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Analyzing Human Papillomavirus Vaccine Stockpiles

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Abstract

The development of a vaccine to prevent the contraction of the high-risk strands of human papillomavirus (HPV) 6, 11, 16 and 18 has the potential to prevent 70% of all cervical cancers. The Center for Disease Control and Prevention (CDC) currently recommends that girls aged 11-12 receive the HPV vaccine. At present, eighteen states have already decided or are considering to make HPV vaccination mandatory for adolescent girls. As the HPV vaccine becomes mandatory, the demand for the vaccine is expected to rise dramatically. This increase in demand could make our nation vulnerable to interruptions in HPV vaccine production. If an interruption occurs, many adolescent girls and women could be at an unnecessary risk of acquiring HPV if they were to miss routine HPV immunizations. One major factor in the prevention of HPV vaccine shortages is the creation of vaccine stockpiles by the CDC. In this paper, mathematical models are used to determine and analyze stockpile levels sufficient to minimize the effects of a production interruption for the HPV vaccine. The results indicate that the stockpile level is highly sensitive to the vaccine coverage rate and the duration of the production interruption. To protect against a six month interruption in vaccine production, a stockpile of at least 3M is recommended.

1. Introduction and background

The human papillomavirus (HPV) is an extremely widespread disease. An estimated 6.2 million Americans get a new genital HPV infection every year, and approximately 20 million people are currently infected with HPV [1]. By the age of 50, at least 80% of women will have had an HPV infection [2]. HPV has been recognized as the sole cause of cervical cancer [3]. In 2006, an estimated 10,000 women in the United States were diagnosed with cervical cancer and nearly 4,000 are expected to die from it [3]. Cervical cancer strikes nearly half a million women each year worldwide and claims a quarter of a million lives, making it the third most common cause of cancer-related deaths worldwide [3, 4, 5, 6].

It is estimated that over 100 types of HPV exist. Of those 100 types, more than 30 types can be passed through sexual contact. Of these 30 types, some are referred to as “low-risk” strands because they rarely develop into cancer, while the other types are referred to as “high-risk” because these strands are more likely to lead to cervical cancer [3]. It is believed that high-risk types 16 and 18 cause approximately 70% of cervical cancers and strains 6 and 11 cause 90% of genital warts [2,7].

At present, there is a single manufacturer of HPV vaccines. In June, 2006, the FDA approved Gardasil, a vaccine for HPV, manufactured by Merck, to protect against the four high-risk strands of HPV (6, 11, 16, 18). Trials for Gardasil showed nearly 100% efficacy against persistent HPV infections [8-11,12]. Gardasil requires three shots of equal dosage. The first shot is administered during a visit to a doctor, the second shot two months after the first, and the third dose six months after the first. All doses are recommended to be given within a one-year period.

There is likely to be a second manufacturer for HPV vaccines. Cervarix is an experimental HPV vaccine manufactured by GlaxoSmithKline, and it is currently being tested by the FDA. It is anticipated to receive FDA approval in late 2009 [13]. Like Gardasil, Cervarix requires three shots of equal dosage. The Center for Disease Control and Prevention (CDC) recommends that all females aged 11-12 years be vaccinated against HPV and that females aged 13-26 years be offered the vaccine [2,14,15]. At present, eighteen states are requiring or considering requiring HPV vaccination [16].

Since there is currently a single manufacturer of HPV vaccines and since demand has been dramatically rising, the system is vulnerable to interruptions in vaccine production. In such an interruption, the manufacturer's production is completely halted, with no new additional vaccines being produced. Existing vaccines would be used for routine immunizations until the existing stockpiles run out, when a shortage is said to occur. Vaccine shortages, including the recent Hepatitis A, *Haemophilus influenzae* type B (Hib), and Varicella vaccine shortage, are a real concern and periodically occur [17,18]. It is important that children follow the CDC recommended immunization schedule to prevent exposure to preventable diseases. Interruptions in HPV vaccine production can put women at risk of acquiring HPV infections.

