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Potential Influenza Effects on Military Populations

John N. Bombardt, Jr.
Heidi E. Brown

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PREFACE

This document was prepared by the Institute for Defense Analyses (IDA) in partial fulfillment of the following task order: "Development of Alternative Operational Concepts for Medical Response to Biological Agent Attacks," Amendment 2, sponsored by the Joint Staff (Director for Logistics) and the U.S. Army Surgeon General.

The authors thank the following reviewers for their many helpful comments and suggestions: Dr. Martin Meltzer (Centers for Disease Control and Prevention), Dr. Gene McClellan (General Dynamics) and Dr. Janet Pavelich (IDA). In addition to serving as a reviewer, Dr. Pavelich was a technical contributor during the study's formative phase.

Lastly, neither the conduct nor the publication of this study would have been possible without the sustained interest and support of LTC Debra Schnelle (Office of the U.S. Army Surgeon General).

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EXECUTIVE SUMMARY

This paper begins with a historical review of the 1918 influenza pandemic as it affected military populations and operations. Our review then serves as a point of departure for the analytical reconstruction of certain influenza epidemics in stateside training camps and overseas units of the American Expeditionary Forces (AEF) in World War I. The main quantitative thrusts are to (a) derive time-varying rates of influenza transmission in unstructured and structured historical military populations and (b) assess potential natural or unnatural influenza effects on modern military populations.

The explosiveness and severity of 1918 influenza epidemics in military populations obstructed the implementation of even rudimentary medical countermeasures (patient isolation, supportive care and quarantine). Neither a vaccine nor drugs were available then to prevent influenza, alter its natural course and deal with sequelae. In the here and now, biosensors, epidemiological surveillance systems and modern medicine might be capable of checking the spread of a 1918-like influenza virus and averting another devastating influenza pandemic. We quantitatively analyze potential influenza effects by emphasizing preventive medical measures (pre-attack immunoprophylaxis, prompt post-attack chemoprophylaxis and combinative prophylaxis).

Our fundamental predictive assumptions are transparent. First, the reemergence of a 1918-like influenza virus is not only a long-standing public health concern; it may become a serious bioterrorist or biological warfare threat as well. Second, influenza effects on stateside and overseas military populations in the autumn of 1918 are representative of what could happen to a current U.S. military population anywhere in the world. Third, time-varying rates of influenza transmission within a 1918 stateside training camp or within an overseas unit of the AEF are applicable to today's analogous military populations. And fourth, enough is known about 1918 influenza viruses to make medical plans and preparations for promptly controlling such a virus in military settings.

Consider a future influenza epidemic at a military base in the U.S. and suppose the daytime population of this base is 50,000 people, which subsumes a small contingent of civilians. The surrounding community is, by assumption, mainly composed of civilians and there are 100,000 of them. If a natural event or an act of bioterrorism were to infect a certain number of military personnel who live and work on the military base, the resultant epidemic might stay within the confines of this base. On the other hand, initially infected military personnel could mix with people who live in the surrounding community,

allowing the at-risk population to quickly grow as large as 150,000 people. Both situations are analyzed in this paper.

The second and last series of numerical results focuses on a forward-deployed U.S. military unit, e.g., a U.S. infantry contingent on the move or a U.S. military population at a foreign fixed facility. This military unit comprises 4,300 personnel in 3 equal subunits. Although a distribution of primary infections among subunits is within our modeling capabilities, primary infections are confined to Subunit 1 in this document to emphasize the influence of military organizational structure. We suppose that this at-risk unit is isolated from either civilians or other military units, because military operations preclude external contacts early in an influenza epidemic and because military commanders impose a strict quarantine upon recognition of a serious health threat.

There are several biodefense implications of our analyses. First, from the standpoint of person-to-person transmission, modern military populations at U.S. bases may be more susceptible to a 1918-like influenza attack than modern forward-deployed military units. Robust and responsive influenza surveillance, detection and identification capabilities for both stateside military bases and overseas units are imperatives. Second, because the level of effectiveness for vaccinations against virulent influenza viruses may be no better than that for vaccinations against circulating viruses of the last 50 years, the wide utilization of anti-viral drugs in a complementary preventive role would enhance the chances of rapidly terminating a deadly outbreak. Third, preparing for “special” force-wide influenza vaccinations and assuring the availability of sufficient anti-viral drugs are critical planning activities. And finally, given the transmissibility of 1918 influenza viruses, even extraordinary military and civil efforts might not be enough to control virulent influenza viruses and prevent a nationwide epidemic or pandemic. More research emphasis on specific therapy for influenza could yield ameliorative or life-saving drugs for the last line of medical defense.

I. INTRODUCTION

A. Background

Battles of World War I (WWI) claimed the lives of more than 50,000 American soldiers, sailors and marines, while nearly as many stateside and in-theater military personnel died of influenza and pneumonia. For every U.S. military trainee or member of the American Expeditionary Forces (AEF) who succumbed to the 1918 influenza pandemic, dozens of other personnel sought medical care, recovered and subsequently returned to duty. Data in Table 1 describe (a) the prevalence of respiratory disease and (b) resultant deaths in the U.S. Army during and immediately after WWI.

Table 1. Respiratory Disease in the U.S. Army: April 1, 1917 through December 31, 1919[1]

	Influenza	Bronchitis	Broncho-Pneumonia	Lobar Pneumonia	Totals
Admissions (Army in the U.S.)	533,649	169,426	16,500	29,429	749,004
Admissions (Army in Europe)	218,718	73,458	14,847	14,225	321,248
Deaths	24,853	469	10,341	11,329	***46,992***

The isolation and identification of an influenza virus did not take place until 1933 and, during the first quarter of the 20th century, many in the medical community still associated influenza with "Pfeiffer's bacillus." Without laboratory test results demonstrating the presence of this bacillus, some WWI military physicians would not diagnose influenza and they confused a mild case of influenza (at the beginning of an outbreak) with bronchitis, pharyngitis or another common respiratory disease. This is one reason why the then Surgeon General found that influenza records alone adequately bounded neither the morbidity nor mortality of influenza in 1918 military populations.

By and large, the above tabular entries for bronchopneumonia and lobar pneumonia tend to represent pulmonary complications of unreported influenza cases.

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1 U.S. Surgeon General Office, *MEDICAL DEPARTMENT OF U.S. ARMY IN WWI*, Volume IX: *Communicable and Other Diseases*, pp. 61-68. Chart V on page 64 indicates that the vast majority of WWI influenza and pneumonia deaths occurred in the last 4 months of 1918 and in the first two months of 1919.

Totals in Table 1 are, therefore, reasonable estimates of relatively severe influenza cases and influenza-related deaths.[2]

In his illuminating and insightful book, Crosby describes the "Spanish" influenza pandemic of 1918 in terms of three epidemic waves.[3] The first epidemic wave appeared at stateside military camps in early spring of 1918 and then it affected American troops in Europe during May and June. For instance, at Camp Funston (Kansas), the month of March saw roughly 1,200 military trainees (out of 29,000) come down with a mild respiratory illness lasting 2 or 3 days. Most of these sick trainees quickly recovered without setbacks and soon returned to duty. However, about 250 trainees developed cases of pneumonia and 48 of those cases resulted in death. Crosby points out that a mortality of 20% for a pneumonia outbreak was not unusual in 1918, *when the patients were either very young or elderly*.

Influenza viruses with enhanced virulence emerged late in the summer of 1918 and gave rise to the second and most deadly epidemic wave. From the beginning of September to the end of October, Camp Devens in Massachusetts housed an average of 44,315 military personnel and it was the first stateside camp to be hit by the fall epidemic wave. A few statistics are indicative of overwhelming influenza effects on Camp Devens: 14,583 influenza cases, 2,817 pneumonia cases and 787 deaths.[4] Fall influenza epidemics similarly ravaged the other (~40) mobilization camps throughout the U.S.

The second epidemic wave wreaked havoc on the AEF in Europe as well. From the beginning of September through the end of November, the strength of the AEF was depleted by 98,656 influenza admissions, 13,189 pneumonia admissions and 9,144 influenza and pneumonia deaths.[5] Understandably, records of WWI hospital admissions in Europe are incomplete and do not reflect the full extent of influenza effects on U.S. combatants. Crosby describes how difficult it must have been for the 88th Division to cope with influenza and still function as a combat unit.[6]

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2 Throughout our discussion of pertinent historical morbidity and mortality data, we assume all reported cases of respiratory disease are influenza related.

3 Alfred E. Crosby, *America's Forgotten Pandemic: The Influenza of 1918*, Cambridge University Press, 1989.

4 Paul B. Woolley, "The Epidemic of Influenza at Camp Devens, Massachusetts," *Journal of Laboratory and Clinical Medicine*, Vol. 4, March 1919, pp. 330-343.

5 *America's Forgotten Pandemic: The Influenza of 1918*, p.159.

6 Ibid., p. 155.

"Flu began on September 20. In the first week 2,254 of the division's 18,000 were officially recognized as flu cases. At times whole companies were paralyzed. The only buildings available for use as hospitals were the French artillery barracks at Hericourt, damp stone buildings without heat.

Shortly after the November 11, the U.S. demobilized rapidly and peacemaking efforts replaced wartime topics in newspaper headlines. Nevertheless, virulent influenza viruses continued to circulate in December 1918. In the third and final epidemic wave, U.S. influenza and pneumonia deaths peaked in late January of 1919, declined over the next month and then fell to more typical levels in March and April. The second and third epidemic waves were similar in that influenza and pneumonia killed disproportionate numbers of young adults. On the other hand, the second wave dominated the third wave with respect to morbidity.

Important scientific issues surrounding the 1918 influenza pandemic remain problematic to this day.[7] Researchers are currently striving to identify origins of the fall 1918 influenza and determine why this disease killed (within a narrow timeframe) so many young adults throughout the world. Evidently, viral remnants from 1918 victims recently yielded genetic sequences that point toward an avian source, but mutations of an avian virus within humans or pigs would have been necessary to produce a virulent and transmissible human virus.

Figures 1 and 2 are bar charts describing U.S. influenza and pneumonia deaths in calendar years 2000 and 1918, respectively. Each individual bar in either chart defines the fraction of influenza and pneumonia deaths occurring in a particular age interval. For example, bars in Figure 1 tell us that people over the age of 45 accounted for almost 95% of U.S. influenza and pneumonia deaths in 2000. But Figure 2 indicates children and adults under the age of 45 developed about 80% of the fatal influenza and pneumonia cases in 1918. Moreover, approximately half of the 1918 influenza and pneumonia deaths happened in the range from 20 to 45 years of age.

To be sure, the age structure of the U.S. population has changed over the last 80 years or so. As Taubenberger points out, the average life expectancy in 1915 was only

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The 88th had no or short supplies of a number of essential items because the troops engaged in the Meuse-Argonne offensive, which started on September 26, had first priority on all transport and supplies. Until October 6 the division had to make do with only two ambulances, which were used to serve the French in the area, too.

Because of the lack of transport, the division had to march days to get to the sector where it was to take up front-line positions. Sometimes it marched as many as 25 kilometers a day over congested, muddy roads, the men pulling their own machine-gun carts and field wagons. In some units the average weight pulled per man was 250 pounds.

By the last days of October the epidemic was nearly over in the division, which entered combat for the first time on the twenty-fourth and fought for the rest of the war. The total of all combat losses for the 88th – killed, wounded, missing, and captured – was 90. The total of its flu cases during the fall wave was 6,845, approximately one-third of the division. One thousand and forty-one contracted pneumonia, and 444 died."

7 Gina Kolata, *Flu*, New York: Farrar, Straus and Giroux, 1999, pp. 281-306.

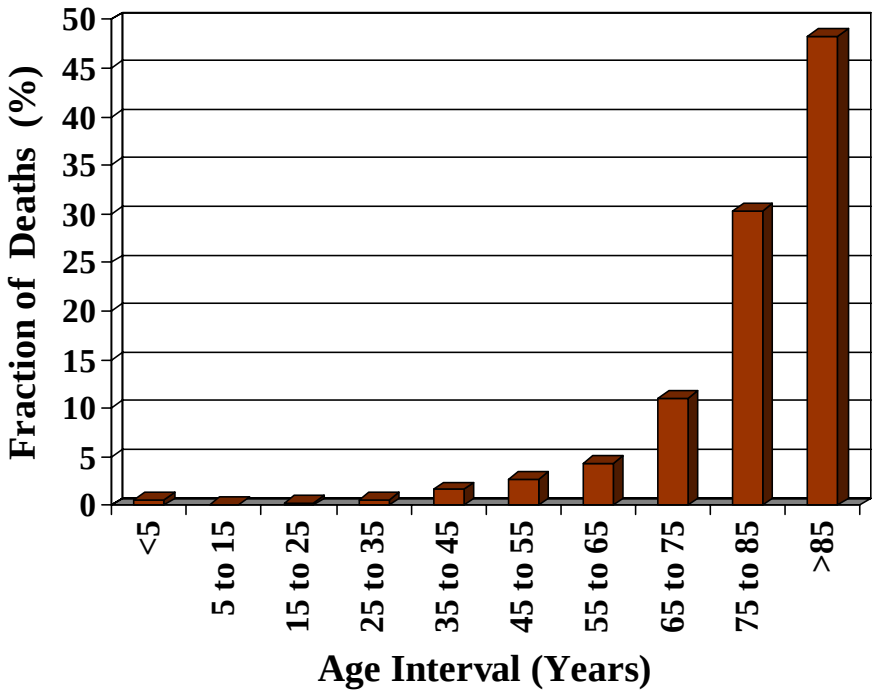

Figure 1. Age Distribution of U.S. Influenza and Pneumonia Deaths in 2000: ~65,000 in a Total Population of ~280,000,000
(Source: American Lung Association, *"Trends in Morbidity and Mortality: Pneumonia, Influenza and Acute Respiratory Conditions,"* September 2002)

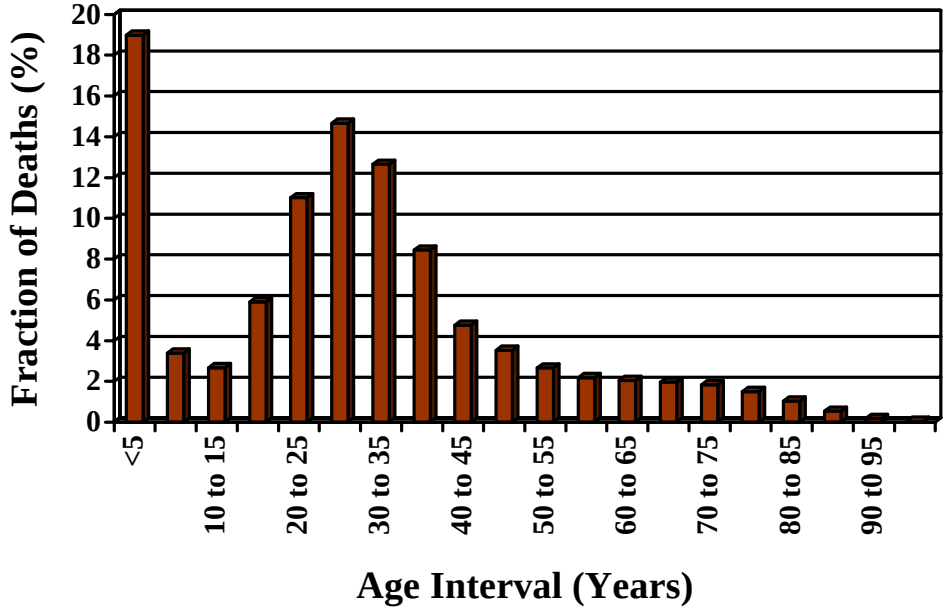

Figure 2. Age Distribution of U.S. Influenza and Pneumonia Deaths in 1918: ~500,000 in a Total Population of ~100,000,000
(Source: Bureau of Census, *Mortality Statistics, 1919, p.30)*

about 55 years and, during 1918, the specific influenza and pneumonia death rate (deaths per 100,000 people in each age group) looks like a "W." This W-shaped specific death rate appears to be a unique characteristic of the 1918 influenza pandemic.[8]

The development of a vaccine to serve as a hedge against the reemergence of a 1918-like virus is certainly a near-term possibility. But such a vaccine might or might not protect people against a new killer strain of the influenza virus. As Gina Kolata points out, the nature of influenza makes it hard to be complacent.

In a series of previous studies,[9] one of the present authors endeavored to assist military health care planners in their efforts to understand and deal with acts of biological warfare or bioterrorism that involve a contagious disease. Basic analytical thrusts of those studies included (a) construction of plausible scenarios (encompassing medical and non-medical countermeasures), (b) development or improvement of semi-empirical mean-field epidemic models, and (c) casualty estimation. Similar thrusts characterize this investigation of influenza effects, although reported operational implications of the 1918 pandemic enable us to broaden our scope of analysis.

B. Objectives and Scope

The Spanish influenza[10] of 1918 temporarily sidelined or killed hundreds of thousands of military personnel in Europe as well as in stateside military camps. In general, these incapacitating and fatal cases of influenza impeded the flow of U.S. military units into Europe, hampered operations of the AEF and overloaded the military medical system. An important twofold objective of this study is to: (a) review 1918 influenza effects on U.S. military populations and resultant war fighting impacts, and, (b) identify military consequences of the 1918 pandemic that could be germane to a natural or an unnatural reemergence of a 1918-like influenza virus.

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8 Jeffery K. Taubenberger, "Seeking the 1918 Spanish Influenza Virus," ASM News, Vol. 65 (No. 7), July 1999.

9 John N. Bombardt, Jr., *Contagious Disease Dynamics for Biological Warfare and Bioterrorism Casualty Assessments*, IDA Paper P-3488, Institute for Defense Analyses, February 2000; *Smallpox Transmission and BW Casualty Assessments*, IDA Paper P-3488, Institute for Defense Analyses, October 2000, For Official Use Only; *Primary Pneumonic Plague Transmission and BW Casualty Assessments*, IDA Paper P-3657, Institute for Defense Analyses, December 2001, For Official Use Only.

10 Crosby, *America's Forgotten Pandemic: The Influenza of 1918*, pp 25-26.

"… In a month or two (after the first wave passed through the U.S.) everyone outside of Spain was calling it 'Spanish influenza,' not because it originated there, but probably because Spain, still a nonbelligerent, had no wartime censorship to keep its health problems secret from the world. An estimated eight million Spaniards caught flu in May and June. The Spanish claimed that it had come from the battlefields in France, blown over by the strong winter winds, and that it would have been even worse but for the snowy Pyrenees."

