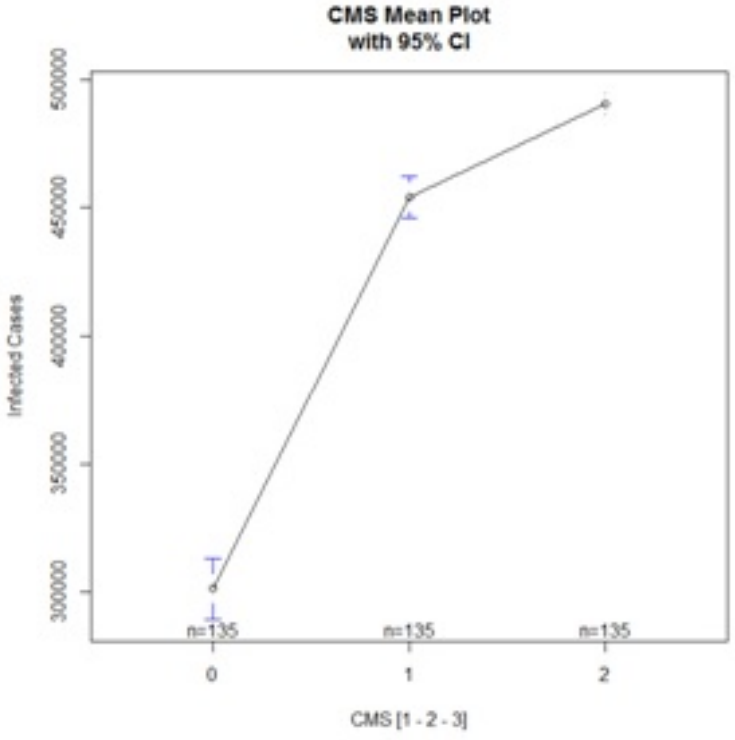
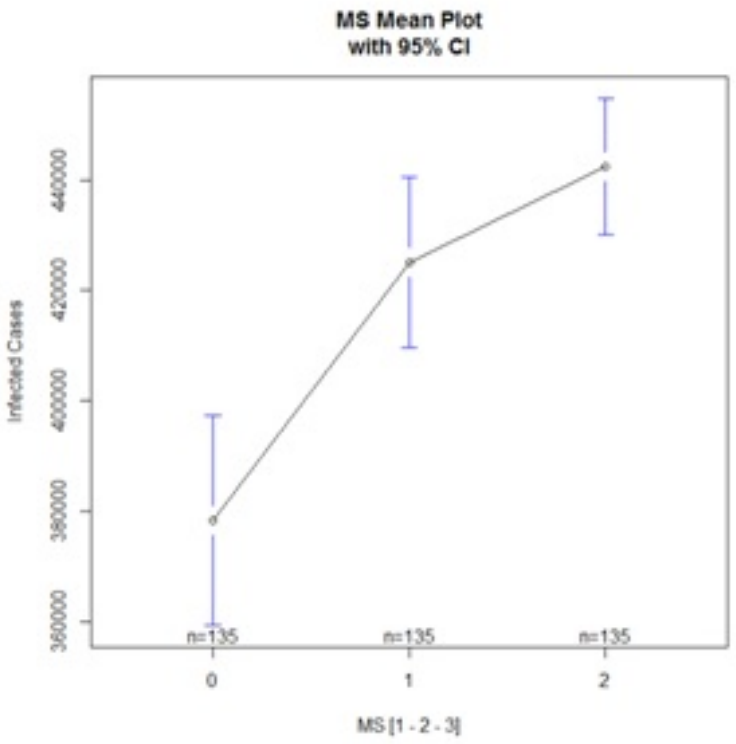


Figure 45: (Continued)



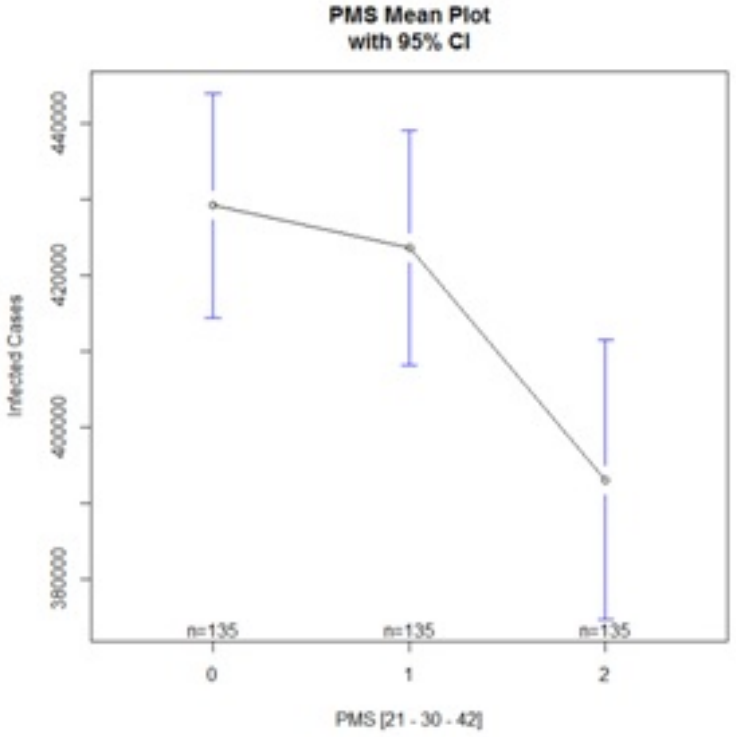


Figure 45: (Continued)

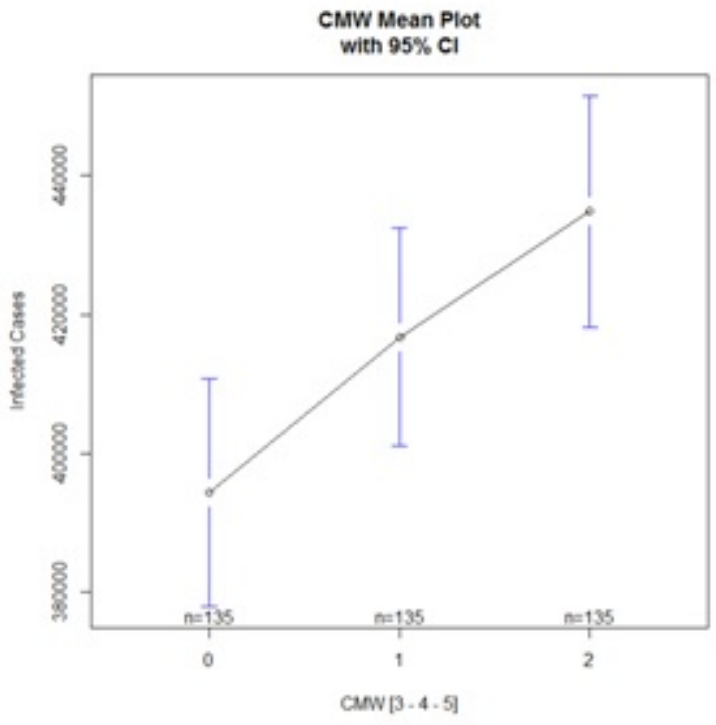


Figure 45: (Continued)

Table 58 shows the mean infected values for the interaction between global threshold and deployment delay for the three-level high transmissibility scenario experiment. Figure 46 shows this interaction graphically. From this information we can observe that when the deployment delay is 3 days, an increase in global threshold from 10 to 30 cases, results in a decrease by 0.57% in total number of infections. An increase in global threshold from 30 to 50 cases, results in an increase by 0.17% in total number of infections.

Table 58: Mean infected values for the interaction between global threshold and global delay for the high transmissibility scenario

GT $\downarrow$ \ GD $\rightarrow$	Low level	Medium level	High level
Low level	410,984.9	403,713.1	404,242
Medium level	405,226.3	407,061.5	423,742.6
High level	406,937	421,805	454,123.5

When the deployment delay is 5 days, an increase in global threshold from 10 to 30 cases, results in an increase by 0.33% in total number of infections. An increase in global threshold from 30 to 50 cases, results in an increase by 1.45% in total number of infections.

When the deployment delay is 7 days, an increase in global threshold from 10 to 30 cases, results in an increase by 1.92% in total number of infections. An increase in global threshold from 30 to 50 cases, results in an increase by 3% in total number of infections.

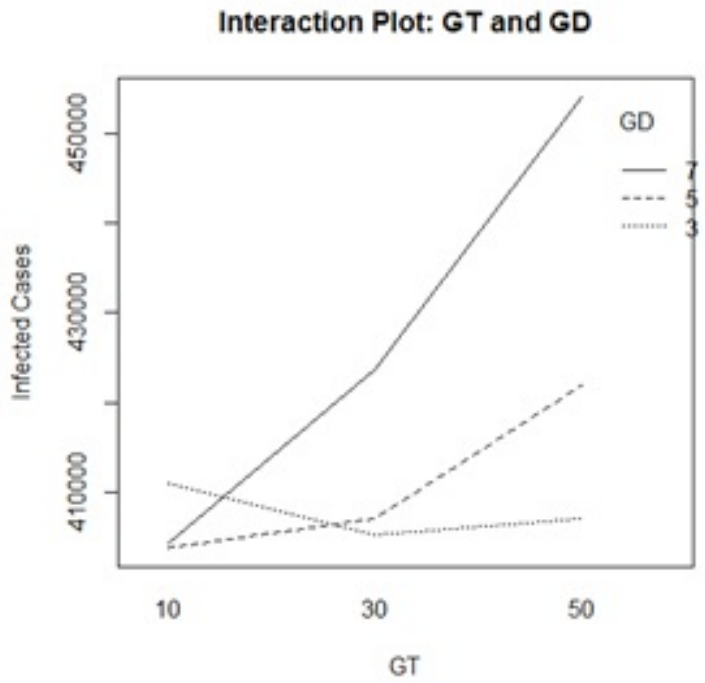


Figure 46: Interaction between global threshold and global delay for the high transmissibility scenario

Table 59: Mean infected values for the interaction between deployment delay and number of classes to close a school for the high transmissibility scenario

GD ↓ \ CMS →	Low level	Medium level	High level
Low level	283690.2	449729.4	489728.6
Medium level	289868	452268.7	490442.9
High level	490442.9	460511.1	491348

Table 59 shows the mean infected values for the interaction between deployment delay and the number of cases to close a classroom for the three-level high transmissibility scenario experiment. Figure 47 shows this interaction graphically. We can observe that when the number of cases to close a class is one, an increase in deployment delay from 3 to 5 days results in an increase by 0.61% in the total of infections. And an increase in deployment delay from 5 to 7 days results in an increase by 3.98% in the total number of infected.