To avoid possibilities of widespread vaccine shortages, the CDC maintains vaccine stockpiles for pediatric and adolescent vaccines. These stockpiles were first developed by CDC in 1983, and can be used to counteract short-term production problems, which are likely to occur periodically [19]. The CDC maintains stockpiles for a number of childhood vaccines; for example, 6-month stockpiles of measles, mumps, rubella (MMR), varicella, and inactivated polio (IPV) vaccines

[19]. CDC has also purchased partial stockpiles of hepatitis B, hepatitis A, pneumococcal conjugate (PCV), *Haemophilus influenzae* type b (Hib), hepatitis B, diphtheria, tetanus and acellular pertussis vaccines, a combination vaccine containing DTaP, IPV, and hepatitis B, rotavirus, and a combination vaccine containing hepatitis B and Hib [19]. The CDC realizes that shortages are a serious problem and plans on continuing to purchase those vaccines and others, including new and combination vaccines, for the stockpiles.

Mathematical modeling has been used to predict the level of a vaccine stockpile necessary to minimize the effect on the public from a shortage. Elsewhere, these models have been used to determine appropriate vaccine stockpile levels for the vaccines on the pediatric recommended immunization schedule [20,21]. In this paper, these existing mathematical models for analyzing vaccine stockpiles for pediatric vaccines are applied to HPV vaccines. The analysis focuses on the sensitivity of the stockpiles with respect to the vaccine coverage rate (i.e., the fraction of girls aged 11-12 who receive all three doses of the HPV vaccine), since the vaccine coverage rate for adolescent vaccines is lower than that of pediatric vaccines, more states are requiring HPV vaccination (additional changes are anticipated), and estimates for the vaccination rates of girls and women against HPV are not currently available. The results indicate that the stockpile level changes significantly, depending on the vaccine coverage rate and assumptions regarding the production interruption. The analysis is performed to analyze whether stockpile levels are sufficient to absorb the impact of a vaccine production interruption and maintain low risk of a shortage under a variety of production interruption scenarios.

This paper is organized as follows. In Section 2, the mathematical models used in the analysis are summarized. In Section 3, the models are applied to anticipated scenarios of HPV vaccination and potential interruptions in its supply. Finally, concluding remarks are given in Section 4.

2. Methods: model overview

The mathematical model to analyze HPV vaccine stockpiles is formulated as a stochastic inventory model to capture the relationship between a vaccine supply and demand when production is interrupted [20]. During a production interruption, the manufacturing of any new vaccines is suspended, and hence, no new vaccines are available, and vaccine stockpiles will be used until they run out. This model can be used to analyze various vaccination stockpile levels to determine if they are adequate to cover the demand for HPV vaccination. It is assumed that the production interruption lasts for a random amount of time and that production resumes at time $t = 0$. Note that these models are not specific to the HPV vaccine; they can be applied to any pediatric or adolescent vaccine.

The models take several input parameters:

- D = the number of doses required to provide full immunization.
- I = initial stockpile level.
- λ = expected number of people (i.e., 11 year old girls) that require the vaccine.
- σ = standard deviation of people who require the vaccine.
- α = vaccine coverage rate (proportion of 11 year old girls who receive the vaccine).
- T = random variable describing the duration (in days) of a vaccine production interruption.
- $T \sim NT(\eta, \sigma_T)$ = T is distributed as a truncated normal random variable with parameters η and σ_T .
- $T \sim \text{Exp}(\eta)$ = T is distributed as an exponential random variable with parameter $1/\eta$
- β = the ratio between the maximum vaccine production rate ($\beta D\lambda$) and the vaccine demand rate ($D\lambda$), where $\beta > 1$.

- t_M = the time at which the vaccine production returns to its maximum rate.
- t_m = time the at which the expected vaccine supply level reaches its minimum.
- $t = 0$ = time at which the production is restored

Note that the last three parameters t_M , t_m , and t are relative to the time that production resumes (time $t = 0$).

The function $u(t)$ captures both the vaccine production rate and the vaccine distribution rate. To capture both these scenarios, two possible functional forms for $u(t)$ over time period $[0, t_M]$ are considered to define two possible vaccine supply ramp-up rate functions. The ramp-up rate function is quantified as the supply rate moves from zero to its maximum production capacity.