Another primary objective is to develop a quantitative understanding of how a 1918-like influenza virus might affect forward-deployed and stateside military populations in the 21st century. In pursuing this objective, we utilize historical data to derive time-varying influenza transmission rates that typify epidemics in military populations during the fall of 1918. Such historically derived rates of disease transmission have predictive value, assuming past and future epidemiological circumstances are similar.[11]

Why or how a 1918-like influenza virus would reappear and initially infect some number of military personnel is not a subject for analysis herein. The natural emergence of virulent influenza viruses has been a serious concern in the U.S. public health community and has spurred worldwide surveillance efforts for many years. Regarding a man-made 1918-like influenza virus, there can no longer be any doubts. Researchers have already (a) found fragments of deadly 1918 influenza viruses, (b) used the recovered fragments to discover and publish nucleotide sequences for 1918 hemagglutinin, neuraminidase and matrix genes, (c) generated recombinant influenza viruses containing these genes, and (d) demonstrated that recombinant viruses were deadly in mice and sensitive to antiviral drugs *in vitro* and *in vivo*.[12]

A military unit like a brigade is a structured population with well-defined subunits that may constrain opportunities for disease transmission. Face-to-face interactions among personnel in the same regiment, for instance, generally occur more often than contacts between individuals in different regiments. Conceivably, certain training activities or combat operations could mix personnel from different subunits in a homogeneous fashion. In quantitatively analyzing either a 1918 influenza epidemic or possible future outbreak, we examine influenza transmission in a military population under both heterogeneous and homogeneous mixing assumptions.

The explosiveness and severity of 1918 influenza epidemics in military populations obstructed the implementation of even rudimentary medical countermeasures (patient isolation, supportive care and quarantine). Neither a vaccine nor drugs were available then to (a) prevent influenza, (b) alter its natural course and (c) deal with sequelae. In the here and now, biosensors, epidemiological surveillance systems and modern medicine might be capable of checking the spread of a 1918-like influenza virus

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11 Epidemiological circumstances are the conditions, facts and events that shape an outbreak of contagious disease. Some epidemiological circumstances intensify person-to-person transmission, while other circumstances inhibit the spread of disease. See Section III.

12 Terrence M. Tumpey, Adolfo Garcia-Sastre, Andrea Mikulasova et alia, "Existing antivirals are effective against influenza viruses with genes from the 1918 pandemic virus," *Proceedings of the National Academy of Sciences*, Vol. 99 (No. 21) October 15, 2002, pp. 13849-13854.

and averting another devastating influenza pandemic. Our quantitative analyses of potential influenza effects emphasize foreseeable medical countermeasures (pre-attack immunoprophylaxis, prompt post-attack chemoprophylaxis and combinative prophylaxis).

Figure 3 summarizes influenza threat considerations and salient aspects of our quantitative analyses. Descriptions of the selected historical outbreaks are in Section III, while epidemic models and numerical results are discussed in Sections IV and V.

FLU THREAT CONSIDERATIONS	RECONSTRUCTING 1918 FLU OUTBREAKS	ESTIMATING POTENTIAL (1918-LIKE) FLU EFFECTS
• ACCIDENTAL RELEASE OR NATURAL REEMERGENCE OF 1918-LIKE INFLUENZA VIRUSES – Laboratory Mishaps Involving Recombinant Influenza Viruses – Antigenic Shift/Drift • BIOTERRORISM – Agent in a Usable Form & Ad Hoc Means of Delivery (Letters, Human Vectors, …) – Primary Targets: Civilians and/or Military Personnel in the U.S. • BIOLOGICAL WARFARE – Weaponized Agent & Military Delivery Systems – Primary Targets: Forward-Deployed Military Units	• MILITARY CAMPS IN THE U.S. – Good Epidemiological Data for Outbreaks in Several Camps – Selected Data Set: Camp Custer (Michigan) • AEF IN EUROPE – Little Epidemiological Data for Outbreaks in Front-Line Military Units – Selected Data Set: 6th Field Artillery Brigade at Camp du Valdahon, France • TECHNICAL CHALLENGES – Going from a Given Set of Hospitalization Data to an Appropriate New Infection Rate – Utilizing Regimental New Infection Rates to Infer Intraregimental and Interregimental Time-Dependent Transmission Rates	• MILITARY BASE IN THE U.S. – Total Population Is Either Fixed or Time-Dependent (50,000 up to 150,000) – When the Total Population Is Fixed, It Is Either Unstructured or Structured (as a Scale-Free Network) – Same Baseline Scenarios as Below • FORWARD-DEPLOYED U.S. MILITARY UNIT – Fixed Total Population of 4,300 – Unit Is Either Unstructured or Structured (Divided into 3 Equal Subunits of 1,433) – Four Baseline Scenarios (No Intervention, Preattack Immuno-Px, Postattack Chemo-Px, and Combinative Px) • TECHNICAL CHALLENGE – Incorporating a Time-Dependent Transmission Rate into an Existing SIR Model for Scale-Free Social Networks

Figure 3. Influenza Threat and Scope of Quantitative Analyses

C. Approach

The historical record is replete with 1918 influenza morbidity and mortality statistics for civilians and military personnel in the U.S. However, with respect to the AEF in Europe, specific operational consequences of the 1918 influenza pandemic are much harder to discern. The enormity of this pandemic and wartime reporting constraints (including voluntary or involuntary censorship) probably conspired against a full public disclosure of serious problems involving training time, troop replacement, morale, operational planning, war fighting capabilities, etc. Notwithstanding this dearth of official documentation, we found some evidence (assessments by historians, statements by WWI military leaders in cablegrams and letters, etc.) of substantial influenza effects on military operations. Our historical review and its implications are discussed in Section II.

In quantitatively estimating potential influenza effects on 21st century military populations, we've adopted a semi-empirical approach and invoked two fundamental assumptions. One basic assumption is that epidemiological circumstances surrounding certain Spanish influenza outbreaks are also germane to future influenza outbreaks of concern. This is to say, a virulent influenza virus could attack a contemporary unprotected military population in much the same way that the Spanish influenza virus attacked military personnel in 1918. In addition, the overarching assumption of deterministic or mean-field outbreak dynamics emphasizes the compartmented evolution of influenza infections and enables the exploitation of standard temporal data sets (e.g., hospitalizations or symptom onsets per day). Although our semi-empirical approach doesn't explicitly deal with the spatial spread of influenza, the derived time-varying rates of influenza transmission are implicitly linked with historical spatial influences.

In accordance with Figure 4, the identification of pertinent historical outbreaks and the acquisition of suitable epidemiological data are initial steps in our semi-empirical approach. An acquired set of epidemiological data then serves as input for Monte Carlo calculations that define average new infections per day.[13] By introducing the index infections and average new infections per day into a mean-field compartmental model, the evolution of all infections in a historical outbreak becomes quantifiable in terms of several time-varying cohorts. Subsequently, these cohorts and population mixing assumptions are necessary to calculate the historical time-varying rate(s) of disease transmission. The derived rate(s) of disease transmission, similar past and future epidemiological circumstances and mean-field model alterations are sufficient to evaluate outcomes of scenarios involving arbitrary numbers of initial infections and current outbreak controls.

[13] In the present analytical framework, new infections per day do not include index ("primary") infections. The person-to-person transmission of a disease gives rise to new infections per day. Index infections happen at the outset of day zero (D+0), while new infections per day occur on D+1 or thereafter.

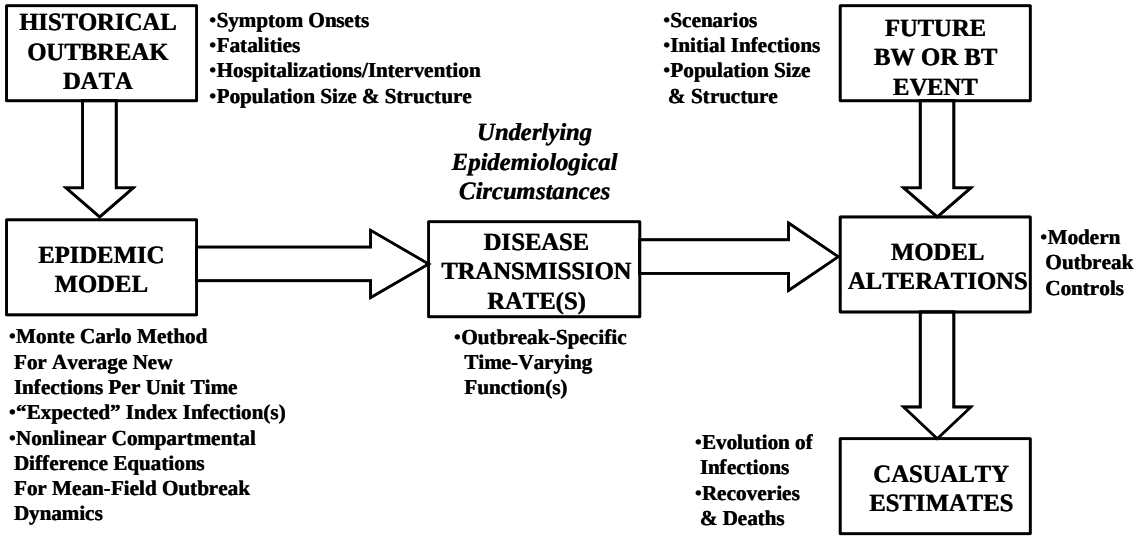

Figure 4. Semi-Empirical Approach for Assessing Casualties of Disease Transmission

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II. MILITARY CONSEQUENCES OF THE 1918 INFLUENZA PANDEMIC

A. Influenza-Related Hospital Admissions and Fatalities

The quality of casualty and fatality data represents the first obstacle in an investigation of 1918 influenza effects on U.S. military personnel and operations. As one might expect during wartime, inconsistent and incomplete influenza-related case reports were commonplace. An ill individual at a stateside camp could be temporarily excused from duty and reported as an influenza case, even though medical personnel never examined him. But soldiers in Europe had to leave their units and be admitted into hospitals before their illnesses were (or were not) counted as influenza-related cases. Generally speaking, military medical staffs in the U.S. and Europe were so overwhelmed with patients that the underreporting of influenza-related illnesses was likely.

Returning to Table 1 and the timeframe from April 1917 through December 1919, the tabular data suggest that military trainees in the U.S. were hit hardest by influenza and pneumonia. Army camps in the U.S. accommodated 2.2 million trainees at the peak of the 1918 pandemic and a rough estimate of the influenza attack rate is 24%. Similarly, based on 1.7 million troops in Europe, an approximate influenza attack rate for the AEF is 13%. Considering all reported respiratory illnesses (influenza, bronchitis, bronco-pneumonia and lobar pneumonia), trainees in the U.S. and troops in Europe experienced overall attack rates of about 34% and 21%, respectively.

Table 1 also shows that close to 47,000 stateside and overseas Army personnel died of respiratory diseases. Influenza was directly or indirectly responsible for the vast majority of those deaths. Notably, during the last 4 months of 1918 and the first 4 months of 1919, influenza and pneumonia took the lives of 23,000 Army personnel in the U.S. and 11,000 personnel in Europe.[14]

During the second and third epidemic waves, several epidemiological circumstances contributed to the relatively high incidence of respiratory disease within the stateside training camps. First, levels of acquired immunity for recruits in U.S. camps tended to be lower than the immunity levels for overseas military personnel.[15] Second, crowded barracks and mess halls in military training camps were conducive to indoor face-to-face contacts over a period of six weeks or so. And third, Crosby argues that usual “ailments” of trainees may have lessened their resistance to disease in general.

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14 Crosby, *America’s Forgotten Pandemic: The Influenza of 1918*, pp. 150-151.

15 By the fall of 1918, soldiers of the AEF had (a) completed training regimens in the U.S., (b) crossed the Atlantic ocean in overcrowded troop ships, and (c) already been exposed to (or infected with) less virulent strains of the 1918 influenza virus.

B. U.S. Military Trainees

Table 2 summarizes influenza-pneumonia epidemics that occurred within 12 large stateside camps during the fall of 1918. Based on influenza admissions per se, the average attack rate was 27%. Looking at deaths per camp as a percentage of the camp's total strength, an average of 1.7% of the at-risk population died of either influenza or pneumonia. Influenza-pneumonia casualties in the U.S. camps had adverse effects on training missions and, ultimately, on AEF capabilities.

Table 2. Admissions & Deaths for 12 Large U.S. Camps in the Fall of 1918[16]

Camp Or Station	Period Of Influenza-Pneumonia Epidemic	Absolute Number Of Hospital Admissions	Influenza Admissions (% Of Strength)	Pneumonia Admissions (% Of Strength)	Absolute Number Of Deaths	Deaths (% Of Strength)
Sherman	9/24-11/19	13,161	33	6.6	1,101	3.3
Grant	9/21-11/3	13,071	26	5.7	1,060	2.6
Dodge	9/18/-10/22	11,931	30	5.8	702	2.1
Dix	9/9-11/1	13,733	26	4.0	808	1.8
Devens	9/8-10/29	17,400	33	6.3	787	1.8
Meade	9/17-10/20	14,280	27	6.8	763	1.8
Custer	9/23-11/3	12,773	26	5.9	660	1.7
Funston	9/16-11/7	16,963	28	4.6	841	1.6
Lee	9/13-11/10	13,597	24	3.9	674	1.4
Taylor	9/22-11/3	14,761	20	4.1	720	1.2
Pike	9/23-10/31	13,124	23	2.5	423	0.83
Travis	9/19-11/9	12,120	28	7.2	199	0.58

1. Training Time

High numbers of hospital admissions in stateside camps decreased the amount of training time that was available to many affected personnel. Trainees were often too sick to participate in exercises and whole camps were shut down to deal with explosive outbreaks. At one camp, for example, the arrival of the second epidemic wave meant training had to be postponed for 142,000 new recruits.[17]

A host of medical personnel left the U.S. to support the troops overseas and, when virulent strains of the influenza virus visited the stateside camps in the fall of 1918, remaining military medical resources were stretched too thin to effectively manage epidemics. As a consequence, healthy recruits had to limit their training activities and provide nursing support for their sick comrades.[18] Although reductions in training time

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16 *MEDICAL DEPARTMENT OF U.S. ARMY IN WWI*, Volume IX: *Communicable and Other Diseases*. See Table 27 on page 138.

17 W. L. Sanford, "The Influenza Epidemic of 1918 and its Effects on the Military," *Indiana Medical History Quarterly*, Vol.9 (No.4), 1983, p. 16.

18 E. M. Coffman, *The War to End All Wars*, Madison, Wisconsin: The University of Wisconsin Press, 1986, p. 82.

usually led to less proficiency with military equipment and less indoctrination, pressing needs for troops in Europe outweighed concerns about readiness.

2. Troop Replacement

In the final months of WWI, the U.S. met AEF manpower requirements by drawing upon undertrained troops from disease-ridden stateside camps. The second epidemic wave slowed the flow of military personnel out of U.S. training camps and clear evidence of an incipient influenza outbreak within a new military unit could postpone the embarkation of this unit.[19] Moreover, if a U.S. troopship did enter a European port with numerous ill personnel on board, the imposition of quarantine would also hold up the arrival of replacements at the front.[20]

Serious influenza-pneumonia epidemics marked the voyages of many troopships in the fall of 1918; i.e., a typical ocean trip took 9 days or so and upwards of 20% of the passengers often became very ill and needed medical attention. Even a "low-incidence" crossing of the Atlantic Ocean was not a sure sign of a low infection rate. More specifically, a modest number of initial cases and a weeklong voyage were sufficient to ignite an epidemic involving thousands of infections. The vast majority of those infections would become influenza cases only after the troops disembarked, taxing medical resources of the Allies and delaying the deployment of new U.S. military units.[21]

3. Morale

Official efforts to manage epidemics in U.S. camps usually had negative effects on the morale of military trainees. Controls included quarantine and actions to restrict the congregation of men.[22] These measures were not well received by most trainees, who were anxiously awaiting opportunities to prove themselves in battle.

Since there was little beyond bed rest and food that helped patients recover, the powerlessness of medical countermeasures created a feeling of despondency. And when medical personnel came down with influenza, morale took another turn for the worse.[23]

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19 Crosby, *America's Forgotten Pandemic: The Influenza of 1918*, p. 123.

20 Sanford, "The Influenza Epidemic of 1918 and its Effects on the Military," p.20.

21 Crosby, *America's Forgotten Pandemic: The Influenza of 1918*, p. 135.

"The extreme example of this was the case of the transport *Olympic*, which arrived at Southampton, England, on the night of September 21 after a voyage of only six days. She carried 5,600, of whom only 450 had clearly shown symptoms of flu while at sea, and only one had died. By 4:00 P.M. on September 29 the cases of flu among their fellow travelers had reached full maturity: 1,947 cases had been admitted to the hospital, fully one-third of the entire number of troops the *Olympic* had carried, and 140 had died."

22 M. Burch, "I Don't Know Only What We Hear: the Soldiers' View of the 1918 Influenza Epidemic," *Indiana Medical History Quarterly*, Vol. 9 (No. 4), 1983, pp. 25-26.

23 Crosby, *America's Forgotten Pandemic: The Influenza of 1918*, pp. 146-147.

C. American Expeditionary Forces

Table 3 contains monthly data that describe the mean AEF strength, influenza cases, pneumonia cases and pneumonia deaths. Focusing on the month of October in 1918, the gross attack rate for the AEF was only 2.48%, compared with an average of 27% for stateside camps. Pneumonia deaths in October amounted to 0.18% of the mean AEF strength, while influenza-related deaths in the camps reached an average of 1.7% of the at-risk military population. To be sure, attack rates and death tallies can't tell us much about how influenza affected operations of the AEF. We must examine the historical record more closely to assess 1918 influenza effects on war-fighting abilities and the length of WWI.

Table 3. Estimated Influenza-Related Cases and Deaths within the AEF[24]

Month/ Year	Mean Strength AEF	Influenza Cases	Pneumonia Cases	Pneumonia Deaths
06/1917	14,361	5	0	0
07/1917	15,555	50	18	0
08/1917	26,703	117	15	0
09/1917	44,744	180	28	0
10/1917	70,079	735	98	0
11/1917	106,990	2,120	192	0
12/1917	141,995	3,520	508	0
01/1918	188,652	3,660	980	0
02/1918	229,316	2,195	480	0
03/1918	286,521	2,420	625	0
04/1918	437,063	1,850	252	0
05/1918	503,265	Unavailable	456	0
06/1918	739,042	4,520	660	0
07/1918	988,015	3,983	478	64
08/1918	1,275,595	6,393	792	142
09/1918	1,545,812	12,769	1,683	422
10/1918	1,741,593	37,904	5,353	3,129
11/1918	1,865,343	25,287	4,077	1,935

1. Ability to Fight

Generals on both sides of the war were well aware of the fact that influenza was wreaking havoc on their men. In October 1918, General John Pershing sent desperate cablegrams to Washington requesting more hospitals, medical personnel and equipment.[25] The Germans likewise felt the burden of influenza, which congested supply

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24 Ward J. MacNeal, "The Influenza Epidemic of 1918 in the American Expeditionary Forces in France and England," *Archives of Internal Medicine*, Vol. 23 (No. 6), June 1919, p. 681.