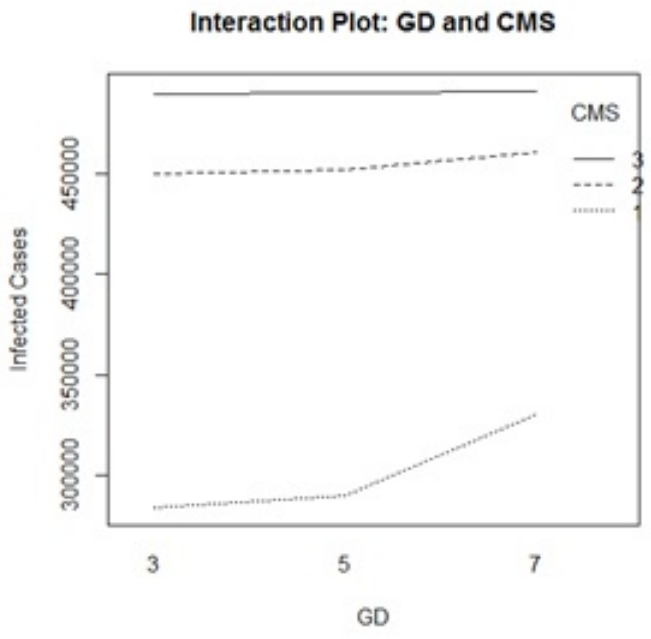


Figure 47: Interaction between deployment delay and number of classes to close a school for the high transmissibility scenario

When the number of cases to close a class is two, an increase in deployment delay from 3 to 5 days results in an increase by 0.25% in the total number of infections. And an increase in deployment delay from 5 to 7 days results in an increase by 0.81% in the total number of infected.

When the number of cases to close a class is three, an increase in deployment delay from 3 to 5 days results in a decrease by 0.07% in the total number of infections. And an increase in deployment delay from 5 to 7 days results in an increase by 0.09% in the total number of infected.

Table 60: Mean infected values for the interaction between the number of cases to close a classroom and school closure duration for the high transmissibility scenario

CMS $\downarrow$ \ PMS $\rightarrow$	Low level	Medium level	High level
Low level	323,216.9	321,756.7	258,833.6
Medium level	465,211.7	455,118.2	442,179.2
High level	499,127	494,195.2	478,197.2

Table 60 shows the mean infected values for the interaction between the number of cases to close a classroom and school closure duration for the three-level high transmissibility

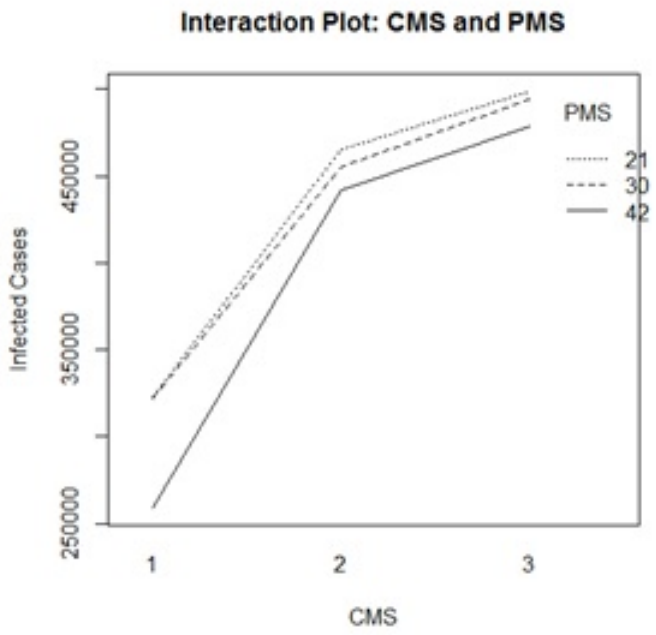


Figure 48: Interaction between the number of cases to close a classroom and school closure duration for the high transmissibility scenario

scenario experiment. Figure 48 shows this interaction graphically. From this information we can observe that when school closure duration is 21 days, an increase in the number of cases to close a classroom from 1 to 2 cases, results in an increase by 14.01% in the total number of infections. And an increase in the number of cases to close a classroom from 2 to 3 cases, results in an increase by 3.35% in the total number of infections.

When school closure duration is 30 days, an increase in the number of cases to close a classroom from 1 to 2 cases, results in an increase by 13.16% in the total number of infections. And an increase in the number of cases to close a classroom from 2 to 3 cases, results in an increase by 3.86% in the total number of infections.

When school closure duration is 42 days, an increase in the number of cases to close a classroom from 1 to 2 cases, results in an increase by 18.09% in the total number of infections. And an increase in the number of cases to close a classroom from 2 to 3 cases, results in an increase by 3.55% in the total number of infections.

The regression analysis for the high transmissibility scenario three-level fractional factorial experiment is shown in Table 61.

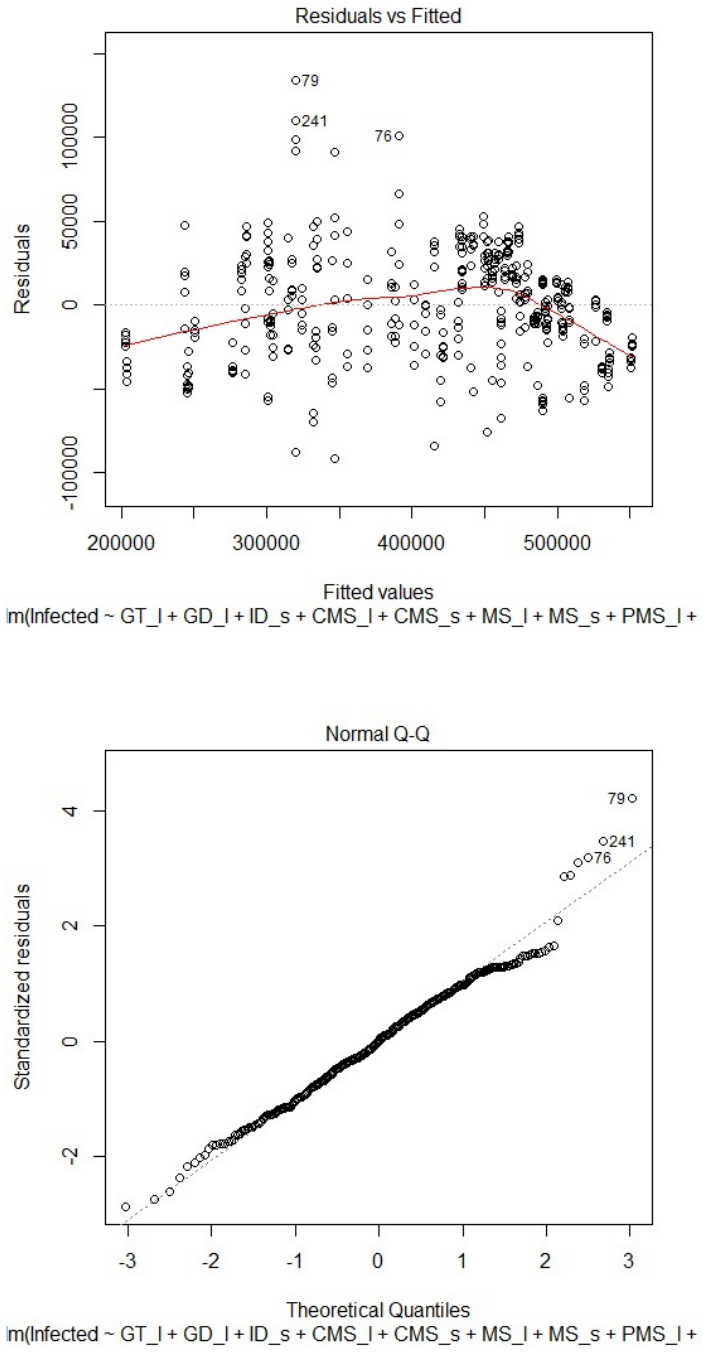


Figure 49: Residuals plot and normal probability plot for regression analysis of the high transmissibility scenario for the three-level fractional factorial experiment

Table 61: Regression analysis for the high transmissibility scenario for the three-level fractional factorial experiment

Factor	Estimate	Std. Error	t value	Pr(>|t|)	Signif.
(Intercept)	457001.6	6227.8	73.381	< 2e-16	***
GT_l	10654.3	1969.4	5.41	1.11E-07	***
GT_s	4957.4	3411.1	1.453	1.47E-01	
GD_l	9826.6	1969.4	4.99	9.16E-07	***
GD_s	6682.8	3411.1	1.959	5.08E-02	.
ID_l	642.6	1969.4	0.326	7.44E-01	
ID_s	13556.5	3411.1	3.974	8.42E-05	***
CMS_l	94618.7	1969.4	48.045	< 2e-16	***
CMS_s	-58281.9	3411.1	-17.086	< 2e-16	***
MS_l	32089.5	1969.4	16.294	< 2e-16	***
MS_s	-14749.2	3411.1	-4.324	1.95E-05	***
PMS_l	-18057.6	1969.4	-9.169	< 2e-16	***
PMS_s	-12562.5	3411.1	-3.683	2.63E-04	***
CMW_l	20236.1	1969.4	10.275	< 2e-16	***
CMW_s	-2132.9	3411.1	-0.625	5.32E-01	
GT_l:GD_l	11484.3	2491.1	4.61	5.48E-06	***
GD_l:CMS_l	-11234.8	2412	-4.658	4.40E-06	***
CMS_l:PMS_l	7992.3	2491.1	3.208	1.45E-03	**

This model has an R-square value of 88.82%. The regression analysis is shown in Table 61 and the analysis of residuals and normal probability plot of residuals is shown in Figure 49. The optimization of the resulting regression equation resulted in a significantly better strategy than the typical NPI strategy shown before. The strategy resulting from the three-level experiment performs better than the strategy resulting from the two-level experiment. However the difference between the two is not as notable as with the low transmissibility scenario.

Table 62: Optimal NPI strategy for the high transmissibility scenario based on the three-level fractional factorial experiment

Factor	**Optimal Value**	**Factor**	**Optimal Value**	**Factor**	**Optimal Value**
GT	50	GD	3	ID	1
IP	7	ICW	0.75	ICNW	0.84
HD	1	HP	7	HCW	0.75
HCNW	0.57	CMS	1	MS	1
PMS	42	CMW	3	MW	0.3
PMW	14				

Table 63: Performance measures for baseline vs. optimal NPI strategy for the high transmissibility scenario based on the three-level fractional factorial experiment

Measure	**Baseline**	**NPI**	**Measure**	**Baseline**	**NPI**
IAR	64.53%	16.42%	Infections 0-19 yrs.	229,952	57,012
CFR	2.55%	0.67%	Infections 20-64 yrs.	344,381	86,064
Pandemic Duration (Days)	83	350	Infections 65-99 yrs.	79,718	23,390
Total Contacts	1,063,751	245,796	Infections Households	136,127	83,511
Contacts 0-19 yrs.	482,881	91,155	Infect. MG Types(1-2)	249,929	60,733
Contacts 20-64 yrs.	468,013	119,228	Infect. Schools	256,796	19,518
Contacts 65-99 yrs.	112,857	35,413	Infect. MG Types(9-12)	11,199	2,704
Contacts Households	234,411	121,651	Total Deaths	25,858	6,770
Contacts MG Types(1-2)	439,368	97,770	Deaths 0-19 yrs.	1,077	256
Contacts Schools	372,678	22,454	Deaths 20-64 yrs.	16,018	3,957
Contacts MG Types(9-12)	17,294	3,921	Deaths 65-99 yrs.	8,763	2,557
Total Infections	654,051	166,466			

The resulting optimal strategy is shown in Table 63 and the results comparing the performance of this strategy with the baseline scenario is shown in Table 63. In the high transmissibility scenario, containment of pandemic was not achieved, also it extends pandemic duration significantly. However, the optimal NPI strategy reduced overall number of infections, contacts and deaths. Figures 50 through 52 shows this information graphically. From these graphs we can see that the optimal strategy not only reduces significantly the total number of infected, but also peak attack rates and peak death rates. However, as opposed to what was observed in the low and medium transmissibility scenarios, the optimal NPI strategy resulting from the three-level experiment for the high transmissibility scenario results in the emergence of new pandemic waves.