The *convex* and *concave* vaccine production ramp-up rate functions are given by

$$u(t) = \beta D \lambda \left(\frac{t}{t_M} \right)^r, \quad (1)$$

where $r = 2$ for the convex ramp-up rate function and $r = \frac{1}{2}$ for the concave ramp-up rate function. The time the at which the expected vaccine supply level reaches its minimum is

$$t_m^* = \left(\frac{\alpha}{\beta} \right)^{\frac{1}{r}} t_M, \quad (2)$$

where $r = 2$ for the convex ramp-up rate function and $r = \frac{1}{2}$ for the concave ramp-up rate function.

During an interruption in vaccine production and during ramp-up phase, there is a probability that the vaccine supply is entirely used, resulting in a vaccine shortage. This means that the demand cannot be met, and therefore the need for the vaccine is actually greater than the supply,

so in essence, the supply becomes negative. The expected accumulated vaccine supply shortage $\delta(t_m)$ during time interval $[0, t_m]$ is given by

$$\delta(t_m) = G(0, t_m) - E[D(0, t_m)] = \int_0^{t_m} u(t) dt - D\alpha\lambda t_m \quad (3)$$

where $G(0, t_m)$ and D denote the (deterministic) cumulative production demand and the (random variable) cumulative demand over time interval $[0, +t_m]$, respectively. Let $S(t_m)$ denote the supply at the time at which the expected vaccine supply level reaches its minimum. The expected minimum vaccine supply $E[S(t_m)]$ is given by

$$I + \delta(t_m) - C\alpha\lambda \lceil E[T] \rceil \leq E[S(t_m)] \leq I + \delta(t_m) - C\alpha\lambda \lfloor E[T] \rfloor \quad (4)$$

Note that in (3) and (4), $\delta(t_m)$ depends only on how fast the manufacturer can achieve its maximum production rate, and that $\delta(t_m)$ is neither a function of the initial stockpile level nor the length of the actual production interruption period.

The probability of a shortage during a vaccine production interruption is estimated by

$$\frac{\int_{\lfloor T_3 \rfloor}^{\lceil T_{-3} \rceil} F(T) dT}{\lceil T_{-3} \rceil - \lfloor T_3 \rfloor} - F(0) \leq P(S(t_m) \geq 0) \leq \frac{\int_{\lceil T_3 \rceil}^{\lfloor T_{-3} \rfloor} F(T) dT}{\lfloor T_{-3} \rfloor - \lceil T_3 \rceil} - F(0) \quad (9)$$

In (9), the formula is an approximation, and the symbols (\leq, \geq) should not be considered exact.

T_3 and T_{-3} are given by

$$T_3 = \frac{2ID\alpha\lambda + 2\delta(t_m)D\alpha\lambda + 9D^2\alpha^2\sigma_d^2 - 3D\alpha\sigma_d \sqrt{4ID\alpha\lambda + 4\delta(t_m)D\alpha\lambda + 4t_m D^2\alpha^2\lambda^2 + 9D^2\alpha^2\sigma_d^2}}{2D^2\alpha^2\lambda^2}$$

$$T_{-3} = \frac{2ID\alpha\lambda + 2\delta(t_m)D\alpha\lambda + 9D^2\alpha^2\sigma_d^2 + 3D\alpha\sigma_d \sqrt{4ID\alpha\lambda + 4\delta(t_m)D\alpha\lambda + 4t_m D^2\alpha^2\lambda^2 + 9D^2\alpha^2\sigma_d^2}}{2D^2\alpha^2\lambda^2}$$

Since the exact distribution of T is unknown, two distinct distributions were considered. Both distributions have parameters that could be varied to control the coefficient of variation for T . The first distribution is the truncated normal with parameters η and σ_T , and its probability distribution function for T is given by

$$f(T) = \frac{e^{-(T-\eta)^2 / 2\sigma_T^2}}{\int_{-\eta/\sigma_T}^{\infty} e^{-z^2/2} dz} . \quad (5)$$

The second distribution considered is the exponential distribution with parameter $1/\eta$. The exponential distribution for T has a higher coefficient variation, and hence, it models the scenario when the length of the production interruption is highly uncertain. The probability density function for an exponential distribution with parameter $1/\eta$ is given by

$$f(T) = \frac{1}{\eta} e^{-\frac{T}{\eta}} . \quad (6)$$

Note that the truncated normal and the exponential distributions are two particular probability density functions that can be used to model the length of the production interruption and that any probability density functions can be used in the models introduced in this section.