25 Kolata, *Flu*, p. 50.

routes with evacuating patients and made an advance or a retreat more difficult to execute.[26]

Losses due to the 1918 influenza pandemic exceeded the worst expectations of military planners. Each and every day, U.S. military personnel who experienced some form of respiratory disease could have completely filled two divisions.[27] The demand for fresh troops remained high, since arriving soldiers were either stuck in quarantine or down with influenza or pneumonia in hospitals. In the absence of replacements, fighting divisions had to be retained at the front despite their need for rest.[28]

The integrity of front-line military units was degraded by influenza outbreaks, especially since severe influenza cases exacerbated the weakened state of battle-weary troops. As the war progressed, more and more seasoned soldiers were replaced with inexperienced military personnel who had just arrived from military camps in the U.S. This augmentation of in-place military units using fragments of new military units further degraded unit integrity or cohesion.[29]

The prevalence of influenza within the ranks undoubtedly limited the ability of the AEF to conduct some offensive operations. Additionally, military historians have questioned the soundness of battlefield decisions that were made by military commanders under the influence of influenza.[30] And lastly, General Ludendorff identified the debilitating impact of influenza as one reason why the German offensive of July 1918 was unsuccessful.[31]

2. Length of War

Whether the 1918 influenza pandemic shortened or lengthened WWI is still a matter for debate among historians. According to McGinnis, once the U.S. entered the war in 1917, a victory by the Allies was no longer in doubt; rather, the important question

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26 Crosby, *America's Forgotten Pandemic: The Influenza of 1918*, pp. 158 and 160.

27 Ibid., p. 206.

28 Paul F. Braim, *The Test of Battle: the American Expeditionary Forces in the Meuse-Argonne Campaign*, 2nd Edition, White Mane Books (Shippenburg, PA), 1998, p. 105.

29 R. Parkinson, *Tormented Warrior*, Holder and Staughton Ltd (London, UK), 1978, p.163.

30 Braim, *The Test of Battle: the American Expeditionary Forces in the Meuse-Argonne Campaign*, p.105. Braim argues that General Pershing's judgment was adversely affected when he contracted influenza.

31 Kolata, *Flu*, p. 11.

"German General Erich von Ludendorff, the leader of the country's acclaimed offense, complained that the flu, or the Flanders fever, as the Germans called it, was thwarting his battle plans. It was not enough that the fighting men were hungry and cold and wet, trying to slog their way through fields of mud that could swallow a tank. Now there was this flu, which, Ludendorff said, was weakening his men and lowering their morale. The flu, he added, contributed to the failure of his July offensive, a battle plan that nearly won the war for Germany."

was when the Allies would become victorious.[32] McGinnis suggests that the combination of war and influenza simultaneously depleted military resources of both sides, but the exhaustion of Germany's reserves was bound to happen first. From this perspective, the pandemic probably shortened WWI, but not by much.

Crosby, on the other hand, points out that influenza effects on the AEF slowed its operations to a noticeable degree.[33] And if influenza impeded German operations as well, a logical inference is that longer military operations (due to influenza effects) tended to prolong WWI.

D. General Observations Concerning Potential Influenza Effects

The natural or unnatural emergence of a 1918-like influenza virus is an important concern in the domains of public health and national security. In January and February of 1976, a limited outbreak of swine influenza A (Hsw1N1) at Fort Dix, New Jersey, demonstrated that the natural emergence of a 1918-like virus is not an idle threat.[34] And, as mentioned previously, researchers have already created recombinant influenza viruses by utilizing genes of 1918 strains. We've made no attempt to assess when a terrorist organization or rogue nation may be capable of (a) acquiring a 1918-like influenza virus and (b) utilizing it as a weapon. Nonetheless, we argue that prudent civil and military biodefense plans should encompass the emergence of a deadly and transmissible influenza virus, regardless of its origin.

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32 Janice P. Dickin McGinnis, "The Impact of Epidemic Influenza: Canada, 1918-1919," in *Medicine in Canadian Society*, S. E. D. Shortt (Editor), McGill-Queen's University Press, 1981, pp. 470-471.

33 Crosby, *America's Forgotten Pandemic: The Influenza of 1918*, p. 163.

34 Franklin H. Top, Jr. and Philip K. Russell, "Swine Influenza A at Fort Dix, New Jersey (January-February 1976): IV. Summary and Speculation," *The Journal of Infectious Disease*, Vol. 136 (Supplement), December 1977, pp. S376-S380.

"If one accepts the premise that influenza A/New Jersey (Hsw1N1) was introduced into the reception center by an incoming trainee, the virus probably persisted from the week beginning January 5 through that beginning January 19 in order to account for infection of the three cohorts beginning training on January 12, 19, and 26. Since little influenza A/New Jersey activity was detected elsewhere in the United States in 1976, most probably only one or, at most, a few trainees introduced the virus into the reception center. However, because influenza A/Victoria (H3N2) was widely prevalent in the civilian population from January through March, this strain may have been introduced frequently by new trainees who were infected prior to arrival on the post."(p. S378)

"Whereas the simultaneous occurrence of two radically different influenza A strains may permit the emergence of a natural recombinant with the human virulence of an established strain (A/Victoria) and surface antigens of the new strain (A/New Jersey), paradoxically, transmission of the established strain might inhibit spread of the new strain. The rapid disappearance of the influenza A/New Jersey strain at Fort Dix prohibited prospective studies which may have shed considerable light on the interactions between two radically different influenza A viruses infecting humans at the same place and time." (p. S379)

Attributes of the influenza threat and modern military settings are indicators of potential influenza effects on military populations and operations. Our review of 1918 influenza effects on U.S. military camps and the AEF is helpful in qualitatively connecting both threat attributes and modern military settings with possible future impacts.

1. Threat Attributes and Implications

Natural Emergence

The 1918 influenza pandemic compelled the U.S. to meet considerable needs for medical resources (physicians, nurses, hospital beds, etc.) at home and abroad. AEF needs for medical personnel were met by sending volunteers and draftees overseas, but this action drained the available supply of physicians and nurses within the U.S.

The natural emergence of a 1918-like virus may be detected relatively early in an industrialized country like the U.S. (e.g., Fort Dix in 1976) or much later in an economically underdeveloped country. In any event, prerequisites for the prevention of either a future pandemic or regional epidemic include a high state of medical readiness, a prompt worldwide response and some good luck. Interestingly, because overseas military operations in the foreseeable future are unlikely to involve millions of military personnel, even a serious influenza pandemic wouldn't necessarily force the U.S. to substantially reduce civilian medical resources in order to satisfy medical needs of in-theater personnel.[35]

Bioterrorism

Of primary concern here is an act of bioterrorism within the U.S. involving either the intentional release of a pathogen into the environment or the intentional transmission of a pathogen via vectors (infected insects, animals, terrorists, etc.). Bioterrorists may covertly attack millions of civilians in a large city or just a few soldiers, sailors or marines at a military base. The generation of a pathogenic aerosol is an efficient way to mount a large-scale attack and vectors represent one of many ways to initially infect a small number of people.

A small-scale bioterrorist attack on military personnel may well initiate an explosive outbreak at a military base, resembling natural 1918 outbreaks that occurred at dozens of military camps all over the U.S. Without early detection and prompt

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35 Admittedly, a future pandemic would probably disrupt medical services in certain areas of the U.S. For example, in the metropolitan area of Washington, DC, overseas assignments of active-duty medical personnel working at military hospitals (e.g., Walter Reed Army Hospital or Bethesda Naval Hospital) and call-ups of reservists working at civilian hospitals could hamper the provision of medical services to military retirees and a small number of civilians.

implementation of effective outbreak controls, the confines of an existing military base are unlikely to prevent the person-to-person transmission of a 1918-like virus into a surrounding civilian population, a nearby city or another military base. In the fall of 1918, a growing outbreak at a military camp often preceded the first influenza cases within a neighboring civilian community.[36]

Following a large-scale covert attack on a civilian or military population, an unprecedented number of initial infections would rapidly evolve into an overwhelming stream of influenza cases. The intensity of such a man-made outbreak could preclude containment, and a pandemic or regional epidemic might be inevitable. From the standpoint of wartime operations, acts of bioterrorism within the U.S. would tend to lower the morale of forward-deployed military units. In other words, as military personnel risk their lives abroad, some of them will be distraught over family members and friends at home who become casualties of a bioterrorist attack.

Perhaps it goes without saying that our review of the 1918 influenza pandemic yielded few useful insights regarding unique epidemiological aspects of catastrophic bioterrorism. For instance, thousands or hundreds of thousands of nearly simultaneous infections within a relatively small geographical area comprise an ahistorical phenomenon.[37]

Biological Warfare

By using an influenza weapon against forward-deployed U.S. military forces, an adversary commits an act of biological warfare. The target of a virus-laden aerosol attack could be an infantry brigade on the move, a military air base, a port of debarkation, etc. A key tactical objective of the adversary may be to covertly expose a U.S. military unit without respiratory protection. In achieving this objective, the adversary's military personnel are likely to have (a) transattack respiratory protection and (b) medical protection (chemoprophylaxis or immunoprophylaxis).

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36 Ernest E. Irons, "Pneumonia Following Influenza in the Camps in the United States," *The Military Surgeon*, March 1921, pp. 275-305.

The outbreak at Camp Custer, Michigan reportedly began with 29 presumed influenza cases on September 10, 1918, and then peaked with 1,129 cases on the 2nd of October. Initial influenza cases in the town of Battle Creek (about 5 miles from Camp Custer) emerged on September 30.

37 Suppose bioterrorists generated a pathogenic aerosol and thereby exposed a substantial fraction of the total population in a metropolitan area. Unnaturally high doses of inhaled microorganisms, a multitude of initial infections and an unusually rapid progression of index cases would be understandable. But the historical record can tell us little about these unique epidemiological aspects of catastrophic bioterrorism and their significance.

Toward the end of WWI, General Ludendorff fantasized that influenza would somehow annihilate the French army and spare German soldiers.[38] Influenza outbreaks in 1918 actually degraded Allied and Axis troops in a symmetric fashion, more or less. In modern times, advances in biotechnology and the development of influenza weapons could turn General Ludendorff's fantasy (asymmetric influenza effects) into an achievable military objective. The employment of an influenza weapon on the battlefield would essentially be an adversary's attempt to counterbalance the conventional military power of the U.S. through asymmetric means.

The transport of U.S. military personnel across the Atlantic Ocean and movements of armies within Europe contributed to the "quick" worldwide spread of influenza in the fall of 1918. As a result, millions of stateside civilians and a host of overseas military personnel suffered from influenza in roughly the same timeframe. The nation's medical resources were in short supply.

A successful covert aerosol attack on present-day military units may produce fulminant 1918-like influenza cases in a few days and it could take another 24 hours or so to identify the virus. Subsequently, to contain the spread of influenza, U.S. commanders may decide to place infected military units in quarantine (extending up to 10 days after the last case). And quarantining entire military units entails special medical logistics and, possibly, alterations of battle plans. Fortunately, unless large-scale bioterrorist attacks coincide with acts of biological warfare, civilian medical resources should be available to meet military needs.

2. Modern Military Settings and Implications

Training and Specialization

Large numbers of seriously ill military trainees gave rise to closures of some training camps in 1918. Trainees in these camps were either temporarily retained in the U.S. to recover from illness or immediately sent overseas without requisite skills. Occurrences of 1918-like influenza cases within contemporary military populations must be dealt with rapidly and effectively or, otherwise, rampant influenza transmission might permit historical personnel problems to resurface with significant complications.

Military equipment has become increasingly complex, requiring a higher degree of specialization and a broader array of training regimens. Unlike 1918, sending poorly trained or undertrained personnel into a theater of U.S. military operations is not a realistic future option. The Department of Defense (DoD) currently maintains a corps of reserve units, which are trained and ready to replace active military units.

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38 Kolata, *Flu*, p. 50.

Operational Readiness

The strength of the AEF was about 2 million men in the final months of WWI and indications are that the morale of these troops was generally quite high. Furthermore, reported influenza casualties in the AEF were far lower than those in the stateside military camps. But the available evidence also supports the claim that influenza casualties in some units, in conjunction with poorly trained or undertrained replacements, produced noticeably lower levels of operational readiness.[39]

Not since WWII has the U.S. committed millions of men and women to overseas military conflicts. U.S. military operations over the last 25 years or so have involved less manpower and more materiel and technology. Today's agile military units are smaller and more capable than ever before. By the same token, fewer influenza casualties in a 21st century military unit may erode its operational readiness. The DoD, however, is prepared to replace either entire units or individuals.

Medical Capabilities

Military medical personnel were able to do little more than provide influenza patients with food, water and beds in the fall of 1918, and a large influx of patients at a camp hospital often precluded even those rudimentary supportive measures. Saving as many lives as possible was the primary goal of military physicians. Most importantly, caseloads made it extremely difficult to implement infection controls and prevent nosocomial influenza transmission.

Advances in the medical sciences (virology, immunology, pharmacology, etc.) have greatly improved our understanding of influenza viruses and yielded vaccines and antiviral drugs that prevent infection and ameliorate illness. New epidemiological surveillance tools and environmental sensors may also prove to be important capabilities, which should increase the chances of (a) promptly detecting a natural or man-made influenza outbreak and (b) implementing timely countermeasures.

In the remainder of this document, we mathematically reconstruct selected 1918 influenza outbreaks and use the derived transmission rates, along with performance characteristics of current medical countermeasures, to quantify potential influenza effects on contemporary military populations. Our historical review and quantitative analyses then engender some concluding comments about medical planning and preparations.

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39 *Department of Defense Dictionary of Military and Associated Terms*, Joint Publication 1-02, 12 April 2001 (As Amended Through 5 June 2003), p. 387.

"The capability of a unit/formation, ship, weapon system or equipment to perform the missions or functions for which it is organized or designed."

III. EPIDEMIOLOGICAL AND CLINICAL CONSIDERATIONS

A. Details of Selected 1918 Influenza Epidemics

Returning to Table 2, it's apparent that the influenza-pneumonia epidemic at Camp Sherman produced the highest death rate (3.3% of camp strength), while the highest influenza hospitalization rate (33% of camp strength) occurred at both Camp Devens and Camp Sherman. We also see that the death and hospitalization rates for Camp Custer (1.7% and 26%, respectively) are virtually the same as the corresponding average rates (1.7% and 27%) for all 12 large camps under consideration. This observation and the availability of published daily hospitalization data[40] motivated our selection of the Camp Custer epidemic as a stateside exemplar.

A suitable overseas exemplar in the realm of 1918 influenza effects is more difficult to identify, primarily because the open literature provides few epidemiological data sets for individual AEF units. Chesney and Snow published useful epidemiological data for the 6th Field Artillery (F.A.) Brigade.[41] The second wave of the 1918 pandemic hit this military brigade just prior to its front-line emplacement, while it was receiving combat instruction at an Army post in France (Camp du Valdahon). From the perspective of person-to-person transmission within forward-deployed military units, 1918 influenza effects on regiments of the 6th F.A. Brigade appear to be at least indicative of outbreaks within similar WWI front-line units.

1. Camp Custer, Michigan

Medical facilities at Camp Custer dealt with a steady stream of mild respiratory illnesses (in the main, bronchitis and pharyngitis with uneventful recoveries) from September 10 through 24, 1918. On September 27, as the number of admissions spiked upward, physicians began to see a more serious symptom complex that sometimes eventuated in a life-threatening case of pneumonia. September 28 saw the first influenza-pneumonia death.

Camp Custer was occupied by 39,675 troops in the fall of 1918 and 10,728 of them were admitted to medical facilities with influenza or pneumonia. The case fatality rate for pneumonia was over 24% and the total number of influenza-pneumonia deaths was 674. Figure 5 displays time series data for hospital admissions and deaths.

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40 Irons, "Pneumonia Following Influenza in the Camps in the United States," p. 277.

41 Alan M. Chesney and Frank W. Snow, "A Report of an Epidemic of Influenza in an Army Post of the American Expeditionary Forces in France," *The Journal of Laboratory and Clinical Medicine*, Vol. 6, 1920-21, pp. 78-95.

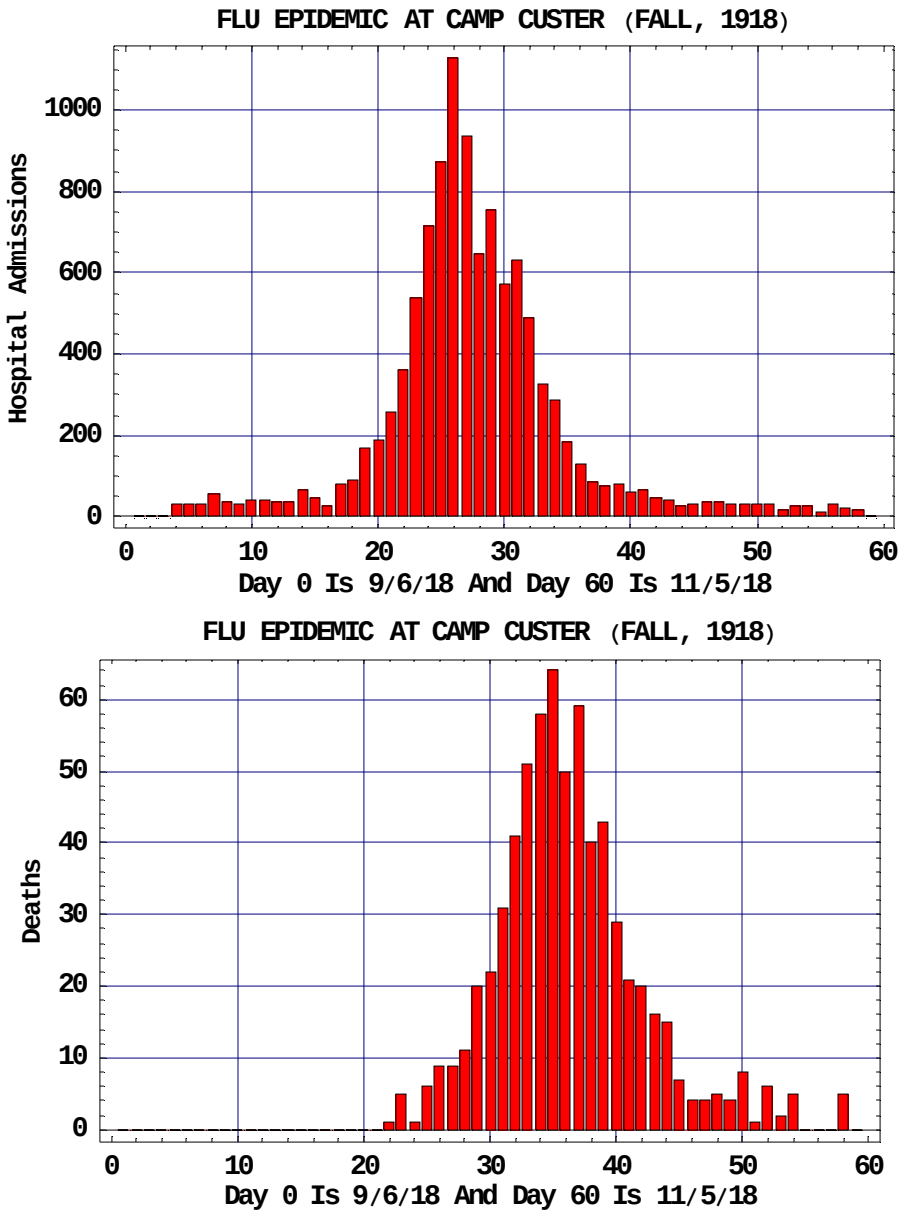

Figure 5. Camp Custer Influenza Epidemic:
Daily Hospital Admissions (upper graph) and Deaths (lower graph)

Influenza and pneumonia patients at Camp Custer came largely from the following organizations: 10th Infantry Brigade, 78th Infantry Brigade, 41st F.A. Brigade, 160th Depot Brigade and Sanitary Train.[42] The 41st F.A. Brigade was hit the hardest (~550 cases per 1,000 men) and the 10th Infantry Brigade had the lowest morbidity (~160 cases per 1,000 men). Lastly, almost 91% of the troops slept in barracks (versus tents).