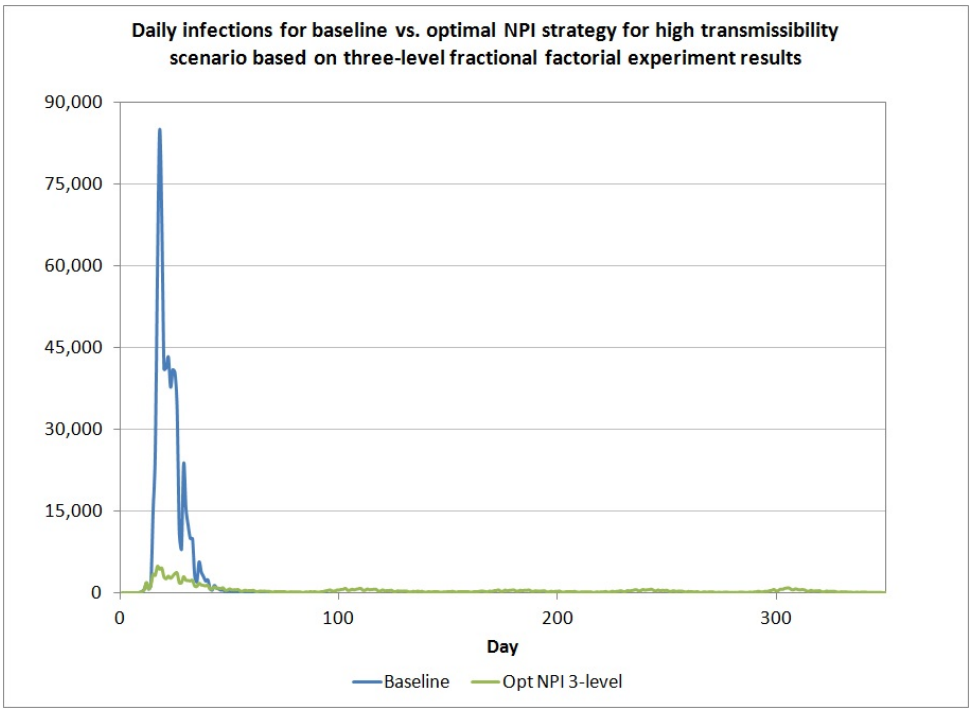


Figure 50: Daily infections for baseline vs. optimal NPI strategy for the high transmissibility scenario based on the three-level fractional factorial experiment

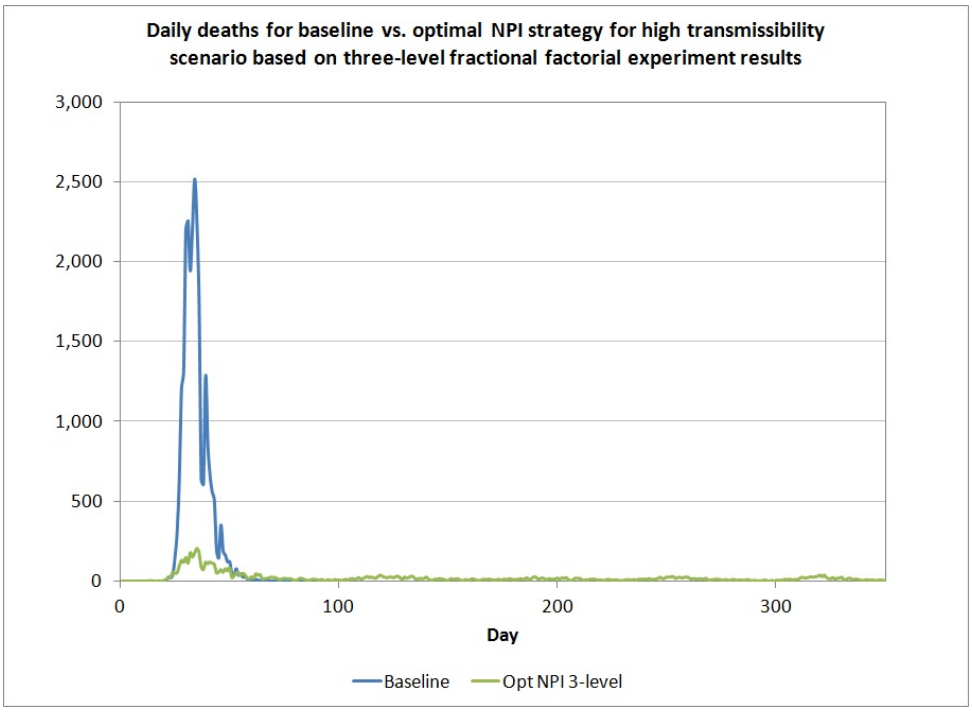


Figure 51: Daily deaths for baseline vs. optimal NPI strategy for the high transmissibility scenario based on the three-level fractional factorial experiment

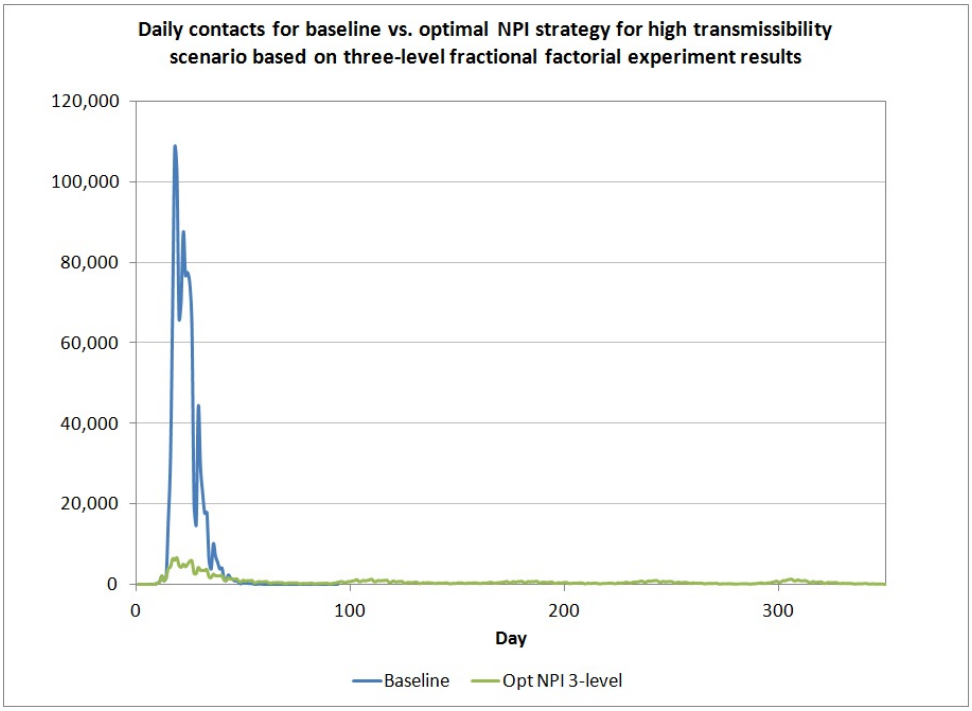


Figure 52: Daily contacts for baseline vs. optimal NPI strategy for the high transmissibility scenario based on the three-level fractional factorial experiment

6.4 Comparison Between Optimal Strategies and Scenarios

In this section we compare the results from the optimal strategies resulting from the two and three-level experiment and across scenarios. Table 64 shows the optimal implementation parameter values for the low, medium and high transmissibility scenarios. This table helps to visualize the changes in parameter values depending on the transmissibility scenario. For example, compliance values for workers during case isolation seem to not be as important in a medium scenario as it is for the low and high scenarios. Similarly, case isolation compliance for non-workers optimal value is low for the low scenario and high for the medium and high scenarios. Another example is school closure duration, optimal values of duration for the medium and high scenarios is 42 days, however in a low transmissibility scenario, a closure of 35 days is optimal. Also, school closure in general is more relaxed for the low transmissibility scenario, we can see the same results for workplace closure in the low and medium transmissibility scenarios. However, in a high transmissibility scenario, a stringent school and workplace closure policy is what resulted optimal.

Table 64: Comparison of the two-level and the three-level optimal strategies across transmissibility scenarios

Factor	Opt NPI 2	Opt NPI 3	Opt NPI 2	Opt NPI 3	Opt NPI 2	Opt NPI3
Global threshold	10	10	10	32	10	50
Deployment delay	7	3	3	3	3	3
Case isolation threshold	1	1	1	1	1	1
Case Isolation duration	10	10	7	7	7	7
Case isolation compliance for workers	0.75	0.75	0.53	0.53	0.75	0.75
Case isolation compliance for non-workers	0.57	0.57	0.84	0.84	0.84	0.84
Household quarantine threshold	1	1	1	1	1	1
Household quarantine duration	7	7	7	7	7	7
Hosuehold quarantine compliance for workers	0.53	0.53	0.75	0.75	0.75	0.75
Household quarantine compliance for non-workers	0.84	0.84	0.84	0.84	0.57	0.57
Cases to close a class	1	1	1	1	1	1
Classes to close a school	3	1	1	1	1	1
School closure duration	21	35	42	42	42	42
Cases to close a department	3	3	3	3	3	3
Percentage of departments to close a workplace	0.3	0.3	0.5	0.5	0.3	0.3
Workplace closure duration	7	7	14	14	14	14

Table 65 shows in one place all results from baseline, non-optimal NPI, optimal NPI from the two-level experiment, and optimal NPI from the three-level experiment. As seen in this table, NPIs in general reduce IAR, CFR, total number of contacts, total number of infections and total number of deaths. However, the resulting strategies from our model, performed significantly better than a non-optimal NPI strategy and a scenario with no intervention. For the low transmissibility scenario, containment was achieved with the optimal 2-level and 3-level strategy. Additionally, the optimal 3-level strategy performed significantly better than the optimal 2-level strategy.