3. Results

This section provides an analysis of the vaccine stockpile models provided using parameters for the HPV vaccine using the models introduced in Section 2. Specific parameters and distributions for the HPV vaccine are provided in order to analyze stockpile levels under a wide variety of assumptions regarding the vaccine production interruption.

- $T \sim \text{NT}(\eta, \sigma_T)$. T is distributed as a truncated normal random variable with parameters $\text{NT}(60, 10)$, $\text{NT}(60, 20)$, $\text{NT}(120, 20)$, $\text{NT}(120, 40)$, $\text{NT}(180, 30)$, $\text{NT}(180, 60)$.
- $T \sim \text{Exp}(\eta)$. T is distributed as an exponential random variable with parameter $1/\eta = \{60, 120, 180\}$

In addition, two scenarios are considered with an expected production interruption of six months.

- *Optimistic Scenario* has parameters $T \sim NT(\eta=180, \sigma_T = 60)$, $t_M = 60$, and a concave ramp-up function.
- *Pessimistic Scenario* has parameters $T \sim NT(\eta=180, \sigma_T = 30)$, $t_M = 180$, and a convex ramp-up function.

Depending on the scenario used, and the distribution specified, the vaccine stockpile changed significantly. Based on only girls aged 11 years receiving vaccinations, $\lambda = 5500$ and $\sigma_d = 950$ [23, 24]. The models were analyzed using Mathematica 5.2 and Matlab 6.

Table 1 shows the minimum initial stockpiles levels of the HPV vaccine in order to maintain less than a ten-percent risk of a shortage under various scenarios. Depending on the vaccine coverage rate (α) and the type of scenario considered, the stockpile levels change significantly, varying between 2.175M and 8.775M. The cost is determined by multiplying the CDC cost per dose (\$96.75) by the given initial stockpile levels. Note that the stockpile increases linearly with the vaccine coverage rate. As the vaccine coverage rate increases by ten-percent for the optimistic case, it is recommended that the corresponding stockpile increases by 475K and 730K for the truncated normal and exponential scenarios. As the vaccine coverage rate increases by ten-percent for the pessimistic case, it is recommended that the corresponding stockpile increases by 605K and 935K for the truncated normal and exponential scenarios.

Table 1: Minimum stockpile level such that $P(t_m) < 0.1$ (Millions of doses) and its corresponding cost (\$M)

α	Optimistic Case				Pessimistic Case			
	Truncated Normal		Exponential		Truncated Normal		Exponential	
	Stockpile(M)	Cost(\$M)	Stockpile(M)	Cost(\$M)	Stockpile(M)	Cost(\$M)	Stockpile(M)	Cost(\$M)
0.5	2.175	210	3.475	336	2.5	242	4.1	397
0.6	2.625	254	4.175	404	3.075	298	5	484

0.7	3.075	298	4.9	474	3.65	353	5.925	573
0.8	3.55	343	5.625	544	4.275	414	6.85	663
0.9	4.05	392	6.375	617	4.875	472	7.8	755
1.0	4.55	440	7.125	689	5.525	535	8.775	849