42 J. S. Billings, "Influenza in Camp Custer," *Journal of Laboratory and Clinical Medicine*, Vol. 4, 1919, pp. 225-228.

2. Camp du Valdahon, France

Three American artillery brigades were stationed at Camp du Valdahon for firing instruction during the summer and early autumn of 1918: 5th F.A. Brigade (July 1 through 27, 1918), 58th F.A. Brigade (July 27 through August 23) and 6th F.A. Brigade (August 24 through October 21). Each of these brigades included roughly 4,000 men in 3 field artillery regiments (~18 batteries). Another 500 permanent personnel handled the administration of Camp du Valdahon and they belonged to the Cavalry, Engineer Corps, Quartermaster Corps and Medical Corps.

While the 5th F.A. Brigade was at Camp du Valdahon, 68 brigade personnel and 9 permanent camp personnel developed mild cases of influenza and were admitted to the camp hospital. The bulk of those personnel came from this brigade's Headquarters Company, 5th Trench Mortar Battery and 20th F.A. Regiment. How the virus got into the camp is uncertain, but troops were permitted to visit the nearby town of Besancon and some of its civilians experienced a similar illness in the same timeframe.

The 58th F.A. Brigade was billeted in surrounding neighborhoods for 4 weeks before entering Camp du Valdahon, and there were no hospital admissions for acute respiratory illness in that period. After occupying the camp for a week or so, the camp hospital admitted dozens of ill troops from the 123rd and 124th F.A. Regiments. (The 122nd F.A. Regiment did not stay at the camp, but its personnel entered the camp everyday for instruction and remained in billets about 1 kilometer away.) When the 58th F.A. Brigade left Camp du Valdahon, 200 of its personnel had previously been admitted to the camp hospital with influenza or pneumonia; however, only 6 of these patients came from the 122nd F.A. Regiment.

Because of the substantial influenza-pneumonia outbreak in the 58th F.A. Brigade, the Post Surgeon recommended that the Commanding General of the 6th F.A. Brigade either (a) keep his brigade billeted outside of the camp or, alternatively, (b) have his men sleep under tents rather than in the camp's barracks. (At the time of this recommendation, a few elements of the 6th F.A. Brigade were already in the camp and 13 personnel had been ill with influenza.) The 6th F.A. Brigade did not follow the Post Surgeon's advice. Instead, upon the departure of the 58th F.A. Brigade, detachments from the 6th F.A. Brigade spent a week cleaning the barracks and then the entire brigade (~4,300 men) entered the camp on August 27.

The 6th F.A. Brigade encompassed the 3rd, 11th, and 78th F.A. Regiments and each of these regiments contained upwards of 1,400 men. One soldier from the 3rd F.A. Regiment was diagnosed with influenza at the camp hospital on August 27 and, over the next two weeks, a few influenza-related admissions occurred each day. When 29 sick

personnel of the 3rd F.A. Regiment were admitted to the hospital on the 10th of September, a severe influenza epidemic was well underway and it quickly spread throughout the brigade. From August 27 through October 4, 1,264 men in the regiments became hospitalized with influenza and approximately 70 of these personnel died of pneumonia or complications.

Figure 6 shows the number of daily hospital admissions for (a) the 6th F.A. Brigade as a single entity, (b) 3rd F.A. Regiment, (c) 11th F.A. Regiment and (d) 78th F.A. Regiment. In this figure, day number 0 is August 23 and day number 40 is October 2.

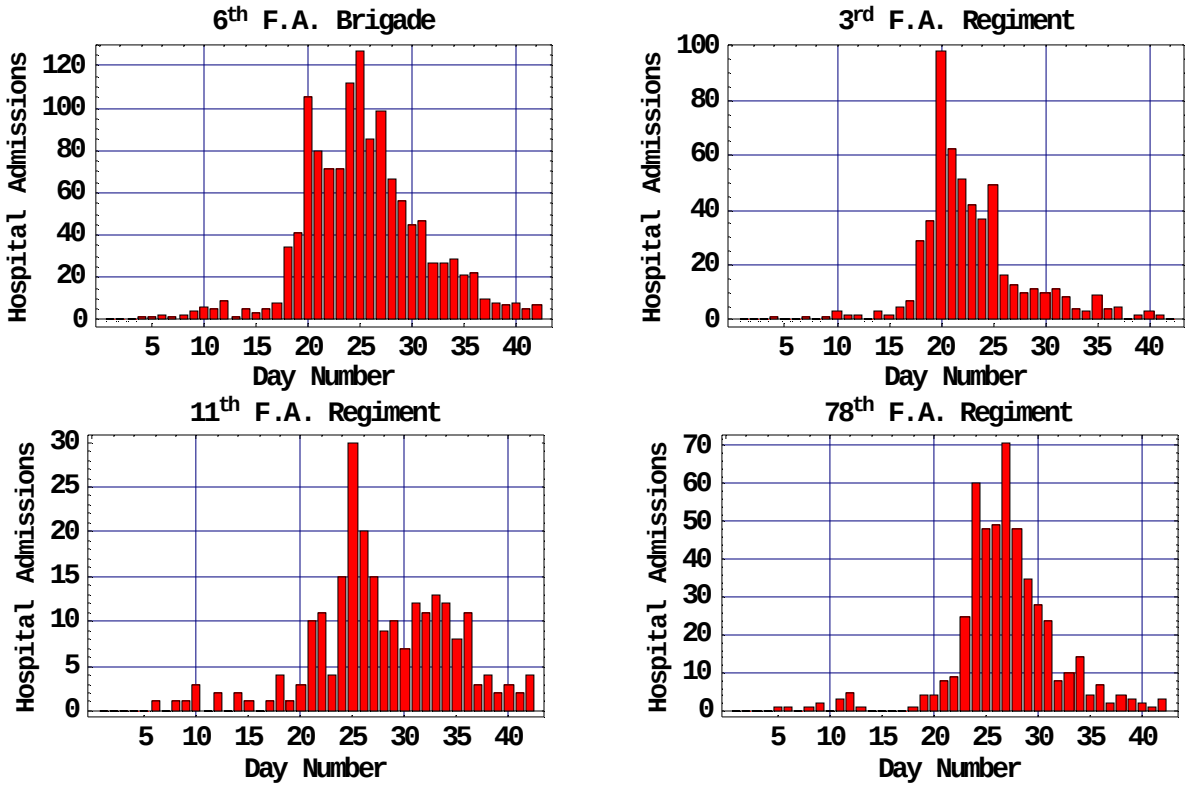

Figure 6. Influenza Epidemic at Camp du Valdahon:
6th F.A. Brigade (in toto, upper-left graph), 3rd F.A. Regiment (upper-right graph)
11th F.A. Regiment (lower-left graph), 78th F.A. Regiment (lower-right graph)

Chesney and Snow noted that the three successive epidemics at Camp du Valdahon involved "step-like" increases in the virulence of the influenza virus and in the attack rate. In their view, this series of epidemics "would seem to offer an instance of increased virulence acquired by the virus of influenza as a result of successive human passage."[43]

43 Chesney and Snow, "A Report of an Epidemic of Influenza in an Army Post of the American Expeditionary Forces in France," p. 94.

B. Influenza and Influenza-Pneumonia Cases in the Fall of 1918

The second wave of the 1918 influenza pandemic engulfed the Johns Hopkins Hospital in late September and October, when a nosocomial epidemic gave rise to 268 influenza cases and 13 deaths among health care providers. Since essentially all of the infections occurred in nurses, medical students, doctors and other hospital workers, medical professionals were able to observe many patients from the actual onset of symptoms through the entire course of illness. Bloomfield and Harrop discuss three types of invasion:

> Three distinct types of invasion were noted – abrupt invasion, gradual invasion and invasion with intermittent symptoms. The departure from health was extremely sudden in many of the cases, especially the severe ones at the height of the epidemic, definite symptoms beginning after only a few hours of vague malaise. In some cases the patient was knocked flat, literally dropping in his tracks. The most common symptoms were sudden and marked malaise and prostration, chills or chilly sensations, intense headache and general aching, pain in the eyes and photophobia. In a few instances, acute abdominal pain, vomiting or diarrhea ushered in the disease. In these severe cases the temperature usually rises rapidly, reaching its height within 24 hours. Coincident with, or shortly following onset, as the hyperemia of the mucous membranes develops, there is dryness, tightness, fullness, or slight rawness of the throat, substernal discomfort, and tight, racking cough, without sputum. There may be stoppage of the nose from swelling of the mucous membrane, with slight watery nasal discharge, and conjunctivitis is practically always present. The remarkable flushed appearance of the face and buccal cavity to be described below is usually fully developed in twenty-four hours. In another large group of cases the invasion is gradual, the symptoms unfolding themselves over a period of one to three days before the disease becomes full blown. It is in this group that isolated symptoms, such as headache, sore eyes, "coryza," raw throat, dry cough, anorexia, insomnia, or pain in the back may for a time predominate, masking at first the essential identity of all the cases. During such a period of invasion the temperature is usually normal, or only slightly elevated. In the early part of the epidemic, we observed many cases of this sort for two or three days, uncertain as to the diagnosis, until sudden high fever and frank symptoms and signs made the condition obvious. In a third group of cases the early symptoms were very puzzling, because of their intermittent nature. Thus, headache and malaise might be present one day and gone the next. Nausea might then come on for a few hours, again leaving the patient feeling well. After alternating periods of minor symptoms and well-being, lasting for several days, the full-blown disease finally made its appearance.[44]

Bloomfield and Harrop also discuss the typical course of an uncomplicated influenza case and the corresponding period of convalescence:

> Once fully established, the disease picture was remarkably constant. The fever usually continued high for from three to eight or nine days, with morning drops, the constitutional symptoms persisting until the temperature began to fall.

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[44] Arthur Bloomfield and George A. Harrop, Jr., "Clinical Observations on Epidemic Influenza," *Bulletin of the Johns Hopkins Hospital*, Vol. XXX (No. 335), January 1919, p. 3.

> At this time, particular discomfort, such as headache, backache, nausea, etc., gradually or suddenly disappeared, giving place to a profound feeling of collapse or exhaustion. The tight, racking cough often increased after the first day, with the production of more or less whitish, yellowish or greenish mucoid sputum, which is a regular feature of the disease, but other respiratory tract involvements must be regarded as complications. Some of the cases ran their whole course without cough, sputum or respiratory symptoms. Epistaxis was noted in 10 per cent of the patients. It occurred at onset, or at any time during the active stage, and in a few cases there were repeated epistaxes. This bleeding is doubtless associated with the hyperemic condition of the nasal mucosa. Nearly all the more severe cases had marked anorexia or nausea. The feeding problem became very difficult, and even fluid was refused. Stubborn constipation was the rule, although a few patients had brief attacks of diarrhea. In no other disease does one see such constant lack of cheer in the patients' faces. Nothing satisfies them, they are extremely unhappy and gloomy, and seem to feel that things can never be normal or comfortable again. Pathological depressions were, however, strikingly absent in our cases.
>
> The classical post-influenzal asthenia described in previous epidemics was noted in these cases. Profound prostration persisted for weeks into convalescence. The patients for the most part feel fairly comfortable while lying flat in bed, but the slightest exertion is followed without warning by exhaustion, a feeling of collapse, sweating and palpitation. Apart from actual physical weakness, which is marked, they complain of an intensely disagreeable sensation, which may be best characterized as an extreme lack of well being, rather than any positive pain or discomfort. This state of affairs usually persisted as long as the patients were under observation – about three or four weeks. Physical examination during convalescence is essentially negative. Tachycardia and sinus arrhythmias or extrasystoles are common, and in many cases the racking cough, with more or less mucoid or mucopurulent sputum persists. Anorexia, headache and insomnia were frequent complaints and loss of weight up to 20 pounds was not uncommon.[45]

The above medical observations regarding a nosocomial civilian epidemic are also pertinent to uncomplicated influenza cases that arose in U.S. military camps and AEF units.[46] But influenza was frequently an antecedent of pneumonia in military populations. The fraction of influenza cases resulting in pneumonia was as high as 25% in the camps and, typically, 30% of pneumonia cases ended in death.

The fulminant type of influenzal pneumonia was an especially distressing problem for military health care providers in the fall of 1918. Even though the fulminant type was not the most prevalent, its speed and deadliness were unique. U.S. Army physicians described fulminant influenzal pneumonia in the following manner:

> The onset of the pneumonic complication occurred either after two or three days of normal temperature following an attack of influenza, or it developed gradually without there being an afebrile interval. In the former group the onset was often characterized by chill and sudden rise of temperature. The severity of the disease was correlated with the amount of lung involvement, unilateral cases

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45 Bloomfield and Harrop, "Clinical Observations on Epidemic Influenza," pp. 4-5.

46 *MEDICAL DEPARTMENT OF U.S. ARMY IN WWI*, Volume IX: *Communicable and Other Diseases*, 1928, pp. 154-155.

doing much better than those with both lungs affected. Fulminant cases with severe toxemia showed rapid involvement of the entire lung.

In nonfatal cases, usually presenting a unilateral lesion, the temperature ranged from 100 to 103 degrees Fahrenheit. The pulse was characteristically slow; the blood pressure low, the systolic figure often below 100 mm; respiration was only slightly accelerated. Nonfatal cases usually recovered after an illness of about a week and defervescence was by crisis in some series, by lysis in others. In cases with bilateral lesions the cyanosis was more marked, even to an indigo blue color, the temperature ranged somewhat higher than in the unilateral cases and often showed variations paralleling the advance and recession of the pulmonary lesion as shown by the X ray or by physical signs. Cough was frequent and exhausting; the sputum, blood tinged or mucopurulent. In the more toxic cases, terminating fatally, the color of the patient from the first was either that of an intense cyanosis or a muddy, claylike pallor. The pallor was of particularly bad prognostic import. Nervous symptoms appeared early, restlessness and delirium being marked. The respiration became very rapid and dyspnea was pronounced. Physical signs of irregular consolidation and of edema filled the entire chest. The temperature ranged to 105 degrees Fahrenheit or higher, and death occurred in from three days to a week. It is evident that these groups were not clean-cut and that all degrees of varying severity intervened. Inasmuch as such a proportion of severe pneumonia has in the past seldom been associated with influenza, it is important to record in somewhat greater detail the peculiarities … .

The first point to strike the observer was the universal occurrence of cyanosis. This condition appearing in an apparently uncomplicated case of influenza, if of a degree at all marked, usually presaged the onset of pulmonary inflammation. Whether due to toxic changes in the composition of the blood or to mechanical interference with oxygenation by the exudates in the lungs, the intensity of the cyanosis was, in general, an index to the severity of the case. In milder cases of influenza, a peculiar shade of “pink cyanosis” was observed, an erythematous flush of an unusual shade. The well-established case of pneumonia showed a shade that was usually described as heliotrope, and in the most asthenic group, usually associated with coma vigil, a muddy clay-colored pallor prevailed.

In some series of cases the tendency to hemorrhages from the mucous membranes was very notable. Epistaxis, which occurred in 10% or more of the cases, was of all degrees, but often severe, recurrent, and debilitating in the extreme. Purpura, intestinal, and renal hemorrhages also occurred.

Of respiratory symptoms proper it may be said that these differed relatively little from the respiratory symptoms of the usual pneumonias. Pleuritic pain was frequent, cough was distressing, and frequently there was so much expectoration as to make resorting to narcotic relief seem dangerous. The character of the sputum varied from the tenacious rusty expectoration of typical lobar pneumonia, through varying degrees of mucopus, and frothy bloodstained material to the profuse pink froth in the mouth and nose which characterized the fulminant cases. The typical rusty sputum was rare, but the presence of some amount of blood was the rule.[47]

Influenza and influenzal pneumonia cases in the autumn of 1918 seem like gross exaggerations of today’s familiar maladies. Be that as it may, the above case descriptions elucidate medical dimensions of the influenza threat.

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47 *MEDICAL DEPARTMENT OF U.S. ARMY IN WWI*, Volume IX: *Communicable and Other Diseases*, pp. 158-159.

C. Mathematical Characterization of Influenza Progression

The introduction of several time-dependent subpopulations or cohorts is an essential step in our mean-field analysis of any future influenza epidemic in a military population. Susceptible individuals in the "**S**" cohort are uninfected and unprotected against person-to-person disease transmission, whereas any exposed and infected individual belongs to the "**E**" cohort for the duration of his or her non-contagious incubational period. As an infected individual becomes capable of infecting others through person-to-person contacts, this infectious individual enters the "**I**" cohort and remains there throughout the contagious period. Next is the "**R**" cohort containing influenza survivors and fatalities; i.e., when victims of influenza cease to be active sources of infections, they join the **R** cohort. Lastly, beneficiaries of chemoprophylaxis belong to the "**X**" cohort but, as chemoprophylactic regimens come to an end, these individuals return to the **S** cohort.[48]

The **SEIRX** analytical framework can accommodate the non-uniform natural progression of multiple index infections by incorporating individual-to-individual variations in non-contagious incubation and contagious periods. Assumed parameter values for our mathematical characterization of influenza progression are in Table 4.

Table 4. Influenza Progression Parameters

	Total Incubation Period	**Non-Contagious Incubation Period (E Cohort)**	**Contagious Period (I Cohort)**	**Infection-to-Removal Time (R Cohort)**
Mean (Days)	**2**	**1**	**5**	**1 + 5 = 6**
Maximum (Days)	**5**	**4**	**8**	**$6 + 3(2^{1/2})$**
Standard Deviation (Days)	**(5 – 2)/3 = 1**	**(4 – 1)/3 = 1**	**(8 – 5)/3 = 1**	**$2^{1/2}$**

If t is the elapsed time (starting with the initial day of incubation) and g is a cumulative distribution function (CDF), then g[t] denotes the probability that the infected individual's non-contagious incubation period takes on a value less than or equal to t. The probability of an infected individual staying in the **E** cohort is $P_e[t]$, or

(1) $P_e[t] = 1 - g[t]$.