For the medium transmissibility scenario containment was also achieved with both 2-level and 3-level optimal strategies. However, the difference from both strategies is small compared to that observed in the low transmissibility scenario. As observed in the low transmissibility scenario, both strategies were capable of further reducing total number of contacts, infections and deaths.

For the high transmissibility scenario, containment was not achieved and the difference in performance between the optimal 2-level and 3-level strategies was small. But even though for a high transmissibility scenario containment was not achieved by using NPIs alone, it was successful in reducing overall number of contacts, infections and deaths.

The optimal strategy also extends the pandemic, giving enough time for vaccines to be developed, produced and distributed.

Figure 53 shows the graphs for the optimal 2-level and 3-level experiment for the low, medium and high transmissibility scenarios. These figures show clearly that both optimal strategies were able to reduce peak attack rates and deaths for all scenarios considered. However, the optimal 2-level strategy resulted in the emergence of new pandemic waves in all scenarios considered. The optimal 3-level strategy takes care of this for the low and medium scenario, new waves are observed only for the high transmissibility scenario.

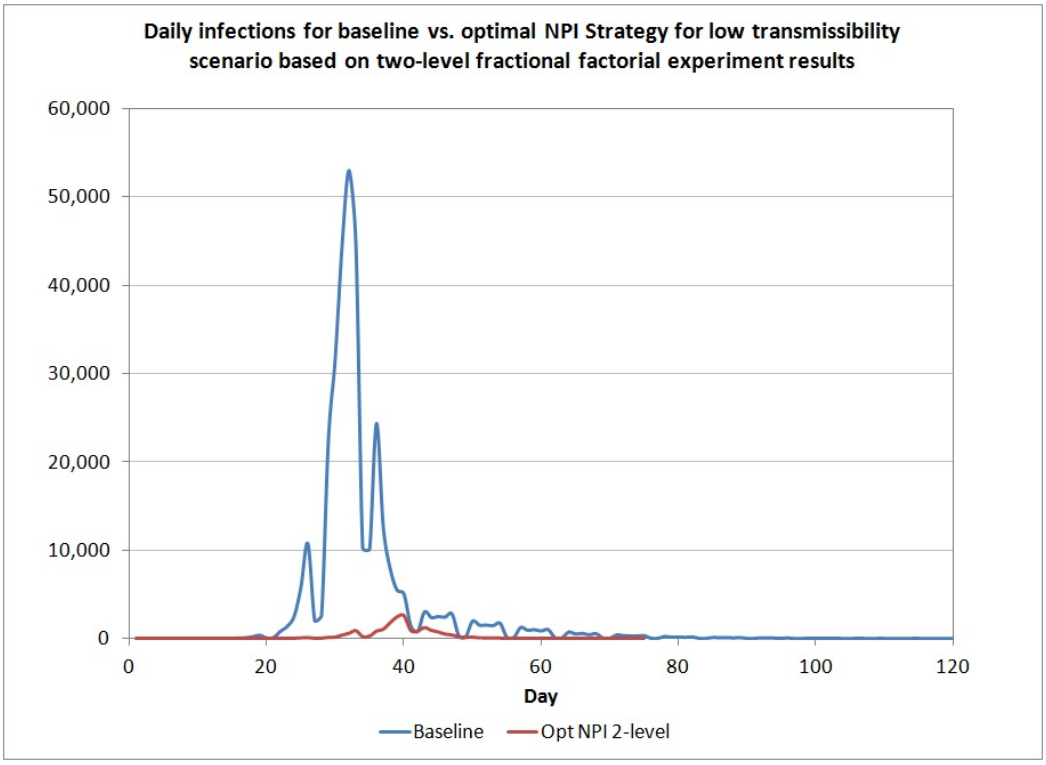
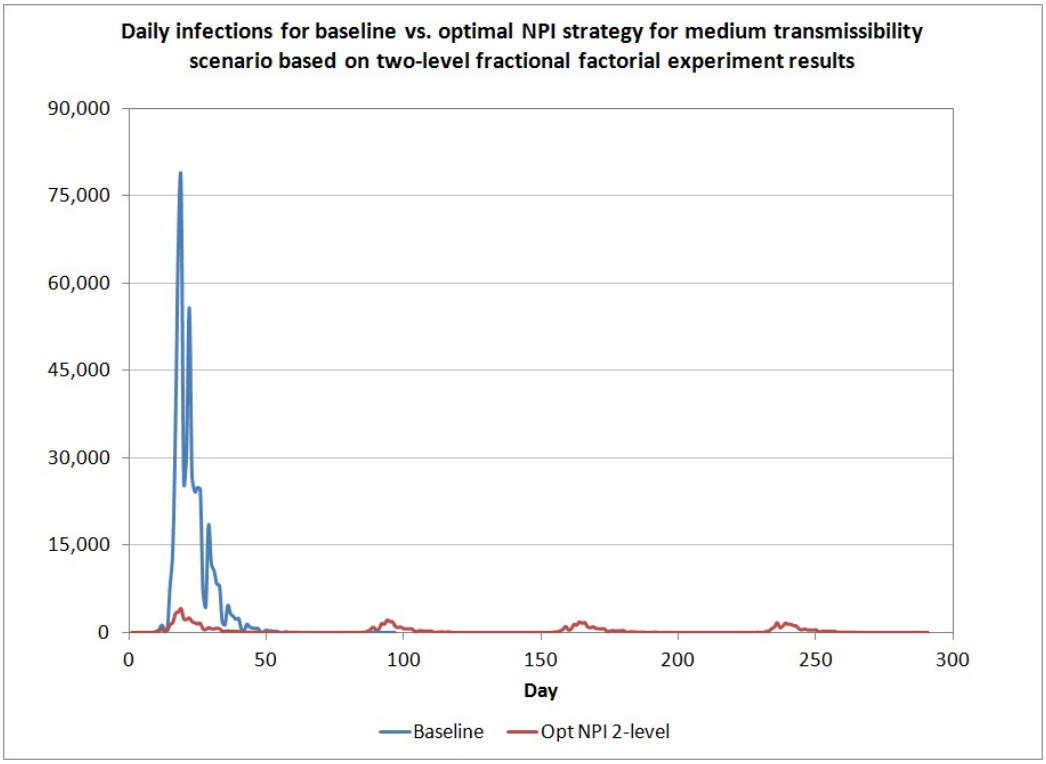
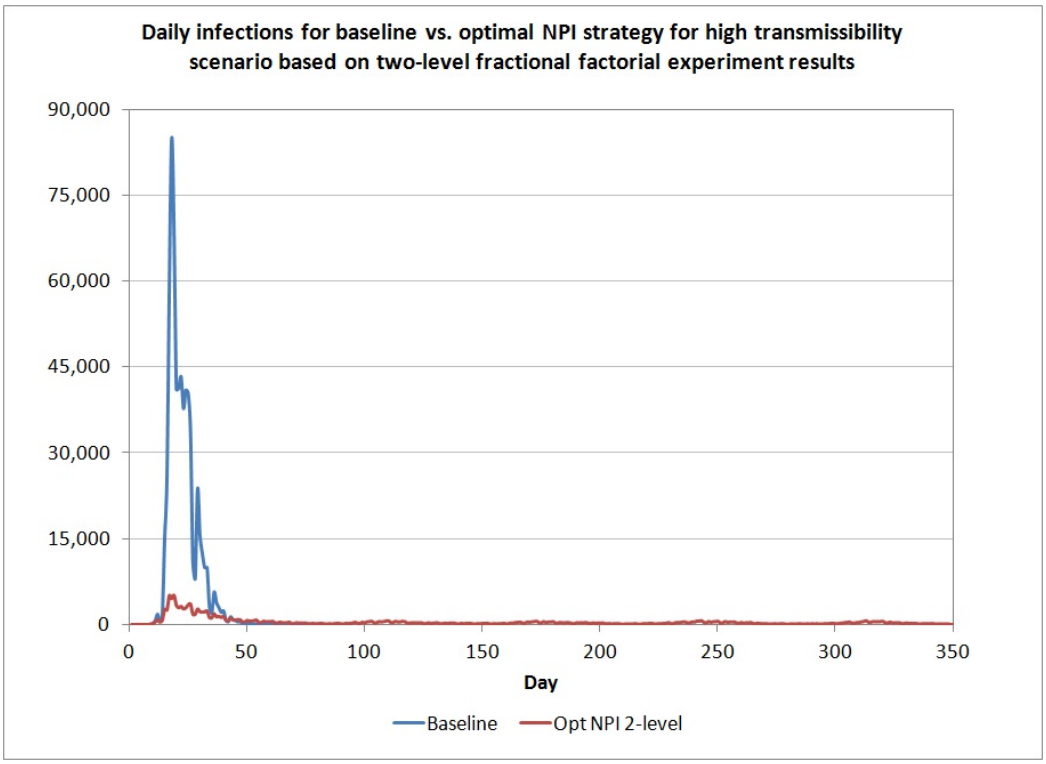


Figure 53: Daily infections, deaths and contacts for baseline and optimal two and three-level NPI strategies for three transmissibility scenarios





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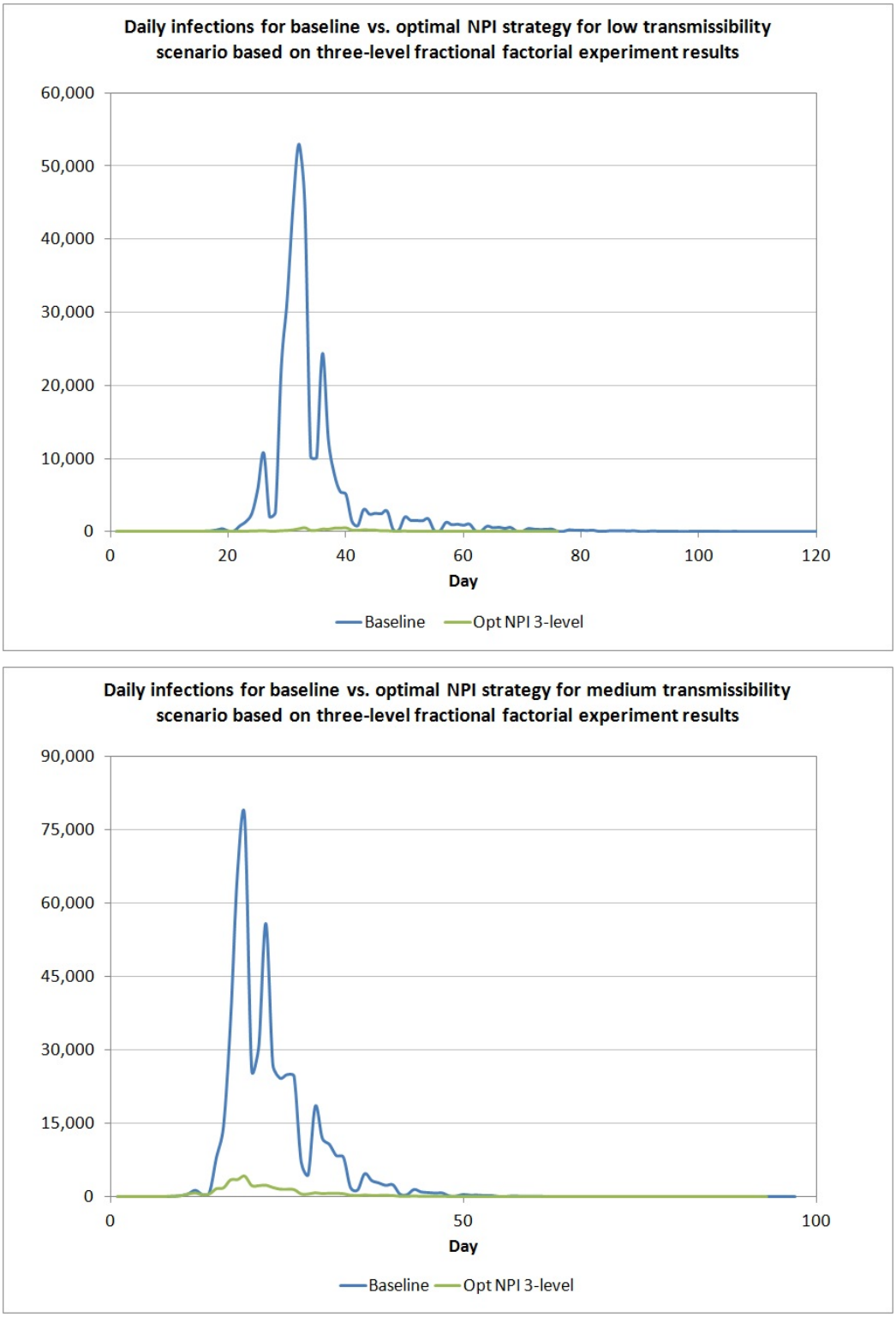