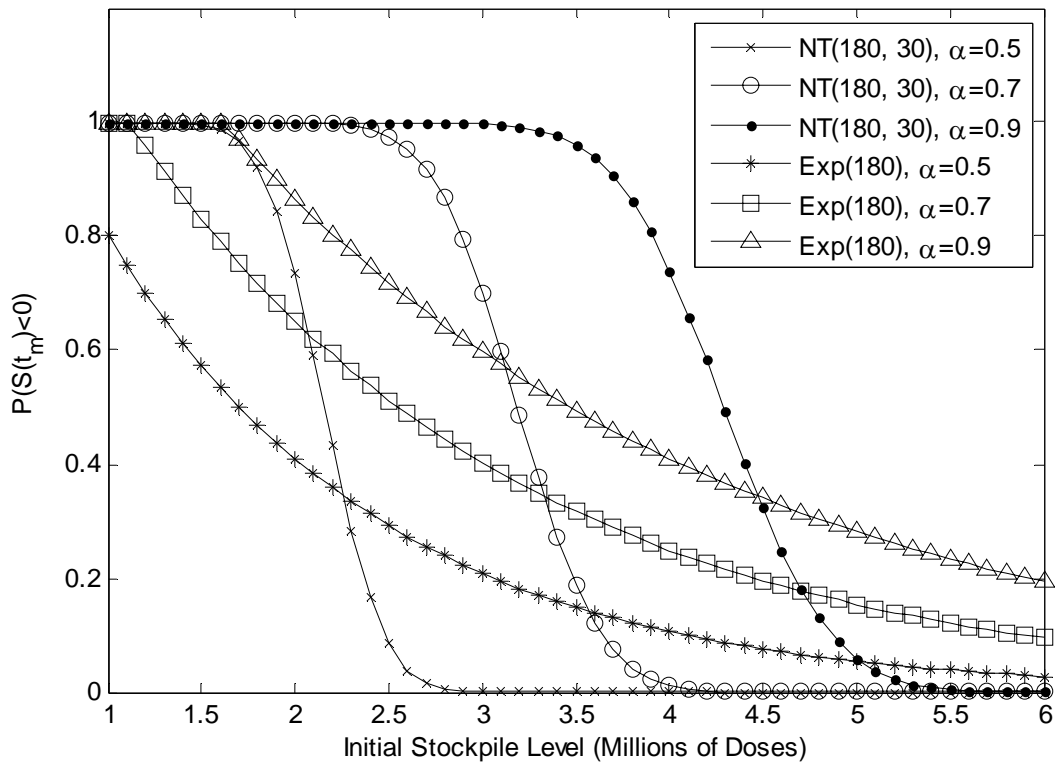
Table 2 shows upper bound for the expected minimum vaccine supply for the convex and concave scenarios given the average duration of the production interruption and the vaccine coverage rate. Problems in HPV vaccine delivery occur when the expected vaccine supply is less than zero. For this reason, the negative values in Table 2 are denoted in bold. When the initial stockpile is 2M, depleting the vaccine supply is likely, even for some scenarios when the duration of the production interruption is 60 days. When the initial stockpile is 3M, the vaccine supply becomes negative for expected production interruptions of 120 days ($\alpha \geq 0.9$) and 180 days ($\alpha \geq 0.7$). The vaccine supply is not expected to be depleted for any scenarios when the initial stockpile level is at least 5M.

Table 2: Upper bound for the expected minimum vaccine supply, $E[S(t_m)]$ (Millions of doses)

η	α	I = 2M		I = 3M		I = 4M		I = 5M		I = 6M	
		concave	convex	concave	convex	concave	convex	concave	convex	concave	convex
60	0.5	1.40	0.84	2.40	1.84	3.40	2.84	4.40	3.84	5.40	4.84
60	0.6	1.23	0.53	2.23	1.53	3.23	2.53	4.23	3.53	5.23	4.53
60	0.7	1.03	0.20	2.03	1.20	3.03	2.20	4.03	3.20	5.03	4.20
60	0.8	0.79	-0.14	1.79	0.86	2.79	1.86	3.79	2.86	4.79	3.86
60	0.9	0.51	-0.50	1.51	0.50	2.51	1.50	3.51	2.50	4.51	3.50
60	1	0.19	-0.88	1.19	0.12	2.19	1.12	3.19	2.12	4.19	3.12
120	0.5	0.91	0.34	1.91	1.34	2.91	2.34	3.91	3.34	4.91	4.34
120	0.6	0.64	-0.07	1.64	0.93	2.64	1.93	3.64	2.93	4.64	3.93
120	0.7	0.33	-0.49	1.33	0.51	2.33	1.51	3.33	2.51	4.33	3.51
120	0.8	0.00	-0.93	1.00	0.07	2.00	1.07	3.00	2.07	4.00	3.07
120	0.9	-0.38	-1.39	0.62	-0.39	1.62	0.61	2.62	1.61	3.62	2.61
120	1	-0.80	-1.87	0.20	-0.87	1.20	0.13	2.20	1.13	3.20	2.13
180	0.5	0.41	-0.15	1.41	0.85	2.41	1.85	3.41	2.85	4.41	3.85
180	0.6	0.04	-0.66	1.04	0.34	2.04	1.34	3.04	2.34	4.04	3.34
180	0.7	-0.36	-1.18	0.64	-0.18	1.64	0.82	2.64	1.82	3.64	2.82
180	0.8	-0.79	-1.73	0.21	-0.73	1.21	0.27	2.21	1.27	3.21	2.27
180	0.9	-1.27	-2.28	-0.27	-1.28	0.73	-0.28	1.73	0.72	2.73	1.72
180	1	-1.79	-2.86	-0.79	-1.86	0.21	-0.86	1.21	0.14	2.21	1.14