[48] Beneficiaries of immunoprophylaxis simply reduce the size of the **S** cohort throughout a particular epidemic under consideration.

As an infected person becomes contagious and leaves the **E** cohort, he or she immediately enters the **I** cohort. And when someone in the **I** cohort can no longer transmit influenza, the **R** cohort gains a new member. The random infection-to-removal time extends over the full duration of non-contagious incubation and contagious periods. Now, introducing h as another CDF, h[t] is the probability that the infection-to-removal time takes on a value less than or equal to t. The probability of removal is $P_r[t]$ and

(2) $P_r[t] = h[t]$.

The two previous equations and a set of three mutually exclusive and exhaustive events lead directly to the probability of an infected individual being contagious, $P_i[t]$, or

(3) $P_i[t] = 1 - P_e[t] - P_r[t] = g[t] - h[t]$.

For some number of initial infections, E[0], expected sizes of the **E**, **I** and **R** cohorts are

(4) $E[t] = E[0]\ (1 - g[t])$,

(5) $I[t] = E[0]\ (g[t] - h[t])$ and

(6) $R[t] = E[0]\ h[t]$.

Mean values and standard deviations in Table 4, the assumption of log normal CDFs, and Equations (4), (5) and (6) allow us to quantify the progression of initial infections. Figure 7 displays the continuous progression of 100 initial infections.

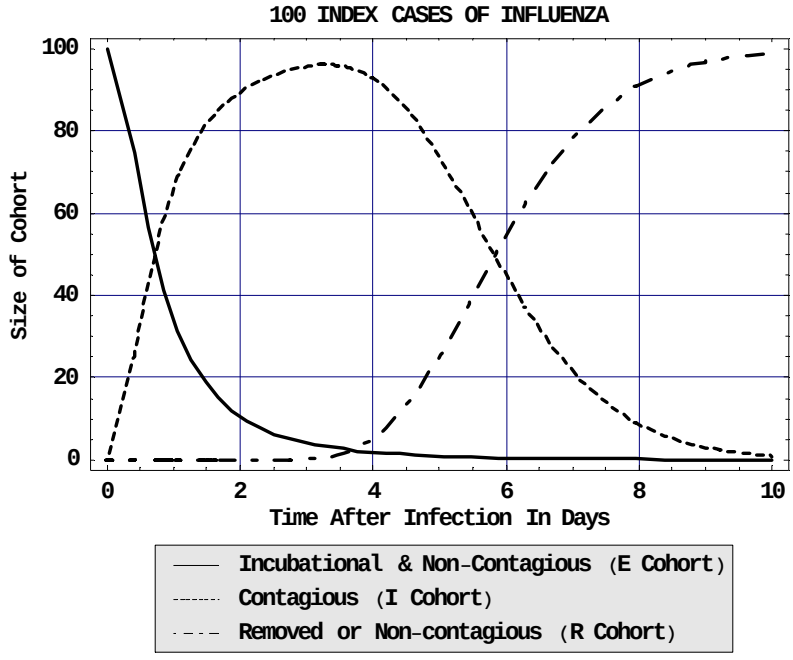

Figure 7. Evolution of 100 Index Cases in a 3-Cohort Model of Influenza Progression

D. Influenza Viruses and Medical Countermeasures

Influenza viruses of types A and B cause epidemics in the U.S. virtually every year and, from 1990 though 1999, influenza was responsible for an average of 36,000 American deaths per year. Influenza A viruses are found in many animals (ducks, chickens, pigs, horses, etc.), whereas wide circulation of influenza B viruses is confined to humans.

Two antigens or glycoproteins on the surface of an influenza A virus, hemagglutinin (H) and neuraminidase (N), determine its subtype. There are currently 15 different H subtypes and 9 different N subtypes. Influenza A viruses of all known subtypes replicate in respiratory or intestinal tracts of wild aquatic birds and usually do not cause avian disease. Over the last 100 years, pandemics of human influenza have involved hemagglutinin subtypes H1, H2 and H3 along with neuraminidase subtypes N1 and N2. Because wild aquatic birds serve as a natural reservoir for influenza A viruses, and because these viruses are able to "jump" from birds to other hosts, the eradication of influenza is infeasible.

Gradual small variations of hemagglutinin and neuraminidase genes may occur within human hosts and this evolutionary process of antigenic drift can produce a new pandemic strain of either an influenza A or B virus. In contradistinction to antigenic drift, when animals transmit a novel subtype of the influenza A virus to humans, there is an antigenic shift (abrupt and large antigenic variation) and the first instances of person-to-person transmission can foreshadow a serious pandemic.[49]

Antigenic drift and shift cause seasonal influenza epidemics and occasional influenza pandemics. In any given year and country, the prevalence of influenza depends on (a) the extent of antigenic variation, (b) immunity of the population and (c) levels of virulence for the circulating viruses. Since H1N1 and H3N2 subtypes of influenza A viruses have co-circulated throughout the world for about 25 years, selected strains of those two subtypes and an influenza B strain continue to provide targeted antigens for annual U.S. inactivated vaccines.[50]

The age distribution and general immunocompetence within a vaccinated population, as well as antigenic similarities between the vaccine and viruses in

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49 Nancy J. Cox and Kanta Subbarao, "Influenza," *The Lancet*, Volume 354 (9186), October 9, 1999, pp. 1277-1282.

50 Morbidity and Mortality Weekly Report, *Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (SCIP)*, Centers for Disease Control and Prevention, Vol. 52 (No. RR-8), April 25, 2003, p. 5.

"The trivalent inactivated influenza vaccine prepared for the 2003-04 season will include A/Moscow/10/99 (H3N2)-like, A/New Calendonia/20/99 (H1N1)-like, and B/Hong Kong/330/2001-like antigens."

circulation, are the principal factors governing vaccinal effectiveness. When the vaccinated population is composed of immunocompetent adults who are less than 65 years old, and when there is a good match between the influenza vaccine and circulating viruses, vaccinations prevent influenza illness in 70% to 90% of the recipients.[51]

Four licensed antiviral drugs (amantadine, rimantadine, zanamivir and oseltamivir) are available in the U.S. to help prevent and control influenza. Amantidine and rimantadine are adamantanes, while zanamivir and oseltamivir are neuraminidase inhibitors. All four drugs are useful in the prevention and treatment of influenza, though none of them is recommended as a substitute for vaccination.

Amantadine and rimantadine do not prevent or ameliorate illness due to influenza B infection, but they are 70% to 90% effective in the chemoprophylaxis of influenza A infection. Moreover, administering either drug less than two days after the onset of symptoms may shorten the duration of influenza A illness. But a therapeutic amantadine or rimantadine regimen can replace (in a period of a few days) a sensitive influenza strain with an insensitive or drug-resistant strain.[52]

The two neuraminidase inhibitors have activity against influenza A and B viruses and these drugs have been approved by the FDA for the treatment of uncomplicated influenza illness. In addition, both neuraminidase inhibitors are approximately 80% effective in preventing influenza, although only oseltamivir is an approved prophylactic agent.[53] In general, the ACIP recommends that: "To be maximally effective as prophylaxis, the drug must be taken each day for the duration of influenza activity in the community."

E. Past and Future Epidemiological Circumstances

Influenza effects on U.S. military populations were shaped by several important epidemiological circumstances in the autumn of 1918: (a) virulent strain(s) of the influenza A/H1N1 virus, (b) age distribution, (c) length of military service, (d) weather and climate, (e) military setting, and (f) response of the military health care system. As indicated before, many younger servicemen between 20 and 40 years of age were

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51 Ibid.

52 Ibid., p. 24.

"Resistant viruses have been isolated from persons who live at home or in an institution where other residents are taking or have recently taken amantadine or rimantadine as therapy; however, the frequency with which resistant viruses are transmitted and their effect on efforts to control influenza are unknown. Amantadine- and rimantadine-resistant viruses are not more virulent or transmissible than sensitive viruses. The screening of epidemic strains of influenza A has rarely detected amantadine- and rimantadine-resistant viruses."

53 Apparently, viral resistance to zanamivir and oseltamivir is infrequent.

particularly susceptible to the circulated influenza viruses and they accounted for almost 95% of the 1918 influenza-pneumonia deaths within the entire U.S. Army.[54] The length of military service was likewise an immunological indicator; specifically, influenza-pneumonia mortality rates for men with less than 6 months of military service were 2 to 4 times higher than those for soldiers with 6 to 12 months of service.[55]

When the second epidemic wave arrived in the U.S., the weather tended to be mild and cool throughout the country. Only 20% of 111 nationwide stations reported severe weather conditions, significantly affecting neither influenza morbidity nor influenza mortality rates in stateside camps. On the other hand, once a recruit or soldier came down with influenza, the chances of developing pneumonia and becoming a pneumonia fatality were much higher in colder climes (northern camps).[56]

Our analyses of 1918 influenza effects on military populations focus on two generic military settings: a stateside camp and an element of the AEF in Europe. Considering all reported respiratory diseases (influenza, bronchitis, broncho-pneumonia and lobar pneumonia), respective average admission rates for the stateside camps and for the AEF were 227.7 and 143.4 per 1,000. The larger average admission rate for stateside military populations is associable with crowded living conditions in barracks and lower levels of immunity. In barracks, the available floor space for each resident could range from about 40 square feet to over 110 square feet and the number of residents with influenza appears to have been inversely proportional to floor space per man.[57] Further, when the second epidemic wave hit the AEF in Europe, a substantial fraction of AEF personnel had been in stateside military camps during the spring of 1918 and they were exposed to, or infected with, influenza viruses in the first epidemic wave.[58]

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54 *MEDICAL DEPARTMENT OF U.S. ARMY IN WWI*, Volume IX: *Communicable and Other Diseases*, p. 90.

55 Ibid., p. 92.

In September of 1918, most men with 6 to 12 months of military service were in stateside camps during the first epidemic wave and they were surely exposed to spring 1918 influenza viruses.

56 Ibid., p.109.

57 Ibid., p. 111.

58 Ibid., p. 127.

"At Camp Shelby, Mississippi, there was in April, 1918, a division of troops numbering about 26,000. An epidemic of mild influenza struck this camp at this time, and within 10 days there were about 2,000 cases, including not only men who were sent to the hospitals but also men who were cared for in barracks. This was the only division that remained in this country from April until the fall of 1918.

During the summer this camp received 11,645 recruits. In late August, 1918, the virulent form of influenza struck this camp. It confined itself almost exclusively to the recruits of the summer and scarcely touched the men who had lived through the epidemic of April. Not only the 2,000 who had the disease in April but also the 24,000 who apparently were not affected escaped the fall epidemic. Vaughan stated: 'It appears from this that the mild form of influenza of April gave a marked degree of immunity against the virulent form of October.' "

The military health care system of 1918 did not have the wherewithal to respond effectively to influenza epidemics. Quarantining a military population, prohibiting gatherings, avoiding crowded conditions in barracks and promptly isolating influenza patients (to the greatest practical extent) were the primary ways to prevent exposures and limit influenza transmission.[59] These countermeasures usually slowed the progress of an epidemic but, over time, they did little to reduce the total number of influenza cases.[60] Similarly, early treatment in the form of bed rest, warmth and appropriate diet may have prevented or ameliorated some pneumonia cases.[61]

Table 5 displays general epidemiological circumstances in categories that encompass: the pathogen's characteristics, susceptible population, person-to-person transmission and medical countermeasures. Certain circumstances (like disease awareness or frequency of face-to-face contacts) may change as an epidemic unfolds.

Table 5. Epidemiological Circumstances Pertaining to Influenza Epidemics

Pathogen
Subtype and strain
Infectious dose
Vaccinal and/or antiviral drug resistance
Effects of heat, light and humidity (viability of influenza virions in projected respiratory droplets)
Population at Risk
Military versus civilian setting
Levels of natural and/or acquired immunity
Urban versus rural location
Living and working conditions
Disease awareness (potential for personal prophylaxis)
Disease Transmission
Indoor versus outdoor encounters
Frequency of face-to-face (2-meter) contacts
"Reach" of infected individuals (via accessible transportation systems)
Community hygiene
Customs and traditions (home care for sick family members or friends, burials, etc.)
Random encounters
Health Care System
Epidemic response time (correct diagnosis and initiation of controls)
Implementation of, and adherence to, traditional infection controls
Immunoprophylactic, chemoprophylactic and chemotherapeutic options
Capacity

59 Ibid., pp. 123-124.

60 Ibid., p. 115.

"In a military camp this is an accomplishment of no small value inasmuch as it serves to reduce greatly the daily number of admissions during an outbreak, and correspondingly to lessen the strain on hospital facilities and personnel, with the result of giving to the individual patient the possibility of better care and increased chance of recovery. Preventive measures accordingly should be judged by the measure of their ability to prolong an outbreak by the diminution of its explosiveness, as well as by their ability to lessen the percentage of persons attacked."

61 Ibid., p. 163.

The fall 1918 rates of influenza transmission at Camp Custer and Camp du Valdahon were driven by epidemiological circumstances that are more or less pertinent to today's military settings. Current military trainees still live in crowded barracks and face-to-face contacts between these trainees or between military personnel in a modern forward-deployed unit are not unlike the analogous contacts that occurred in 1918. To be sure, a future act of bioterrorism or biological warfare will introduce certain unique epidemiological circumstances that will distinguish the resultant epidemic from predecessors.

In our view, unique future epidemiological circumstances of most concern will be attributes of a man-made influenza attack (subtype and strain of the disseminated influenza A virus, number of initial infections, etc.), the progression of initial infections, and responses of military and civilian health care systems. We argue that (a) these unique circumstances are incorporable in mean-field epidemic models with historical time-varying transmission rates and (b) this analytical approach to the problem of unnatural influenza epidemics yields meaningful estimates for medical planning purposes.

Historical time-varying rates of influenza transmission are clearly stepping stones in our predictive process. The next section of this document deals with the reconstruction of aforementioned 1918 influenza epidemics.

IV. ANALYTICAL RECONSTRUCTION OF 1918 INFLUENZA EPIDEMICS

1. Retrospective Modeling Considerations and Assumptions

Because interesting questions about past and future epidemics are diverse and interdisciplinary, researchers require a broad spectrum of epidemic modeling tools: empirical, semi-empirical, theoretical (first principles), deterministic (mean-field), stochastic, spatiotemporal, temporal, continuous, discrete, etc. Military biodefense planning considerations led to the epidemic modeling choices in Figure 8, which also displays contrasting epidemic modeling possibilities.

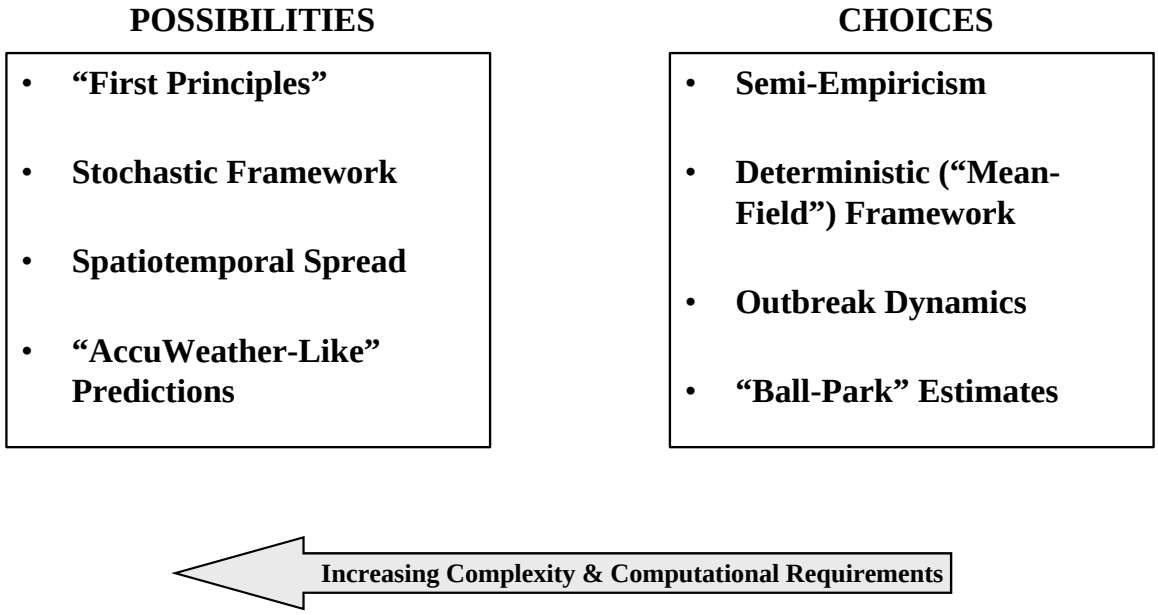

Figure 8. Epidemic Modeling Possibilities and Choices

Military biodefense planners often focus on magnitudes of possible future epidemics, impacts of defensive measures, streams of casualties and accompanying medical requirements. Epidemic modeling choices in Figure 8 spring from this fourfold emphasis. That is to say, semi-empirical epidemic predictions can link bioterrorism or biological warfare medical requirements with actual historical events and, arguably, these predictions are least likely to be either gross underestimates or unreal overestimates. Secondly, mean-field aggregates and a deterministic analytical framework are flexible enough to readily accommodate various defensive measures. And thirdly, the choice of outbreak dynamics keeps casualty streams (as opposed to spatial distributions of casualties) at the forefront of analysis, thereby reducing requisite computations (per epidemic) and allowing more exploration of parameter space.

In the analytical reconstruction of a 1918 influenza epidemic, our first step is to determine average new infections per day using daily hospital admission data and a Monte Carlo backtracking algorithm. Monte Carlo results for the new infection rate(s) then constitute input to the set(s) of difference equations specifying mean-field **S**, **E**, **I** and **R** (or just **S**, **I** and **R)** cohorts. Next, once calculated cohort time histories are in hand, structural and mixing assumptions must be invoked to connect the new infection rate(s) with the time-varying rate(s) of influenza transmission and with **S** and **I** cohorts. As a consequence, the unknown time-varying transmission rate(s) is (are) derivable from Monte Carlo results for the new infection rate(s) and from calculated **S** and **I** cohorts.

We analytically reconstruct the Camp Custer and Camp du Valdahon epidemics in two ways, letting each total population be either unstructured or structured. There is a single new infection rate and a single set of mean-field cohorts for an epidemic in an unstructured population. Individuals in the **S** cohort become infected at a per capita rate called the force of infection, i.e., the disease transmission rate times the ratio of the **I** cohort to the total population. In accordance with the mass-action assumption, the number of new infections per unit time (new infection rate) is thus the product of the **S** cohort and the force of infection.