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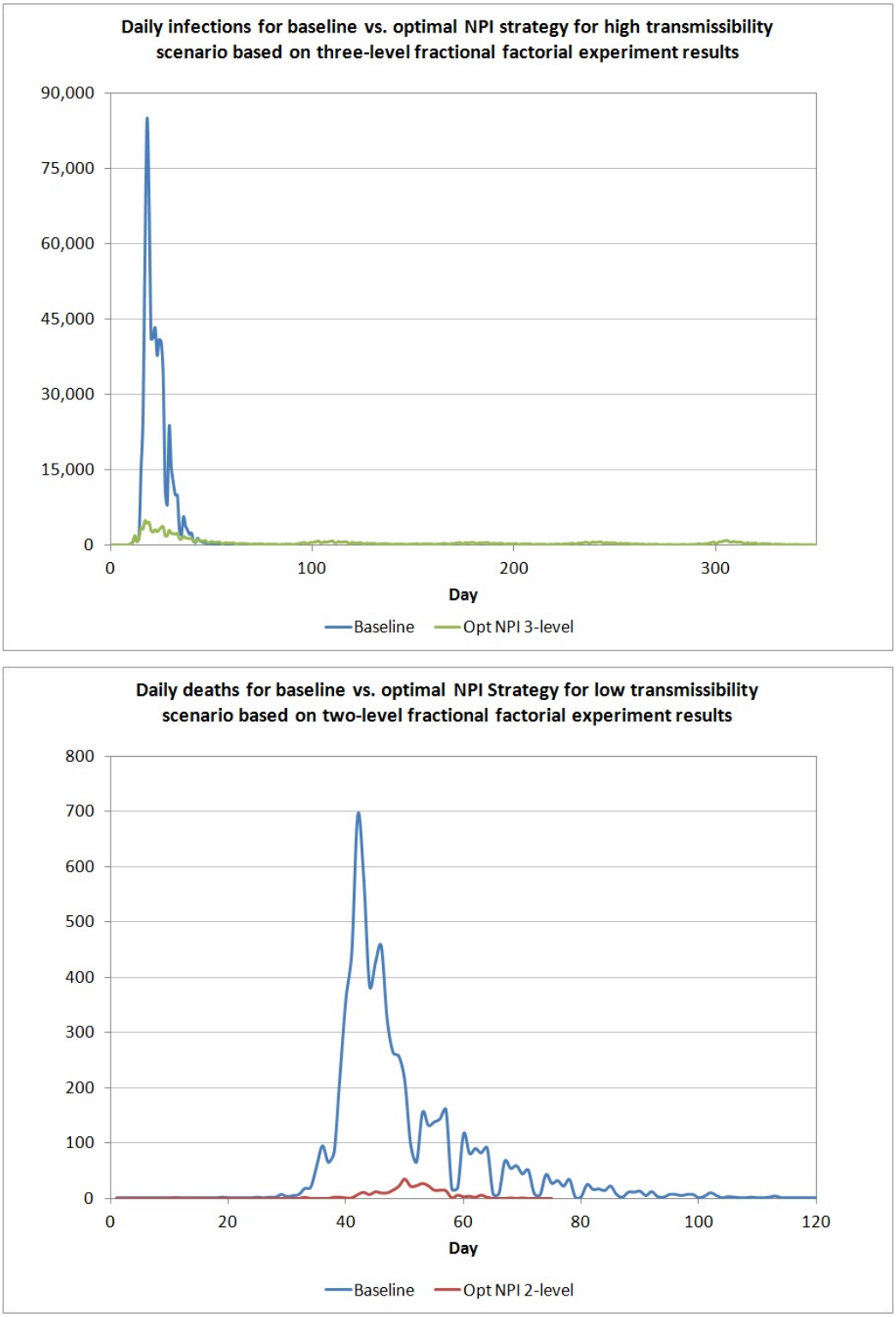

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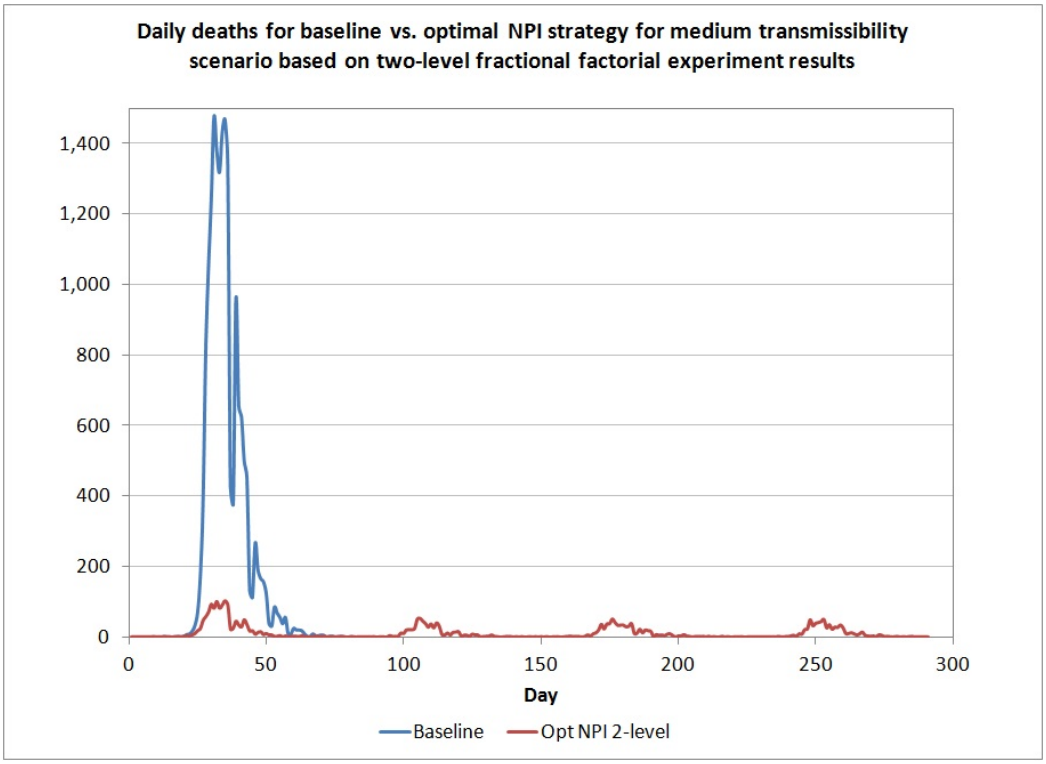