Figure 1 shows the probability of a shortage as a function of the initial stockpile level for pessimistic scenario with the duration of the production interruption being modeled with the truncated normal (NT) or the exponential (Exp) distributions for $\alpha = 0.5, 0.7, 0.9$. The truncated normal scenarios appear to be more sensitive to the initial stockpile level than the exponential scenarios. However, all scenarios appear to be sensitive to the vaccine coverage rate. This suggests that accurate forecasts of the vaccine coverage rate are needed to plan effectively for an initial stockpile. In addition, the stockpile may need to be significantly increased as the vaccine coverage rate increases.

Figure 1: Probability of a Vaccine Shortage with $t_M = 180$ and a convex ramp-up function.



Tables 3 and 4 show the probability of a vaccine supply shortage for various scenarios considered. An initial stockpile of 2M appears to be inadequate to prevent shortages for even low levels of the vaccine coverage rate. An initial stockpile of 3M appears to be adequate for vaccine coverage levels less than 0.7, with the probabilities of a shortage being less than 0.136 for all scenarios considered with the expected duration of the production interruption being 120 days or less. An initial stockpile of 3M has probabilities of a shortage being less than 0.20 for all scenarios considered with $\alpha \leq 0.9$ for the concave case and less than 0.75 for all scenarios considered with $\alpha \leq 0.9$ for the convex case.

4. Discussions and Recommendations

The analysis performed indicates that a stockpile for the HPV vaccine can be a tool to avoid vaccine shortages when production interruptions occur. The stockpile level recommended to ensure a small risk of a shortage is sensitive to changes in the vaccine coverage rate. Therefore, the HPV vaccine stockpile level should be a function of the vaccine coverage rate, and the stockpile should grow as a higher proportion of adolescent girls are vaccinated.

The demand for HPV vaccines is likely to increase, and when this happens, the stockpile for the vaccine will need to grow. To demonstrate the likelihood that the vaccine demand will increase, note that the recommended childhood immunization coverage rates for every vaccine are at an all-time high and that there have been significant increases in the childhood vaccine coverage rates. For example, the vaccine coverage rate for some vaccines increased ten-percent between 2004 and 2005. In the year 2005, the coverage rates for three or more doses of the childhood pneumococcal conjugate vaccine was 83 percent [22]. The recommended stockpile level of at

least 3M vaccines is only sufficient to meet demands consistent with vaccine coverage levels associated with other adolescent vaccines. However, as more state and local school systems make the HPV vaccine mandatory, the vaccine coverage rate is anticipated to increase and the stockpile level necessary will need to increase accordingly.

The analysis performed only took one manufacturer of the HPV vaccination into account. However, since Cervarix is likely to be approved by the FDA in the near future, the recommended results can be modified to account for a second manufacturer. In addition, Cervarix is likely to increase the total number of women who choose to receive the HPV vaccine, since Cervarix is seeking approval to be used on women up to the age of 55 whereas Gardasil can be used for women up to the age of 26. In order to analyze vaccine stockpiles under the scenario when there are two HPV vaccine manufacturers, the expected value and the standard deviation of people who require the vaccine may need to be adjusted in the model.

The HPV vaccine is an important public health tool to prevent HPV infections and cervical cancer. The models analyzed in this paper shed light on appropriate stockpile levels for the HPV vaccine. By creating such a stockpile, adolescent girls and women can be protected from HPV if there is a vaccine shortage, and countless lives could be saved.