When the population is unstructured and the mass-action assumption is invoked, conventional mean-field models include a disease transmission rate that is independent of time. A time-independent rate of disease transmission implies that the probability of a contact between any susceptible individual and any contagious individual is also a fixed constant throughout the epidemic. In turn, a fixed contact probability is a basic prerequisite for classical homogeneous or random mixing.

Our mean-field epidemic models for unstructured populations are similarly rooted in the mass-action assumption, but the disease transmission rate varies with time. This means that (a) the contact probability is time-dependent and (b) the mixing of susceptible and contagious individuals changes over the course of an epidemic. Such “evolutionary” homogeneous mixing takes account of time variations of epidemiological circumstances. The increasing public awareness of an ongoing epidemic and concomitant avoidance of crowded places are examples of changing epidemiological circumstances that modulate the disease transmission rate.

The structure of a military population may substantially inhibit the person-to-person transmission of a contagious disease and we utilize either a scale-free network or a regimental organization to represent this structure in mean-field models. Available epidemiological information on the Camp Custer epidemic contains neither descriptions of the at-risk military units nor hospital admission data for each affected unit. In view of these informational voids, we chose to partition the Camp Custer military population via

a scale-free network. Contrariwise, the epidemiological data in Figure 6 is more complete and covers the three affected regiments that comprise the analyzable structured population at Camp du Valdahon.

A contagious individual in one subgroup of a structured population may transmit a disease to a susceptible individual in either the same subgroup or another subgroup. The disease transmission rates within and between subgroups can all be different functions of time and a transmission matrix thus characterizes evolutionary heterogeneous mixing patterns. Needless to say, epidemiological data constraints force us to make heterogeneous mixing assumptions and thereby reduce the number of unknown functions in this transmission matrix.

B. Semi-Empirical Models with Time-Varying Transmission Rates

Our analytical reconstruction of a 1918 influenza epidemic produces average new infections per day, mean-field cohorts and time-varying rates of influenza transmission. The theoretical basis for these products is summarized below.

1. Average New Infections per Day

New infection rates for unstructured or structured populations at Camp Custer and Camp du Valdahon are derivable from hospitalization data sets in Figures 5 and 6. The derivation begins with the removal of "index hospitalizations" from the only data set for an unstructured population, or from a particular data subset for a structured population. A random "infection-to-admission" interval can then be ascribed to every hospital admission in a censored or an uncensored time series of interest. If t_e is the random non-contagious incubation period, and if t_c is the random contagious period, a linear combination of random variables $(t_e+\eta t_c)$ is a meaningful representation of the infection-to-admission interval (say, t_a). The parameter η is a selectable constant and it denotes the fraction of the contagious period that elapses prior to hospitalization. As before, probability distributions for t_e and t_c are assumed to be log normal and corresponding distributional parameters derive from the mean values and standard deviations in Table 4.

Our Monte Carlo algorithm is straightforward and a single trial involves just a few computations. First, obtain random infection-to-admission intervals and round them off for all hospital admissions in the time series under consideration. Second, backtrack in time to identify when all infections occurred. And third, compile the total score for each time step. Averaging scores per day for a large number of Monte Carlo trials yields the desired new infection rate.

The parameter η warrants more discussion. An infected trainee or soldier at Camp Custer or Camp du Valdahon probably became hospitalized soon after the "full-blown"

disease got under way. Evidently, the full-blown disease could start: (a) within hours of symptom onset (abrupt invasion at the height of an epidemic), (b) about 2 days after symptom onset (gradual invasion at the beginning of an epidemic), or (c) 4 or more days after symptom onset (intermittent invasion at the end of an epidemic). All of this is to argue that an overall average infection-to-admission interval of 4 days (or 3 days longer than our mean non-contagious incubation period) is consistent with available historical evidence. And since 3 days is 60% of the mean contagious period, the selected value of η is 0.6.

2. Unstructured Population and Evolutionary Homogeneous Mixing

Under prevailing epidemiological circumstances of 1918, military health care providers were incapable of preventing or curtailing influenza transmission at Camp Custer and Camp du Valdahon. The 1918 influenza epidemics at these (and many other) camps thus followed a natural course and were unimpeded by available medical countermeasures. Notably, as epidemics unfolded in the two camps under study, the total military population was either fixed (Camp du Valdahon) or slightly variable (Camp Custer).

If the total population (N_0) is indeed fixed and unstructured, six equations[62] represent the point of departure for our development of a discrete **SEIR** algorithm:

(7) $N_0\, u[t] = S[t] + E[t] + I[t] + R[t]$,

(8) $dS[t]/dt = - p[t]$,

(9) $dE[t]/dt = - (N_0 - S[0])\, dg[t]/dt + p[t] - p[t - \mu_e]$,

(10) $dI[t]/dt = (N_0 - S[0])\, (dg[t]/dt - dh[t]/dt) + p[t - \mu_e] - p[t - \mu_r]$,

(11) $dR[t]/dt = (N_0 - S[0])\, dh[t]/dt + p[t - \mu_r]$

and

(12) $p[t] = \beta[t]\, S[t]\, I[t] \div N_0$.

Every time-dependent function in the above equations vanishes when its argument is less than zero and the function u[t] is unity for $t \geq 0$.[63] The new infection rate is p[t] and the time-varying rate of influenza transmission is $\beta[t]$,[64] while μ_e and μ_r are respective mean values of the non-contagious incubation period and infection-to-removal period.

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62 Bombardt, *Primary Pneumonic Plague Transmission and BW Casualty Assessments*, pp. B-1 and B-2.

63 The number of infected individuals at $t = 0$ is $N_0 - S[0]$ and, if $I[0] = R[0] = 0$, then $E[0] = N_0 - S[0]$.

64 Equation (12) is the mean-field definition of evolutionary homogeneous mixing, wherein the force of infection is the product of (a) the time-varying transmission rate and (b) the ratio of the **I** cohort to the total population.

Temporarily putting Equation (7) and Equation (12) aside, the above delay differential equations specify time derivatives of four unknown functions (S[t], E[t], I[t] and R[t]) in terms of 3 "known" functions (g[t], h[t] and p[t]). Laplace transforms systematize the integration of those differential equations and explicitly show how each unknown function depends on initial conditions and the known functions; for example,

$$(13)\ S[t] = S[0]\,u[t] - \int_0^t p[v]dv.$$

Resultant expressions for E[t], I[t] and R[t] contain similar integrals of the new infection rate, but Equation (13) allows us to express these integrals as functions of S[t]. After doing so and replacing Equation (8) with a difference equation, our discrete mean-field **SEIR** algorithm[65] takes the following form:

$$(14)\ S[m] - S[m-1] = -\,p[m-1] = -\,\beta[m-1]\,S[m-1]\,I[m-1] / N_0,$$

$$(15)\ E[m] = E[0]u[m] - (N_0 - S[0])(g[m] - g[0]u[m]) + S[0](u[m] - u[m-\mu_e]) + S[m-\mu_e] - S[m],$$

$$(16)\ I[m] = I[0]u[m] + (N_0 - S[0])\{(g[m] - h[m]) - (g[0] - h[0])u[m]\} + S[0](u[m-\mu_e] - u[m-\mu_r]) + S[m-\mu_r] - S[m-\mu_e]$$

with

$$(17)\ R[m] = R[0]u[m] + (N_0 - S[0])(h[m] - h[0]u[m]) + S[0]\,u[m-\mu_r] - S[m-\mu_r].$$

Input to the foregoing algorithm includes initial conditions, the new infection rate and "expected" progression of initial infections.[66] The left-hand side of Equation (14), S[0] and the new infection rate determine values of S[m], which are necessary to evaluate the defining algebraic expressions for the **E**, **I** and **R** cohorts. Evaluated mean-field cohorts, in conjunction with the new infection rate and right-hand side of Equation (14), define the time-varying rate of influenza transmission.

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65 In this algorithm, we suppress the one-day time step, Δt. This time step should appear as a multiplicand on the right-hand sides of Equation (14) and, when m is the argument of a function, it stands for $m\Delta t$. S[0] is the number of susceptible individuals at the end of day 0 (D+0), S[1] is the number of susceptible individuals at the end of day 1 (D+1), and so on. We define the **E**, **I** and **R** cohorts at each time step in a similar way.

66 At a specific time step ($m\Delta t$), the proportion of initial (or primary) infections in the **E**, **I** or **R** cohort is an expected value: i.e., the total number of initial infections multiplied by $P_e[m]$, $P_i[m]$ or $P_r[m]$. Now consider the average number of secondary infections (infections due to person-to-person transmission) that entered the **E** cohort at the same time step. These infections move in unison into the **I** cohort (or into the **R** cohort), when the dwell time in the **E** cohort (or in **E** and **I** cohorts) equals μ_e (or μ_r).

3. *Structured Population and Evolutionary Heterogeneous Mixing*

Given daily hospital admissions for every fixed and unstructured subpopulation (N_j where j = 1,2…J) in a fixed and structured total population ($N_0 = N_1+N_2+\ldots+N_J$), new infection rates (p_j) for the subpopulations are readily obtainable from the previously described Monte Carlo algorithm. And acknowledging small errors in Monte Carlo calculations, the sum of calculated new infection rates (or $p_1+p_2+\ldots+p_J$) for the subpopulations should be very close to the calculated new infection rate (p) for the total population.

Mean-field cohorts for a fixed and unstructured subpopulation are calculable in the same manner as those for a fixed and unstructured total population. A known new infection rate drives linear delay differential or difference equations that govern cohort time histories. Furthermore, mean-field cohorts for the subpopulations (e.g., $\mathbf{S}_1,\mathbf{S}_2\ldots\mathbf{S}_J$) must add up to the matching overarching cohort for the total population (e.g., **S**). The reconstructive algorithm for cohorts within a subpopulation becomes:

(18) $S_j[m] - S_j[m-1] = - p_j[m-1]$,

(19) $E_j[m] = E_j[0]u[m] - (N_j - S_j[0])(g[m] - g[0]u[m]) + S_j[0](u[m] - u[m-\mu_e]) + S_j[m-\mu_e] - S_j[m]$,

(20) $I_j[m] = I_j[0]u[m] + (N_j - S_j[0])\{(g[m] - h[m]) - (g[0] - h[0])u[m]\}$

$+ S_j[0](u[m-\mu_e] - u[m-\mu_r]) + S_j[m-\mu_r] - S_j[m-\mu_e]$

and

(21) $R_j[m] = R_j[0]u[m] + (N_j - S_j[0])(h[m] - h[0]u[m]) + S_j[0]\, u[m-\mu_r] - S_j[m-\mu_r]$.

In principle, any contagious individual in a structured total population may infect any susceptible individual within a certain subpopulation; in other words, disease transmission might occur within a subpopulation or between two subpopulations. Disease transmission rates within subpopulations (i.e., $\beta_{jj}[m]$ where j = 1,2…J) and between subpopulations (i.e., $\beta_{jk}[m]$ where $k \neq j$ and k = 1,2…J) could all be unique functions of time. Consequently, a transmission matrix links contagious individuals in all subpopulations with susceptible individuals in any single subpopulation: viz.,

(22) $p_j[m] = S_j[m] \sum \beta_{jk}[m]\, I_k[m] \div N_k$,

where the summation extends over the index k.

Even if the new infection rate and mean-field cohorts within each subpopulation were known time histories, Equation (22) would still engender a system of J algebraic equations with J^2 unknown transmission rates. One way of reducing the number of

unknown transmission rates by a factor of J is to employ the proportionate mixing assumption.[67]

Let $a_j[m]$ be the average number of disease-causing person-to-person contacts per unit time that are initiated by an individual in the j^{th} subpopulation. All people in the structured population initiate d[m] contacts per unit time, where

(23) $d[m] = \sum a_k[m] N_k$.

Because each contact involves two individuals, d[m] must likewise represent the total number of people who are on the receiving side of contacts and the proportion of the j^{th} subpopulation on the receiving side is $a_j[m]N_j \div d[m]$. Invoking the proportionate mixing assumption, we obtain

(24) $\beta_{jk}[m] = a_k[m]\, a_j[m]\, N_j \div d[m] = \xi_j[m]\, \xi_k[m]\, N_j$

where

(25) $\xi_j[m] = a_j[m] \div d[m]^{1/2}$

and

(26) $p_j[m] = \xi_j[m]\, S_j[m] \sum \xi_k[m]\, I_k[m]$.

From a mathematical standpoint, the proportionate mixing assumption simplifies the transmission matrix by introducing a single "transmission factor" ($\xi_1[m]$, $\xi_2[m]$… $\xi_J[m]$) for each subpopulation. The upshot is that, under this assumption, reconstructed new infection rates and reconstructed **SEIR** cohorts within the subpopulations are adequate to determine all components of the transmission matrix. For instance, considering Camp du Valdahon in the autumn of 1918, epidemiological data sets for three field artillery regiments of the same size are sufficient to evaluate three intra-regiment rates of influenza transmission ($\beta_{11}[m]$, $\beta_{22}[m]$, $\beta_{33}[m]$) and three inter-regiment rates ($\beta_{12}[m]$, $\beta_{13}[m]$, $\beta_{23}[m]$).[68]

With regard to the fall 1918 epidemic at Camp Custer, we found (a) only one set of hospitalization data for the entire military population (~40,000) and (b) sparse descriptions of subpopulations. This limited amount of epidemiological information is enough to calculate an aggregate new infection rate, aggregate **SEIR** cohorts and an

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67 Valerie Isham and Graham Medley (Editors), *Models for Infectious Human Diseases*, Cambridge University Press, 1996, pp. 215-238. This reference pertains to H.W. Hethcote's article, "Modeling Heterogeneous Mixing in Infectious Disease Dynamics," which covers common heterogeneous mixing assumptions in socially defined groups.

68 Proportionate mixing patterns imply that relative rates of influenza transmission between two subpopulations are equal: $\beta_{jk}[m]/N_k = \beta_{kj}[m]/N_j$. If sizes of all subpopulations are the same, the transmission matrix is symmetric.

overall time-varying rate of influenza transmission within an unstructured total population. However, since the requisite input is unavailable to implement our algorithm for well-defined subpopulations, new assumptions and another algorithm are necessary to analyze how the structure of Camp Custer's population might have affected influenza transmission.

A conventional **SIR** algorithm for each subpopulation is the starting point for our analysis of influenza transmission in the structured military population at Camp Custer. (The rapid progression of influenza infections minimizes the influence of the non-contagious incubation cohort and excluding the **E** cohort from an influenza epidemic model does not introduce large errors.) The ordinary differential equations are

(27) $dS_j[t]/dt = - p_j[t] = - S_j[t] \sum \beta_{jk}[t] I_k[t] \div N_0$,

(28) $dI_j[t]/dt = p_j[t] - I_j[t] \div (\mu_r - \mu_e)$,

and

(29) $dR_j[t]/dt = I_j[t] \div (\mu_r - \mu_e)$.

Viewing a structured population as a social network, nodes in the network are individuals and links are social connections that enable disease-causing person-to-person contacts. The j^{th} subpopulation in a network of this type includes those individuals with j social connections and the probability distribution for the number of social connections per individual may be denoted as $P_c[j]$. Conversely, a level of connectivity (or some number of social connections) implies a subpopulation with a certain size ($N_0 P_c[j]$) and individuals within this subpopulation are susceptible, infected (and contagious) or removed.

A growing body of evidence indicates that various large social and physical networks are scale free; i.e., the connectivity (or "degree") distribution follows a power law.[69] A mature scale-free network can have tens of thousands of nodes and a few of those nodes may each have several hundred connections. The connectivity distribution for a finite scale-free network is

(30) $P_c[j] = j^{-\nu} \div \sum_{n\,min}^{n\,max} n^{-\nu}$,

69 Reka Albert and Albert-Laszlo Barabasi, "Statistical mechanics of complex networks," *Reviews of Modern Physics*, Vol. 74, January 2002, pp. 47-97.

with $2 < \nu \leq 3$ and with the index n running from nmin to nmax.[70] Also, summing the product of j and $P_c[j]$ over all values of j produces the average connectivity per node, <j>.

In their network-based **SIR** model, May and Lloyd assume a random mixing pattern and rely upon time-independent rates of disease transmission.[71] According to this mixing pattern, the probability of a node with connectivity j having a neighbor with connectivity k is $kP_c[k] \div \langle j \rangle$. Here, we adopt the same mixing pattern and consider time-varying transmission rates: i.e.,

(31) $\beta_{jk}[t] = j\ k\ \beta'[t] \div \langle j \rangle$

and, in the reconstruction of an historical epidemic, $\beta'[t]$ must be determined from epidemiological data. The new infection rate for individuals with connectivity j becomes

(32) $p_j[t] = j\ \beta'[t]\ S_j[t] \sum k\ I_k[t] \div (\langle j \rangle\ N_0)$,

wherein the summation index k extends from nmin to nmax.

Daily hospitalization data for the 1918 Camp Custer epidemic and a Monte Carlo algorithm yield the aggregate new infection rate (p[t]) that, along with the number of initial infections, completely determines the aggregate susceptible cohort (S[t]). These calculated aggregate quantities serve as input for our network-based **SIR** algorithm (Equation (27) through Equation (32)). Our derivation of $\beta'[t]$ entails the introduction of 2 intermediate aggregate functions; namely,

(33) $\theta[t] = \sum k\ I_k[t] \div N_0$

and

(34) $\alpha[t] = \left(\int_{-\infty}^{t} \beta'[\tau]\ \theta[\tau]\ d\tau \right) \div \langle j \rangle$.

The previous 5 equations and Equation (27) give rise to a relationship between $\alpha[t]$ and S[t] (or p[t]): [72]

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70 For a given exponent, ν, the values of nmin and nmax must be consistent with the desired total number of nodes or individuals, N_0. The total number of nodes in a particular scale-free network clearly depends on ν, nmin and nmax, but the network's nature appears to preclude an exact mathematical relationship. We will return to this matter in the next subsection.

71 Robert M. May and Alun L. Lloyd, "Infection dynamics on scale-free networks," *Physical Review E*, Vol. 64, 2001.

72 Equations (34) and (35) simplify Equation (27) in that $dS_j[\tau]/d\tau = -\ j\ S_j[\tau]\ d\alpha[\tau]/d\tau$. Integrating this simplified differential equation from $-\infty$ to t, and noting that $S_j[-\infty] = N_0\ P[j]$ and $\alpha[-\infty] = 0$, we arrive at the following result for the j^{th} subpopulation: $S_j[t] = N_0\ P[j]\ \mathrm{Exp}\{-j\ \alpha[t]\}$.

(35) $S[t] = S[0] - \int_0^t p[\tau]\, d\tau = \sum S_j[t] = N_0 \sum P_c[j]\, \mathrm{Exp}\{-j\, \alpha[t]\}$

or, equivalently,

(36) $d\alpha[t]/dt = p[t] \div (N_0 \sum j\, P_c[j]\, \mathrm{Exp}\{-j\, \alpha[t]\})$.