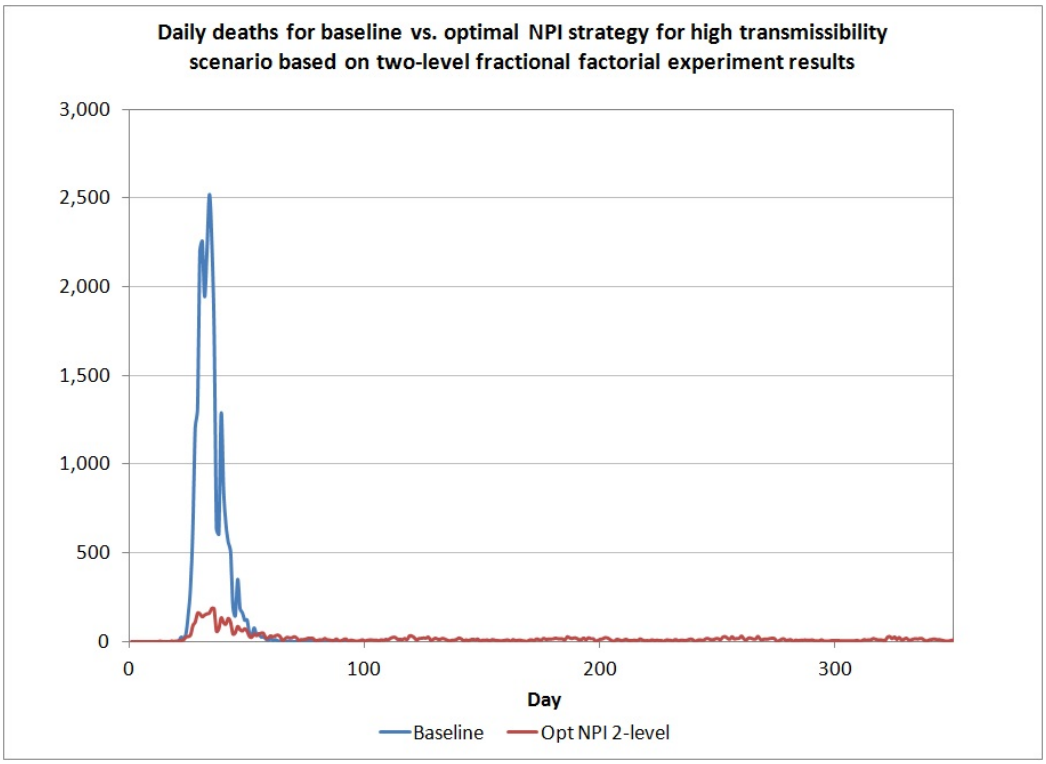

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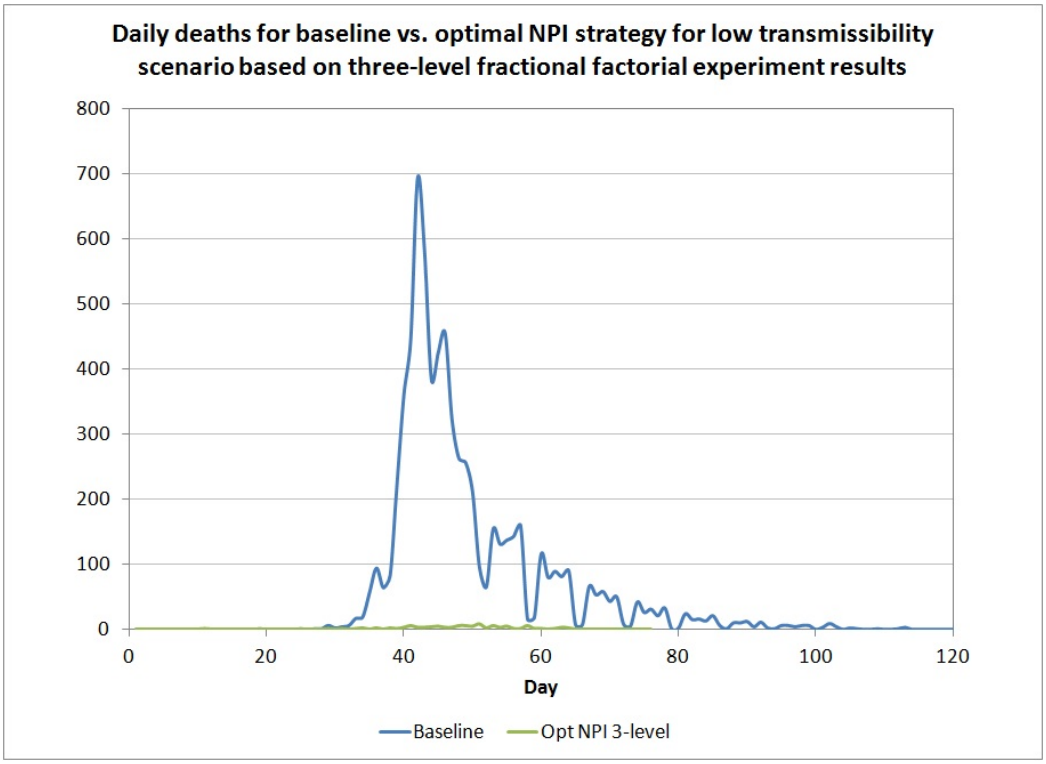

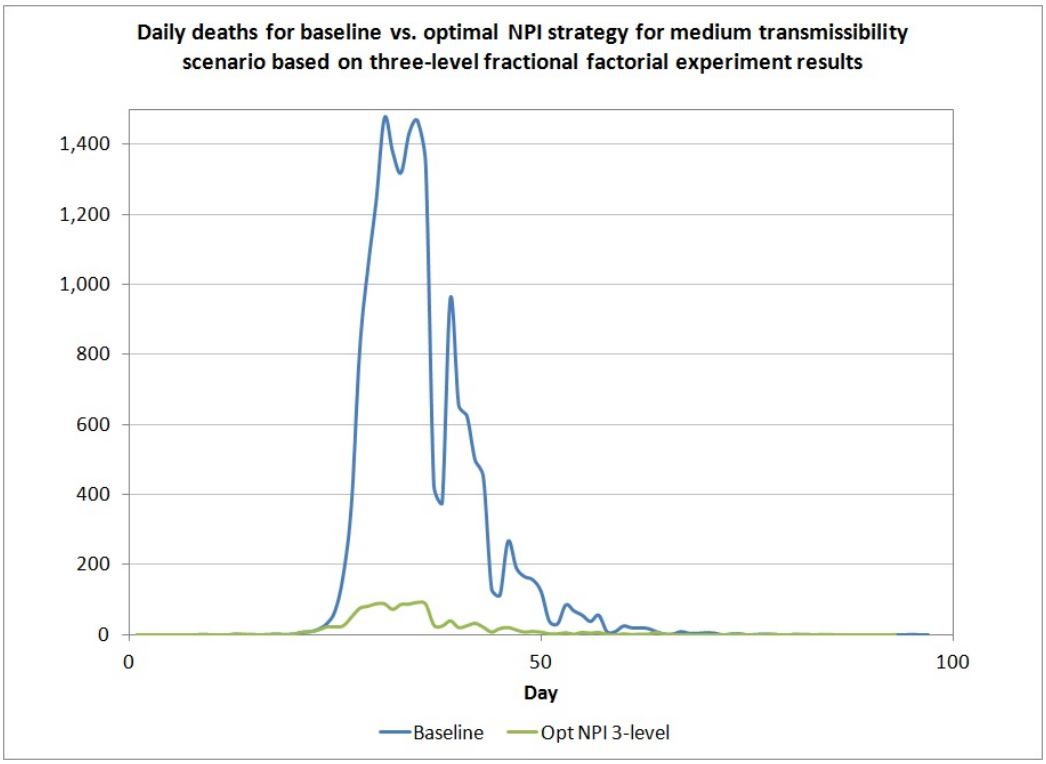

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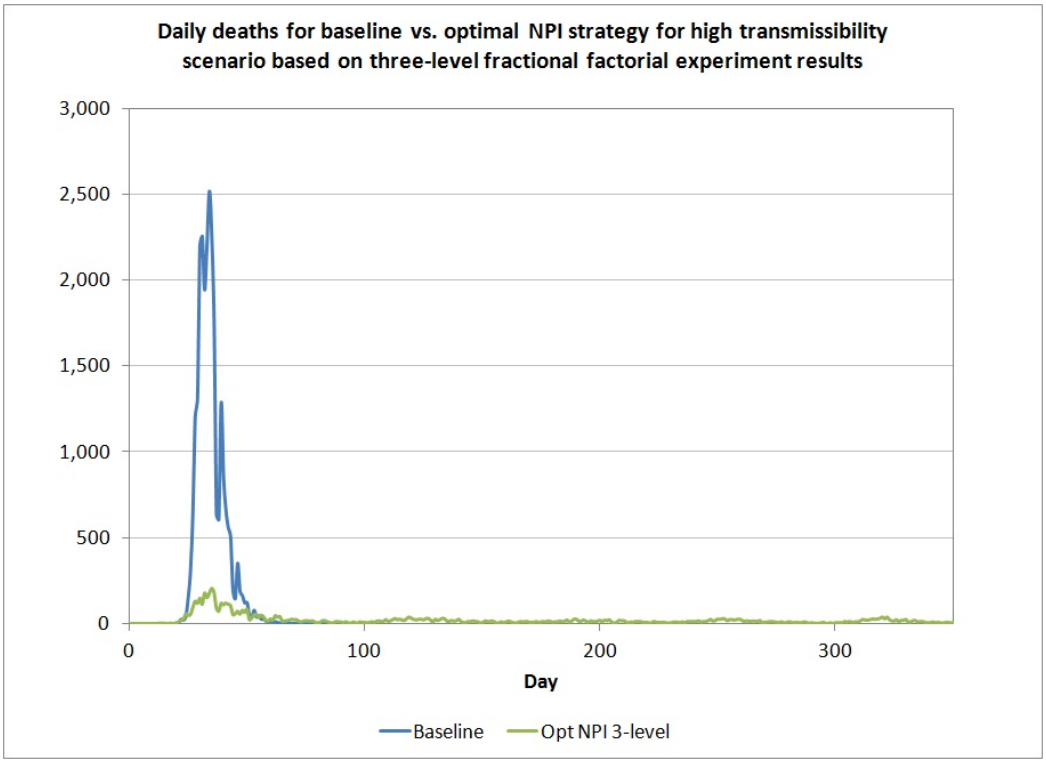