Table 3: Probability of a vaccine supply shortage, Concave case

η	σ_T	α	I = 2M	I = 3M	I = 4M	I = 5M	I = 6M
60	20	0.5	0	0	0	0	0
		0.6	0	0	0	0	0
		0.7	0	0	0	0	0
		0.8	0.001591	0	0	0	0
		0.9	0.044626	0	0	0	0
		1	0.291553	0.000159	0	0	0
120	40	0.5	0.002984	0	0	0	0
		0.6	0.054873	1.86E-05	0	0	0
		0.7	0.242291	0.002023	0	0	0
		0.8	0.510662	0.030437	8.01E-05	0	0
		0.9	0.743157	0.152888	0.003219	0	0
		1	0.890915	0.382605	0.035979	0.000443	0
180	30	0.5	0	0	0	0	0
		0.6	0.000687	0	0	0	0
		0.7	0.080757	0	0	0	0
		0.8	0.519939	8.84E-05	0	0	0
		0.9	0.9032	0.020182	0	0	0
		1	0.992857	0.274253	0.000159	0	0
180	60	0.5	0.202602	0.002189	0	0	0
		0.6	0.474063	0.040113	0.000299	0	0
		0.7	0.704049	0.179902	0.008987	7.24E-05	0
		0.8	0.846487	0.401836	0.064763	0.002694	2.75E-05
		0.9	0.925368	0.625096	0.207339	0.026634	0.001084
		1	0.966671	0.78921	0.421309	0.112017	0.012781
180	30	0.5	0.04779	0	0	0	0
		0.6	0.446965	0.000233	0	0	0
		0.7	0.856939	0.033377	0	0	0
		0.8	0.978991	0.308538	0.001209	0	0
		0.9	0.997926	0.736742	0.0512	5.52E-05	0
		1	0.99986	0.945201	0.344578	0.00748	0

Table 4: Probability of a vaccine supply shortage, Convex case

η	σ_T	α	I = 2M	I = 3M	I = 4M	I = 5M	I = 6M
60	20	0.5	0	0	0	0	0
		0.6	0.00403	0	0	0	0
		0.7	0.19793	0	0	0	0
		0.8	0.709798	0.000578	0	0	0
		0.9	0.956726	0.049538	0	0	0
		1	0.99788	0.36366	0.000337	0	0
	10	0.5	0	0	0	0	0
		0.6	0	0	0	0	0
		0.7	0.044566	0	0	0	0
		0.8	0.864334	0	0	0	0
		0.9	0.999663	0.000483	0	0	0
		1	1	0.241964	0	0	0
120	40	0.5	0.152888	2.56E-05	0	0	0
		0.6	0.57023	0.009399	0	0	0
		0.7	0.859974	0.135849	0.000578	0	0
		0.8	0.963351	0.45087	0.022781	4.82E-05	0
		0.9	0.991952	0.751176	0.15887	0.003472	0
		1	0.999163	0.908641	0.421309	0.044626	0.000746
	20	0.5	0.020182	0	0	0	0
		0.6	0.636831	0	0	0	0
		0.7	0.984222	0.013903	0	0	0
		0.8	0.999807	0.401294	3.17E-05	0	0
		0.9	0.999999	0.911492	0.02275	0	0
		1	1	0.995975	0.344578	0.000337	0
180	60	0.5	0.625096	0.044626	9.46E-05	0	0
		0.6	0.869105	0.285856	0.012241	4.19E-05	0
		0.7	0.958274	0.605955	0.121837	0.004446	2.79E-05
		0.8	0.986826	0.82145	0.369941	0.054873	0.002204
		0.9	0.996211	0.927723	0.631411	0.212142	0.028362
		1	0.999483	0.971484	0.808028	0.447569	0.128178
	30	0.5	0.736742	0.000337	0	0	0
		0.6	0.987237	0.128537	0	0	0
		0.7	0.999702	0.703099	0.009815	0	0
		0.8	0.999994	0.966623	0.252493	0.000687	0
		0.9	1	0.998134	0.747507	0.054799	8.71E-05
		1	1	0.999917	0.958482	0.394863	0.012596

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