With a time history of the aggregate **S** cohort in hand, numerical root-finding techniques are applicable to Equation (35) and values of $\alpha[t]$ for a desired timeframe are easy to get. Alternatively, numerically solving Equation (36) for $\alpha[t]$ is certainly feasible employing known values of the aggregate new infection rate and an appropriate value of $\alpha[0]$ (from Equation (35).

At any point in time, the number of individuals within the j^{th} subpopulation is $N_0 P_c[j]$ and, necessarily,

(37) $\sum j\, P_c[j]\, \mathrm{Exp}\{-j\, \alpha[t]\} + \theta[t] + (\int_0^t \theta[\tau]\, d\tau) \div (\mu_r - \mu_e) = \sum j\, P_c[j] = \langle j \rangle$.

By differentiating this result with respect to t and making substitutions, a differential equation for $\theta[t]$ takes the following form:

(38) $d\theta[t]/dt = -\theta[t] \div (\mu_r - \mu_e) +$

$$(p[t] \sum j^2\, P_c[j]\, \mathrm{Exp}\{-j\, \alpha[t]\}) \div (N_0 \sum j\, P_c[j]\, \mathrm{Exp}\{-j\, \alpha[t]\})$$

with

(39) $\theta[0] = \langle j \rangle - \sum j\, P_c[j]\, \mathrm{Exp}\{-j\, \alpha[0]\}$.

Both $p[t]$ and $\alpha[t]$ must be known to calculate $\theta[t]$ and all 3 of these time-varying functions are determinants of $\beta'[t]$:

(40) $\beta'[t] = \langle j \rangle\, p[t] \div (\theta[t]\, N_0 \sum j\, P_c[j]\, \mathrm{Exp}\{-j\, \alpha[t]\})$.

Mathematical definitions of the aggregate **I** and **R** cohorts are the remaining elements of a network-based reconstruction of the 1918 influenza outbreak at Camp Custer. Summing over the index j in Equation (28) and using Equations (32)-(35), the aggregate **I** cohort must satisfy[73]

(41) $dI[t]/dt = (N_0\, \beta'[t]\, \theta[t])\, (\sum j\, P_c[j]\, \mathrm{Exp}\{-j\, \alpha[t]\}) \div \langle j \rangle - I[t] \div (\mu_r - \mu_e)$

and the aggregate **R** cohort follows from

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[73] Equation (41) is not the simplest form of the differential equation for our reconstructed aggregate **I** cohort. One could write: $dI[t]/dt = p[t] - I[t] \div (\mu_r - \mu_e)$ where calculated values of $p[t]$ originate from epidemiological data. By including $\beta'[t]$, $\theta[t]$ and $\alpha[t]$ in Equation (41), we can show how various scale-free networks alter these constituent time-varying functions while engendering the same I cohort.

(42) $R[t] = N_0 - S[t] - I[t]$.

C. Dynamics of the Camp Custer Epidemic

The first group of numerical results in this subsection is for an unstructured Camp Custer population. Average new daily infections are in Figure 9 and reconstructed **SEIR** cohorts are in Figures 10-12; Figure 13 displays the resultant time-varying rate of influenza transmission.

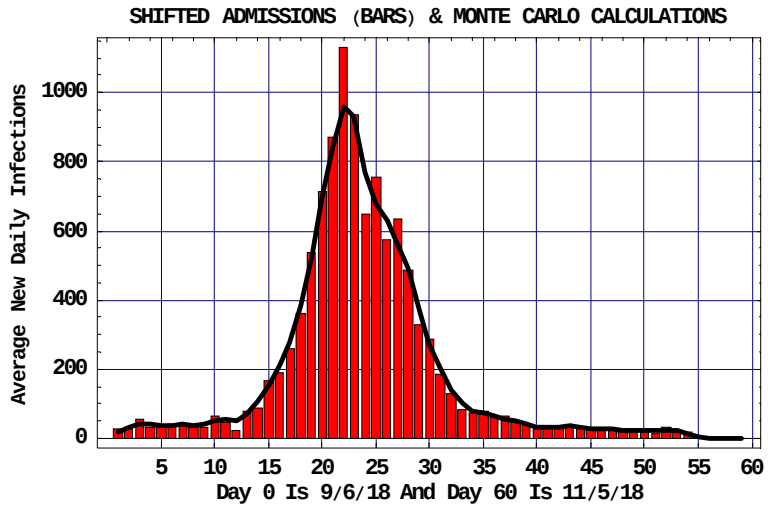

Figure 9. Average New Daily Infections at Camp Custer: 5,000 Monte Carlo Trials (solid line) and Hospital Admissions Shifted Backward in Time by 4 Days (bars)

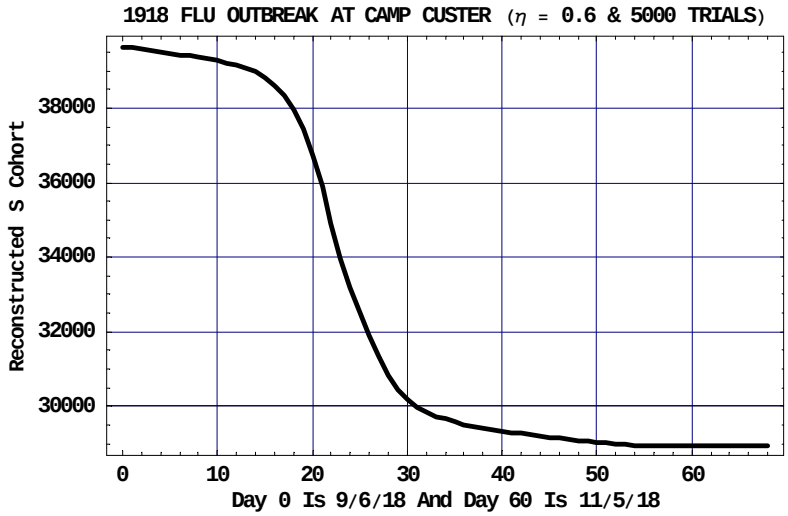

Figure 10. Reconstructed Susceptible Cohort at Camp Custer Using Monte Carlo Calculations in Figure 9

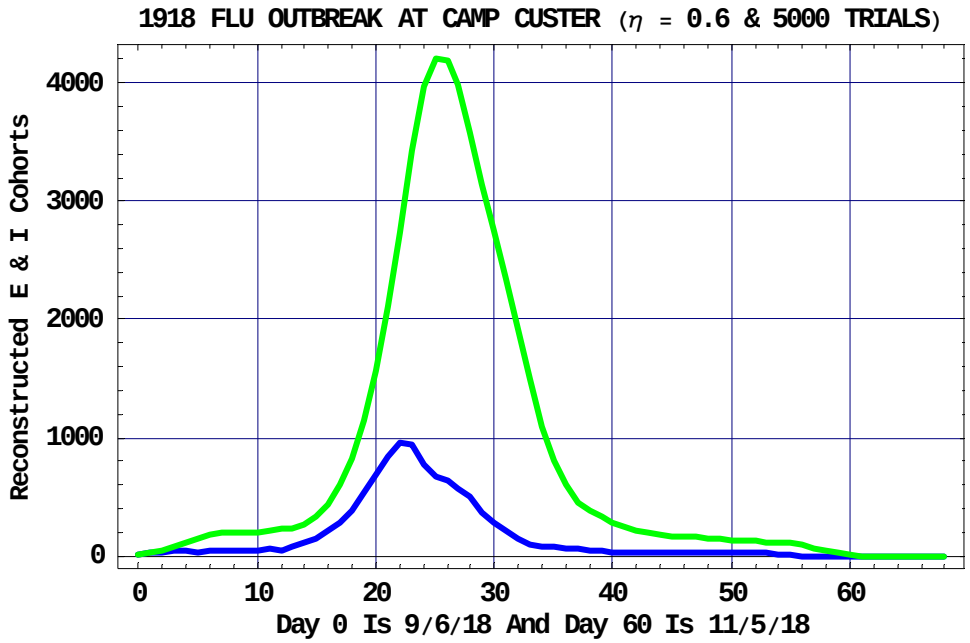

Figure 11. Reconstructed Exposed Cohort (blue line) and Infectious Cohort (green line) Using Monte Carlo Calculations in Figure 9

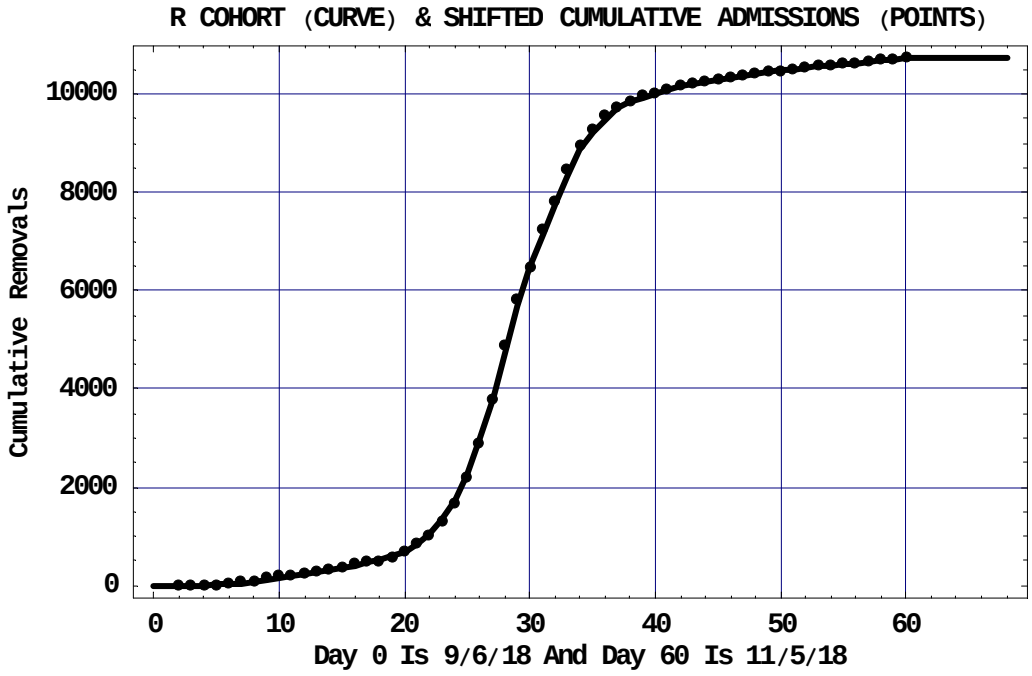

Figure 12. Reconstructed Removed Cohort Using Monte Carlo Calculations in Figure 9 (solid line) and Cumulative Hospital Admissions Shifted Forward in Time by 2 Days (points)

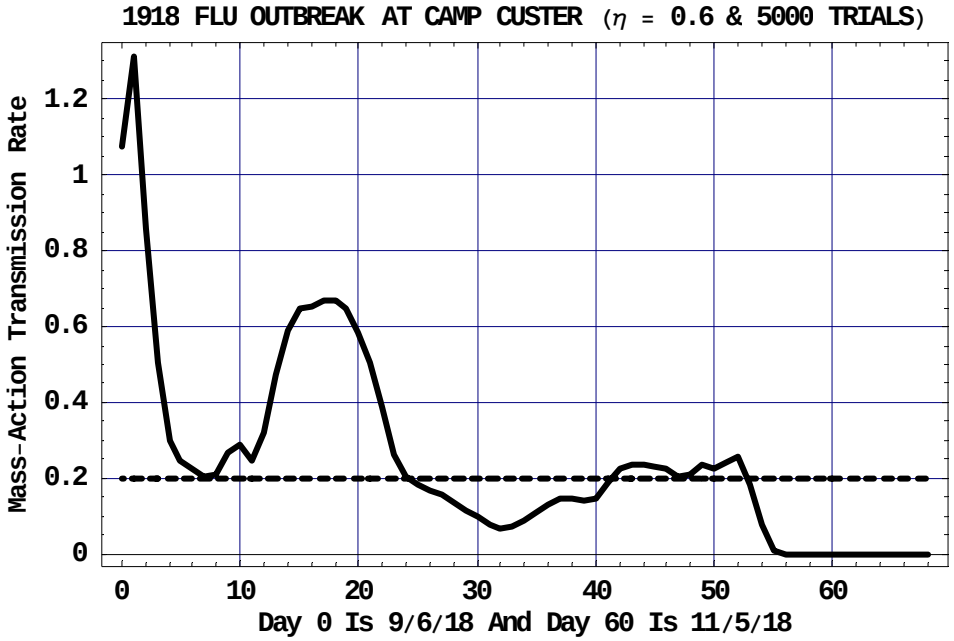

Figure 13. Time-Varying Rate of Influenza Transmission (solid line) Using Monte Carlo Calculations in Figure 9 and Constant Influenza Transmission Rate (dashed line) Based upon the Steady State Assumption with a Basic Reproductive Ratio of Unity

A backward-in-time shift of daily hospital admissions leads to good qualitative agreement with our Monte Carlo results for the average new infection rate, while a forward-in-time shift of cumulative hospital admissions matches our **R** cohort calculations quite well. The previously described Monte Carlo and mean-field **SEIR** algorithms for an unstructured Camp Custer population produce time histories that are fully consistent with published epidemiological data.

Average new daily infections (Figure 9) reach a maximum on D+22, preceding the maxima of the calculated **E** and **I** cohorts (Figure 11) on D+23 and D+25, respectively. Almost 1,000 men were in the **E** cohort (non-contagious incubation phase) on D+23 and over 4,000 men were in the **I** cohort (contagious phase) on D+25. And since $\beta[t]$ is approximately $p[t] \div I[t]$ (when $S[t]$ is near N_0), peaks and valleys in Figure 13 reflect variations in the average new infection rate per contagious individual.

Numerical results from the network-based **SIR** model are in Figures (14)-(19). Our implementation of Equations (27) through (42) draws upon Monte Carlo results in Figure 9, the calculated **S** cohort in Figure 10, and the following sets of scale-free network parameters: (a) $\nu = 3.0$, nmin = 3 and nmax = 102, (b) $\nu = 2.9$, nmin = 3 and nmax = 116, and (c) $\nu = 2.8$, nmin = 3 and nmax = 132. The values of nmin and ν are representative of scale-free networks in the literature, but values of nmax came from $\text{nmax} \sim \text{nmin}\ (N_0)^{1/\nu}$, which generalizes an approximate result in the May-Lloyd paper.

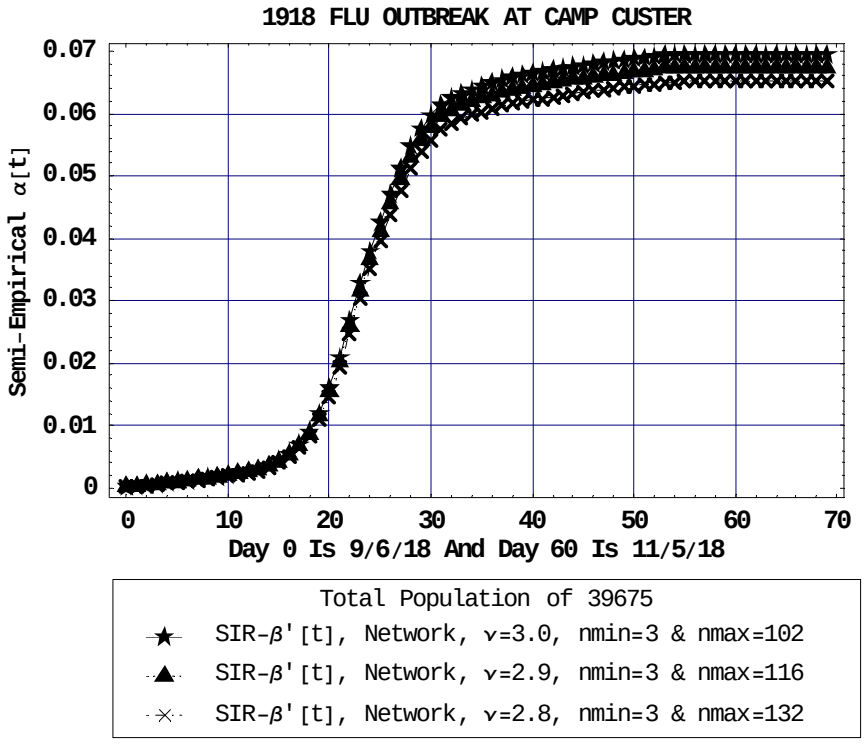

Figure 14. Time Histories of $\alpha[t]$ for 3 Scale-Free Networks (Average New Infection Rate and Aggregate S Cohort Are Known)

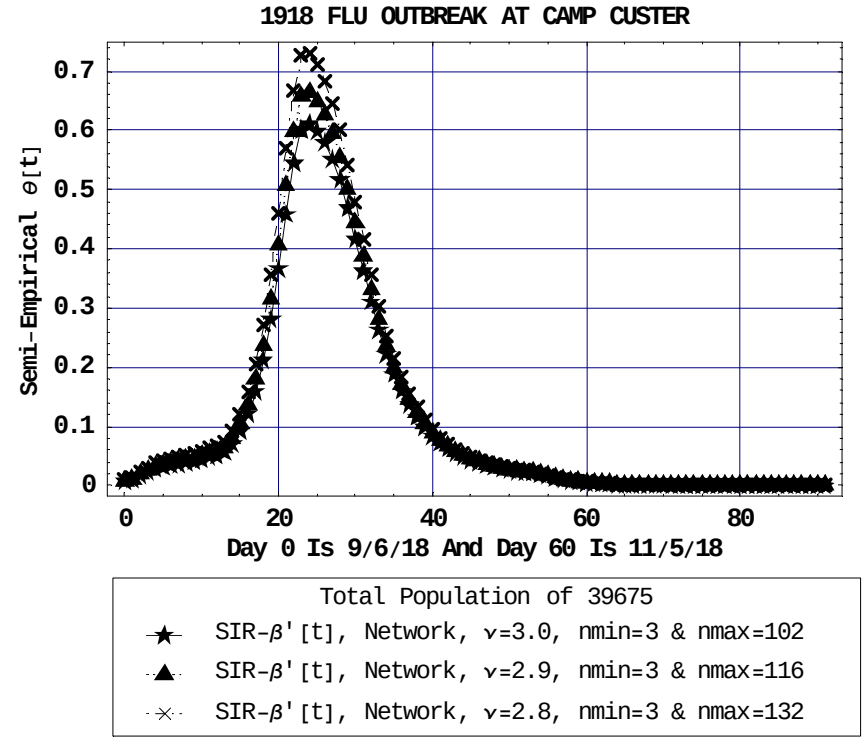

Figure 15. Time Histories of $\theta[t]$ for 3 Scale-Free Networks (Average New Infection Rate and Aggregate S Cohort Are Known)