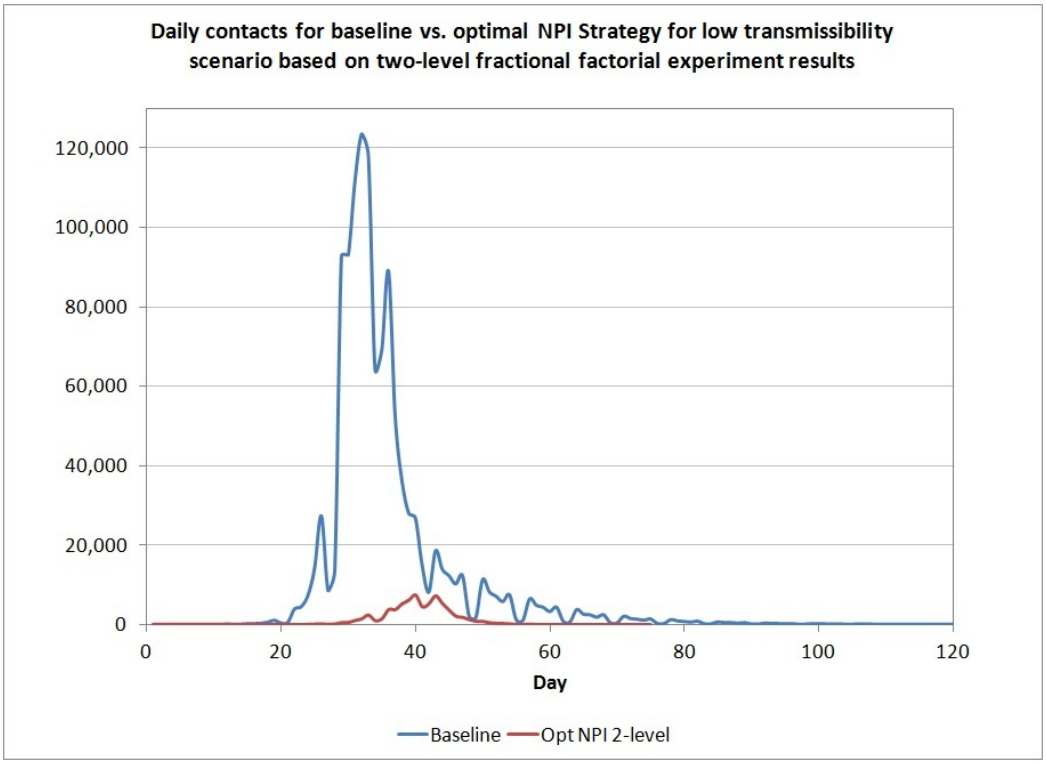

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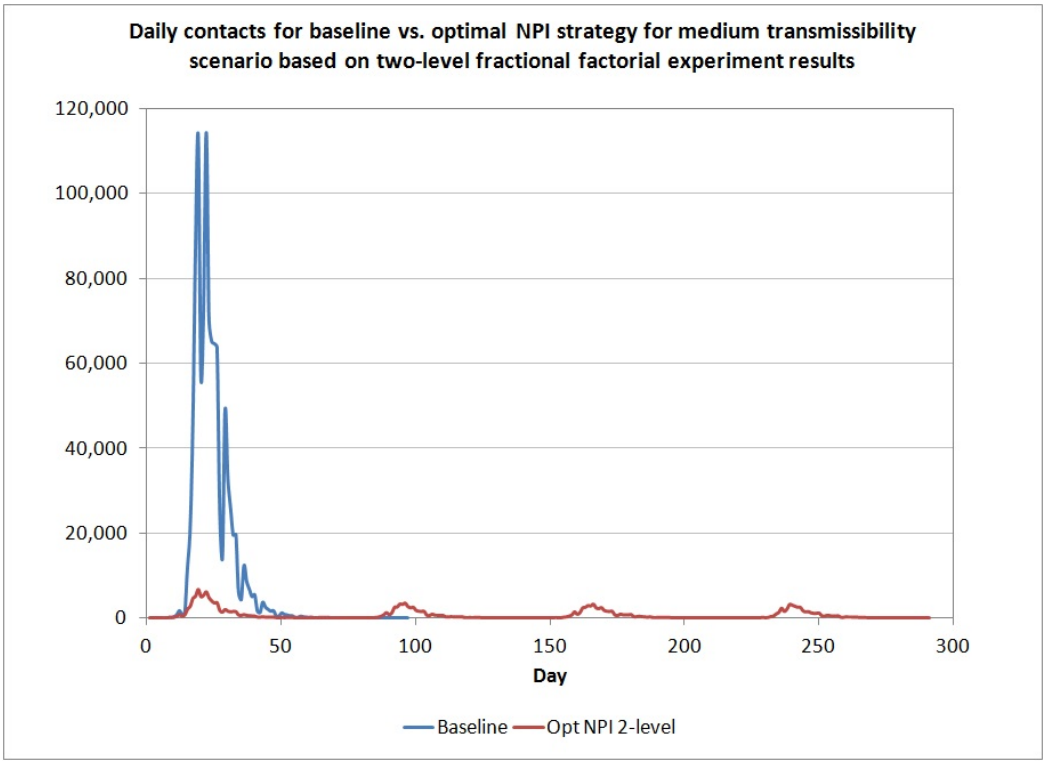

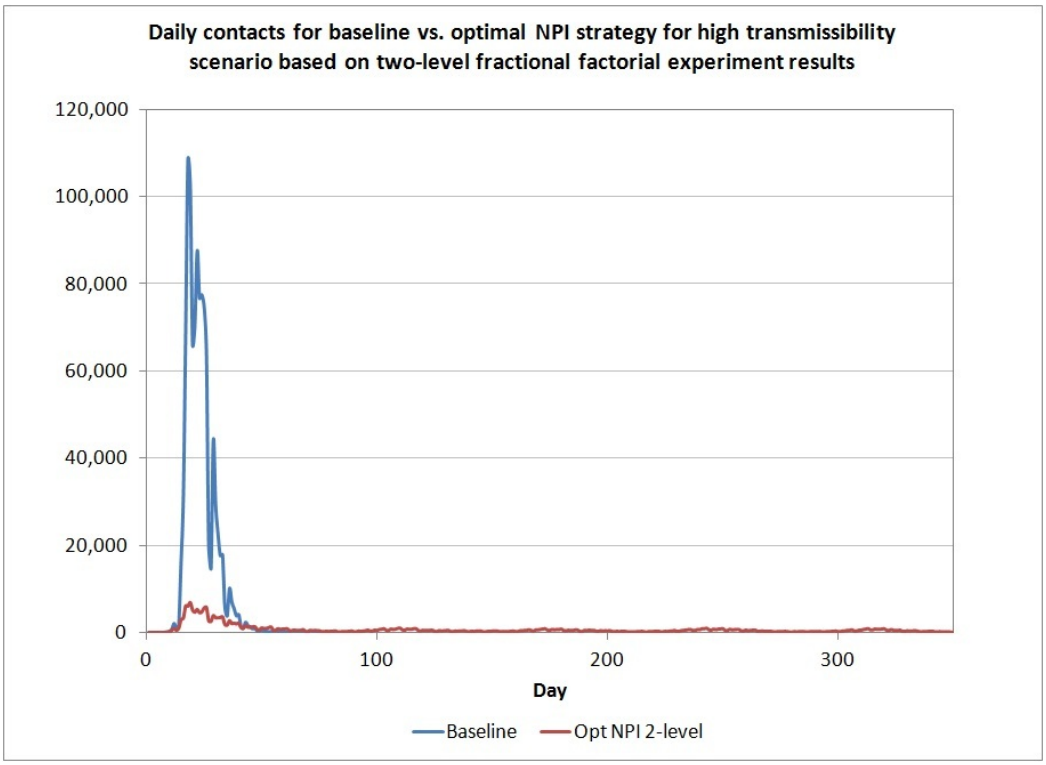

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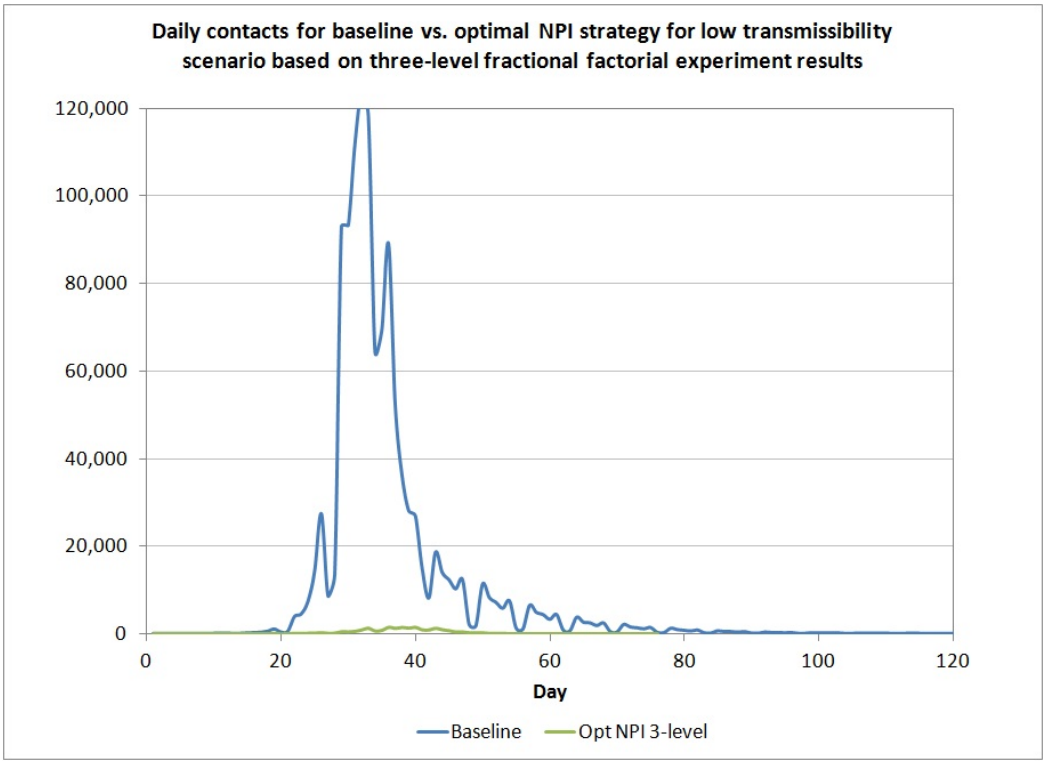

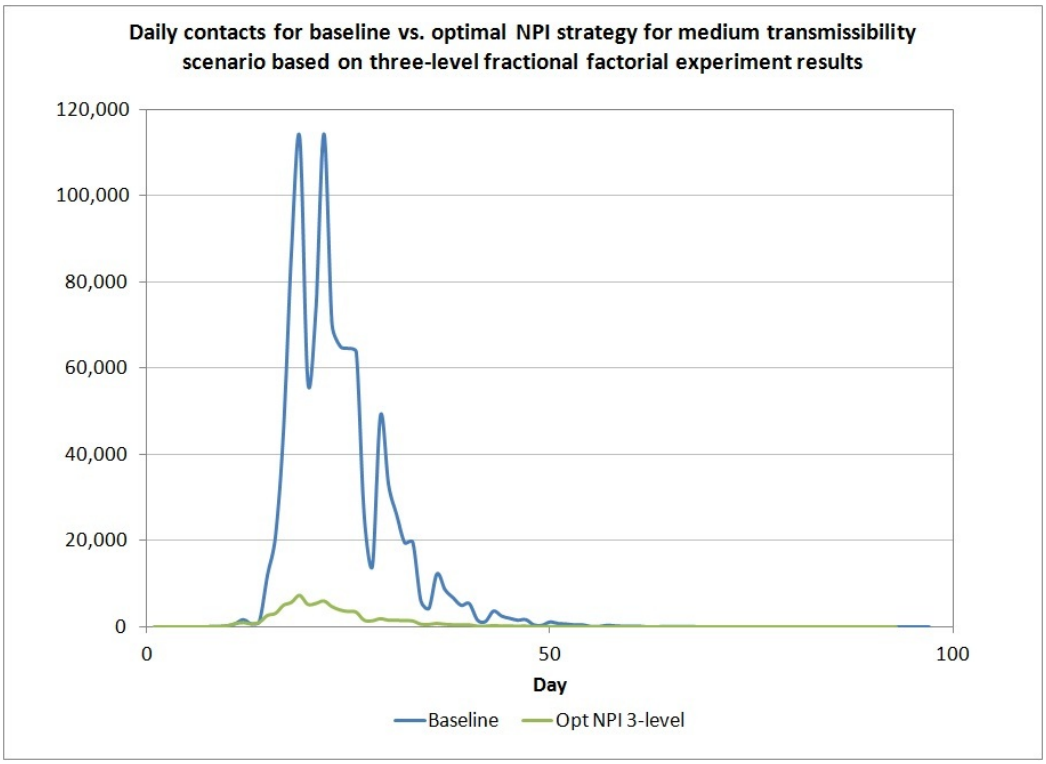

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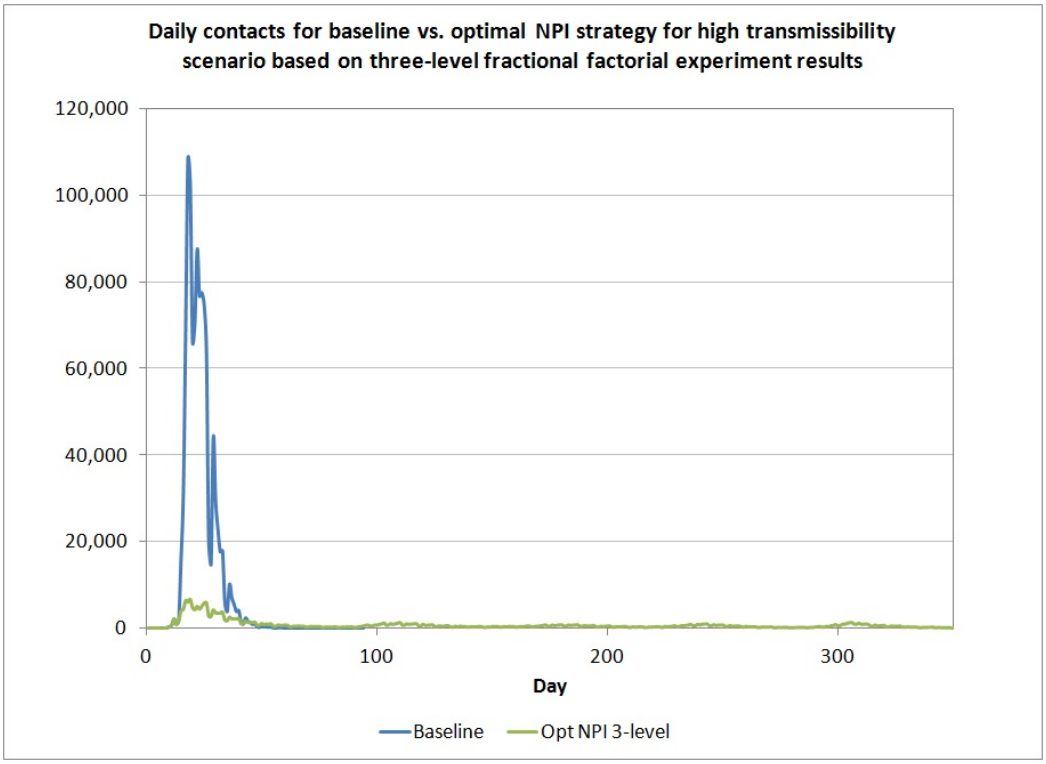

Figure 53: (Continued)

Table 65: Comparison of two-level and three-level optimal strategies across transmissibility scenarios for different performance measures

Scenario	Low Transmissibility			Medium Transmissibility			High Transmissibility		
Performance Measure	Base Line	Non-optimal NPI	Optimal NPI	Base Line	Non-optimal NPI	Optimal NPI	Base Line	Non-optimal NPI	Optimal NPI
IAR	33.06%	20.62%	0.55%	50.80%	36.91%	3.07%	64.53%	46.08%	16.42%
CFR	0.69%	0.37%	0.01%	1.76%	1.10%	0.10%	2.55%	1.60%	0.67%
Pandemic Duration [days]	135	350	76	93	350	60	83	271	350
Total Contacts	1,177,393	738,716	21,440	1,047,302	709,958	60,964	1,063,751	682,295	245,796
0 - 9 years	818,912	618,661	19,066	520,883	484,052	35,465	482,881	432,625	91,155
20 - 64 years	294,046	102,973	1,887	416,307	181,986	19,255	468,013	203,731	119,228
65 - 99 years	64,435	17,082	487	110,112	43,920	6,244	112,857	45,939	35,413
Households	238,684	344,169	11,904	236,850	361,050	35,176	234,411	336,832	121,651
Workplaces type 1 - 2	231,051	37,785	891	392,793	106,101	15,118	439,368	118,571	97,770
Schools	699,427	352,987	8,544	403,908	235,560	9,999	372,678	217,948	22,454
Workplaces type 9 - 12	8,231	3,775	101	13,751	7,247	671	17,294	8,944	3,921
Total Infections	335,071	208,959	5,548	514,844	374,132	31,109	654,051	467,026	166,466
0 - 9 years	225,467	156,849	4,315	230,127	201,319	15,219	229,952	210,941	57,012
20 - 64 years	91,959	43,135	961	228,753	137,328	12,275	344,381	206,455	86,064
65 - 99 years	17,645	8,975	272	55,964	35,485	3,615	79,718	49,630	23,390
Households	37,562	65,107	2,292	92,217	141,603	16,339	136,127	203,884	83,511
Workplaces Type 1 - 2	46,600	7,019	153	168,185	49,784	6,848	249,929	73,968	60,733
Schools	249,304	136,043	3,080	247,838	178,982	7,573	256,796	183,242	19,518
Workplaces Type 9 - 12	1,605	790	23	6,604	3,763	349	11,199	5,932	2,704
Total Deaths	7,009	3,764	99	17,851	11,111	992	25,858	16,238	6,770
0 - 9 years	1,041	744	17	1,090	975	79	1,077	1,047	256
20 - 64 years	4,095	2,059	54	10,681	6,332	498	16,018	9,725	3,957
65 - 99 years	1,873	961	28	6,080	3,804	415	8,763	5,466	2,557

7 Conclusions

In this dissertation we model pandemic influenza outbreaks using an agent-based simulation approach. The model incorporates detailed population demographics and dynamics, variety of mixing groups and their contact processes, infection transmission process, and non-pharmaceutical interventions. Using a statistical experimental design approach we examine the influence of characteristic parameters of virus epidemiology, social behavior, and non-pharmaceutical interventions on various measures of pandemic impact such as total number of infections, deaths and contacts. The experimental design approach also yields the knowledge of the extent of interactions among the above parameters. Using this knowledge we develop effective NPI strategies and demonstrate the efficacy of these strategies on large-scale simulated outbreaks involving three different scenarios of virus transmissibility. The results show that significant improvements in the NPI based pandemic mitigation approaches can be attained by the strategies derived from our methodology.

Our methodology, to the best of our knowledge, is the first to study several NPI parameters at the same time. All other studies focuses on analyzing one factor at a time and do not investigate the effect of various factors on NPI effectiveness. Also, no other study presents an optimal approach for the use of NPIs during a pandemic influenza outbreak.

Key contributions of this dissertation includes a new approach on the infection transmission process which depends on a time varying profile of infectiousness and viral accumulation as a mean of infection. Also, we use an experimental design approach to examine the influence of significant NPI factors and their interactions. Using that knowledge we derive optimal NPI strategies and were able to demonstrate the efficacy of those strategies on a variety of outbreak scenarios that have enriched our knowledge on how different factors behave differently on different situations. This research has also opened many more questions that will require further study.

As it is already known from previous studies, NPIs can reduce infection attack rates, case fatality ratio, and the overall number of infections, contacts and deaths. Some of the key findings from our optimal design approach for effective NPI strategies are now summarized for each one of the virus transmissibility scenarios considered. For the low virus transmissibility scenario, our optimal NPI strategy was able to achieve pandemic containment (IAR <10%) reducing IAR from 33.06% to 0.55%. Moreover, a reduction in pandemic duration from 135 days to 76 days was achieved, and it did not results in the emergence of new pandemic waves.

For the medium virus transmissibility scenario, our optimal NPI strategy was also able to achieve pandemic containment reducing IAR from 50.80% to 3.07%. It also reduced pandemic duration from 93 days to 60 days. The optimal NPI strategy derived for the medium virus transmissibility scenario did not result in the emergence of new pandemic waves.

However, our optimal NPI strategy for the high virus transmissibility scenario was not able to achieve containment. But a significant reduction in the IAR was observed. It reduced an IAR of 64.53% to 16.42%. This strategy was also successful in reducing overall number of infections, contacts and deaths. In this scenario, the NPI strategy extended the pandemic from 83 days to 350 days and it resulted in the emergence of new pandemic waves throughout this period of time. This extension gives time for the development, production, and distribution of vaccines. But in conclusion, for a high transmissibility scenario a combination of NPIs with PHIs will be necessary for containment.

This work have some limitations that guide our future work. Our simulation model for a single region, does not include mass transportation such as trains, buses, and airplane flights. Consequently we did not study the effect of travel restrictions, which is a very important non-pharmaceutical intervention strategy. Also, we did not consider people arriving or leaving the city, which may have a big impact on the contact and infection transmission processes.

Our contact process can also be improved. We assume that if an individual contacts m other individuals in a period of time of an hour, the time will be divided equally among

the contacts. We do not take into consideration that those contacts may be simultaneous or may last more than $1/m$ minutes with each one of the contacts made.

The infection transmission process has several strong assumptions. Even though the profile of infectiousness vary with time and virus transmissibility scenario, it is constant among the population. It does not depend on age and/or health status. Adding a population characteristics dependant profile of infectiousness is important, since the amount of viral shedding also depends on the age of the individuals and their health (weak, moderate, good).

Viral accumulation is assumed to be depleted completely during the night and starts at zero the next day for individuals that did not get infected during that particular day. An immunity driven reduction in the level of accumulation in the body that comprehends simultaneous accumulation and depletion of virus due to the immunity system would be more realistic.

Even though our work shed some new knowledge on the influence of characteristic parameters of virus epidemiology, social behavior, and non-pharmaceutical interventions on various measures of pandemic impact, and the behavior and extent of interactions among the above parameters, we can't really explain why these behaviors were observed. That was the purpose of conducting a statistical design of experiments. Since the underlying physics of these interactions are unknown, our results shed some knowledge in how these different parameters behave, and some of them were even contrary to our beliefs. Even if we try to rationalize individual behaviors, these are not of huge value in developing a complex comprehensive strategy. Designs of experiments takes care of that, is not one or two factors but multiple factors that comprise the strategy in the regression analysis. Further experimentation is needed to further explore the behavior of these factors and their impact on different measures of performance.

Our three-level experiment was highly fractional and it should be expanded. As a result, we could not examine all two-way interactions, and the model is very limited as it only includes a few of these. Expanding this experiment will allow us to examine higher level of interactions and consequently development of better strategies. Also, the values of

the optimal strategies are given by a range. Further experimentation could be conducted with an expanded range of parameter values.

We did not study several important non-pharmaceutical strategies. Because of the limitation that our simulation does not include mass transportation, we did not study the effect of travel restrictions. Also, the only behavioral factor included in our study was compliance. We don't have other changes in human behavior during a pandemic. Some of these changes in behavior include the use of masks, hand sanitizer and personal hygiene. It is expected that such a change in behavior would have an impact on NPI effectiveness. Other social distancing strategies like closing of mass gathering events are also part of our future work.

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About The Author

Dayna Lee Martinez Torres, original from San Juan, Puerto Rico, received her B.S. in Industrial Engineering from the University of Puerto Rico at Mayagez in 2006 which she finished Cum Laude. In the summer of 2006 she moved to Tampa to continue her studies at the University of South Florida. She first got funded by the NSF Bridge to Doctorate Fellowhip from 2006 to 2008. In 2006 she was awarded with the USF Latino Graduate Fellowship and with an invitation to the National Scholars Honor Society.In 2007 she won the SHPE GEM Graduate Award. In 2008, she received her M.E. in Industrial Engineering and continued to pursue her Ph.D. at the University of South Florida. She was awarded the NSF GK-12 STARS fellowship in 2008 and was funded by this program until June 2012. This program gave her the opportunity to work closely with teachers and students from elementary schools of the Hillsborough County. Among her responsibilities were teaching, developing teacher's workshops and summer camps for students. She has received many other awards that include first prize at the HEENAC Technical Poster Competition in 2010, Research Day Poster Award in 2012 and second prize in the Doctoral Colloquium Poster Competition of the IIE 2012 annual meeting. She is an active member of several student societies such as Alpha Pi Mu Honor Society, IIE and INFORMS.