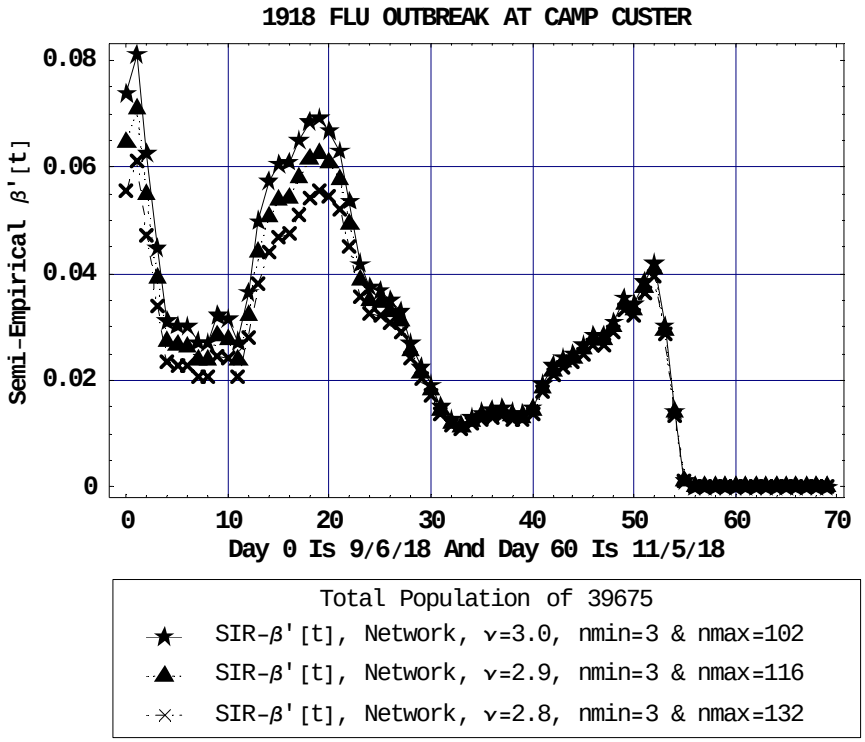

Figure 16. Time Histories of the Transmission Function β′[t] for 3 Scale-Free Networks (Average New Infection Rate and Aggregate S Cohort Are Known)

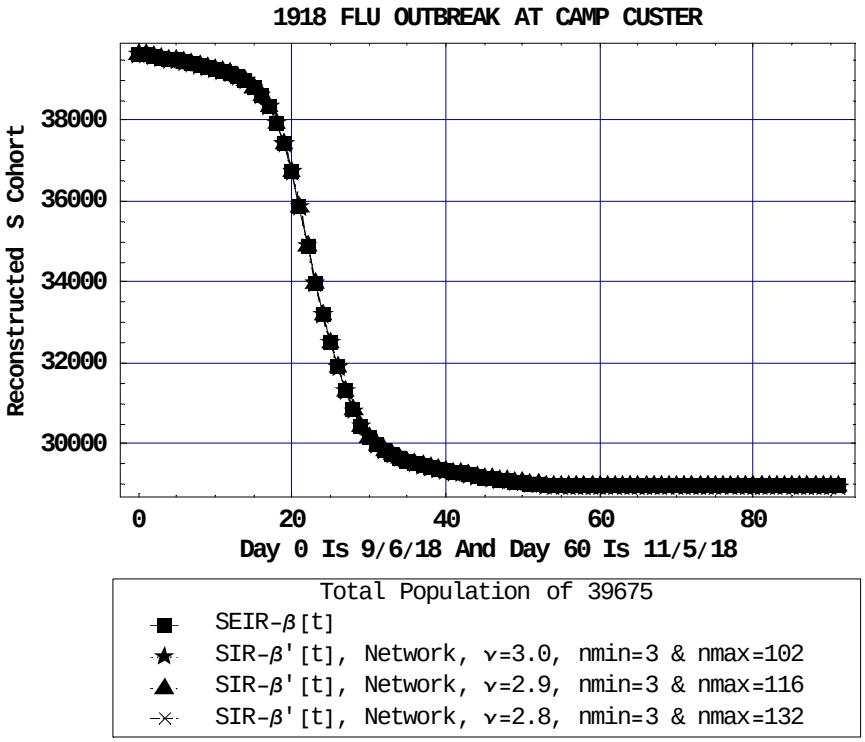

Figure 17. Reconstructed S Cohorts for Unstructured and Structured Populations

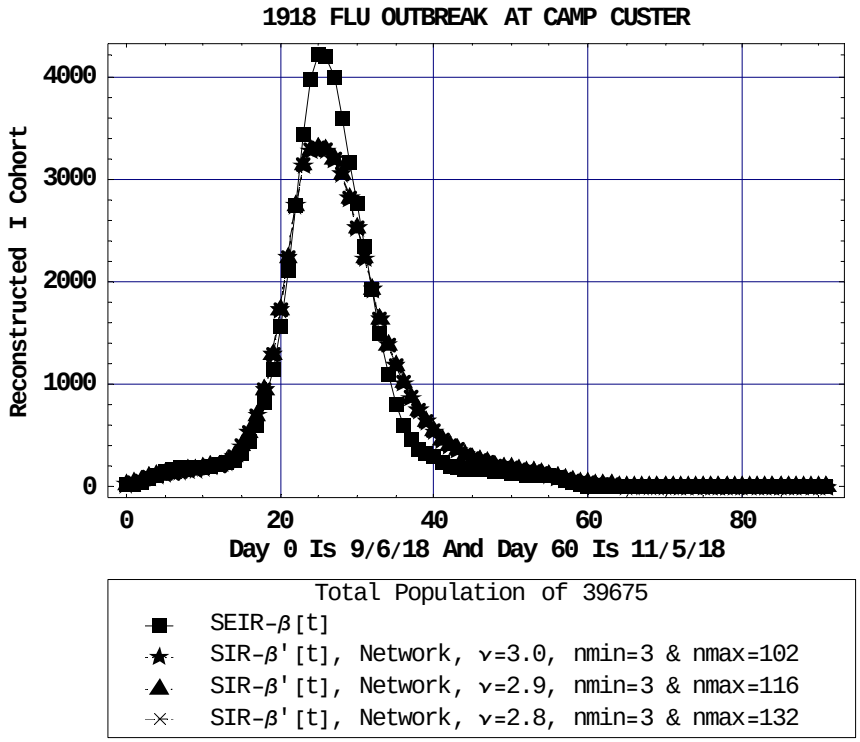

Figure 18. Reconstructed I Cohorts for Unstructured and Structured Populations

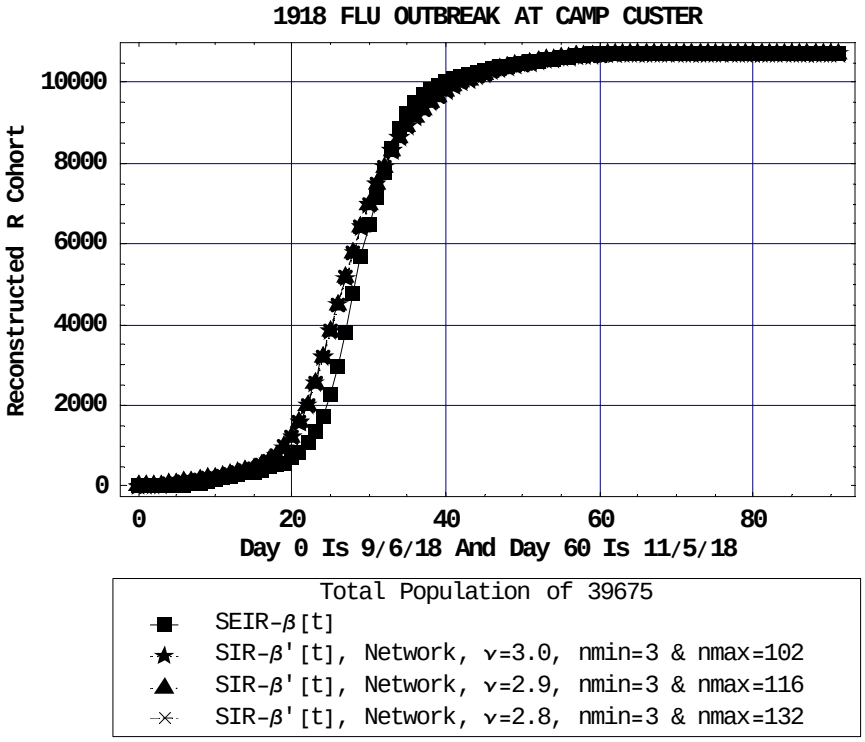

Figure 19. Reconstructed R Cohorts for Unstructured and Structured Populations

Figures (14) through (16) show that a common input (known **S** cohort) and three interesting sets of scale-free network parameters (ν, nmin and nmax) are responsible for significant temporal variations in α[t], θ[t] and β′[t]. But these variations should not and do not affect the recomputed aggregate **S** cohort. And because our **SEIR**-β[t] model for an unstructured population encompasses the non-contagious incubation period (with a mean dwell time of 1 day), **I** and **R** cohort time histories from this model are not identical to matching aggregate **I** and **R** cohort time histories from our network-based **SIR**-β′[t] model.[74]

D. Dynamics of Camp du Valdahon Epidemic

Average new infection rates for the 6th F.A. Brigade and its regiments are in Figure 20 and Figure 21 displays **SEIR** cohorts for these military units. The absence of a subscript implies a new infection rate for the 6th F.A. Brigade as a whole, while subscripts 1, 2 and 3 refer, respectively, to the 3rd F.A. Regiment, 11th F.A. Regiment and 78th F.A. Regiment. The overall transmission rate for the 6th F.A. Brigade is in Figure 22.

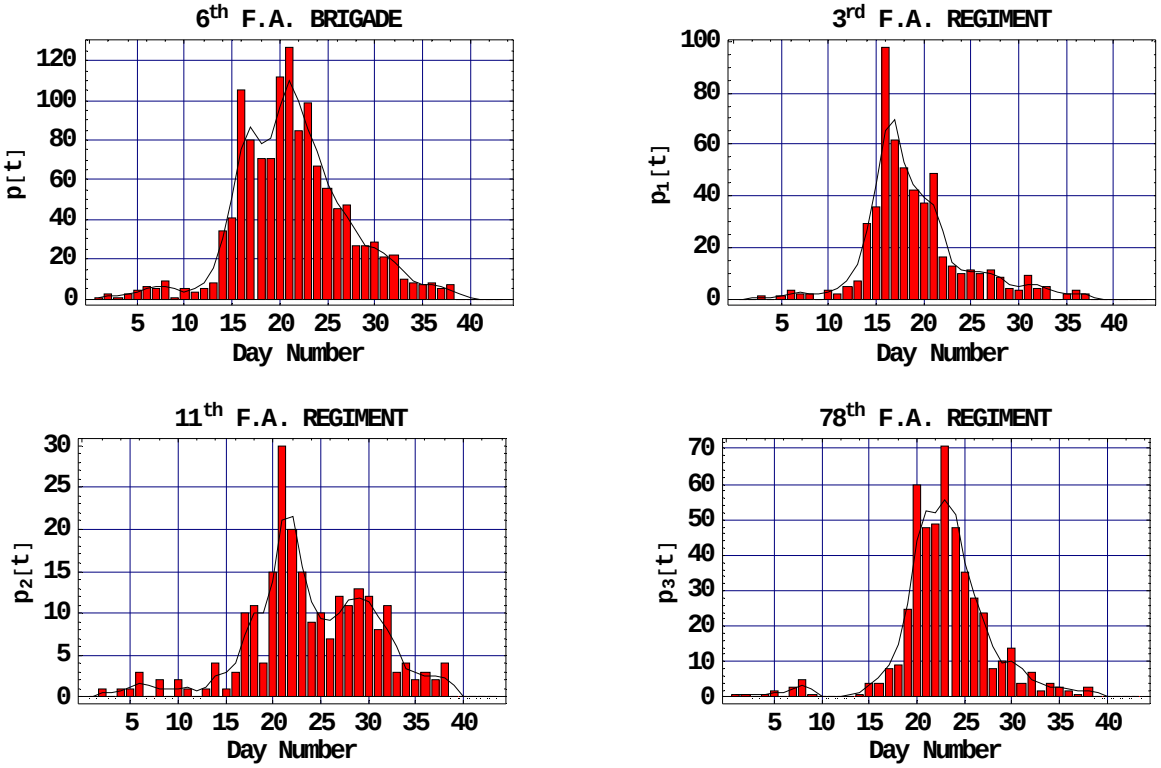

Figure 20. Average New Daily Infections at Camp du Valdahon: 5,000 Monte Carlo Trials (solid line) and Hospital Admissions Shifted Backward in Time by 4 Days (bars)

74 As Figure 19 shows, a common number of initial infections and a common (aggregate) new infection rate for our two semi-empirical models assure that endpoint (D+90) removal calculations are the same.

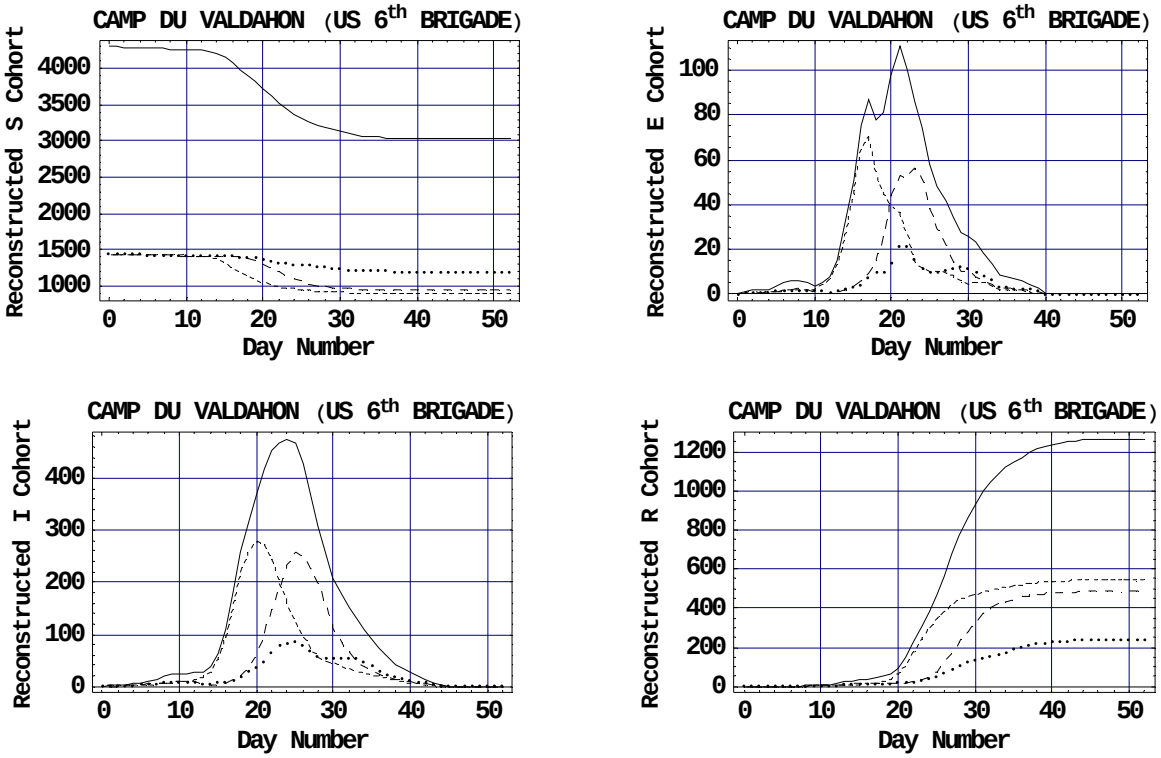

Figure 21. Reconstructed SEIR Cohorts for the Structured Population at Camp du Valdahon: (a) 6th F.A. Brigade as an Entity (solid line), (b) 3rd F.A. Regiment (short dashes), (c) 11th F.A. Regiment (points) and (d) 78th F.A. Regiment (long dashes)

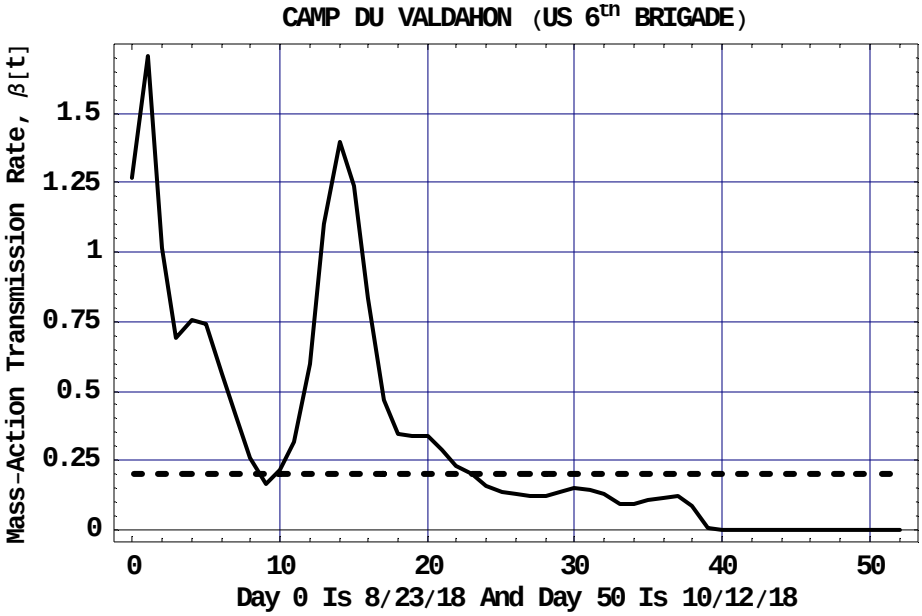

Figure 22. Time-Varying Rate of Influenza Transmission for the 6th F.A. Brigade as an Entity (solid line) and Constant Influenza Transmission Rate (dashed line) Based upon the Steady State Assumption with a Basic Reproductive Ratio of Unity

Comparing aggregate **E** and **I** cohorts in Figure 11 with those in Figure 21, it's apparent that (a) Camp Custer cohort maxima are an order of magnitude larger than the Camp du Valdahon counterparts[75] and (b) maximum values of the two **E** cohorts (or two **I** cohorts) occur near D+22 (or D+24). Interestingly, overall time-varying transmission rates in Figures 13 and 22 have similar shapes and these rates drop below the steady-state epidemic threshold (0.2 per day) on or near D+23, although the Camp Custer rate again rises above this threshold on D+41 and stays there for 12 days or so.

The next threee graphs portray influenza transmission within the regimental structure of the 6th F.A. Brigade and influenza transmission factors ($\xi_j[t]$ in Equations (24) through (26)) are in Figure (23). Pairs and squares of these time-dependent transmission factors, when multiplied by suitable regimental populations, define the desired historical transmission rates between and within individual regiments. Figures (24) and (25) contain the respective intra-regiment and inter-regiment transmission rates.[76]

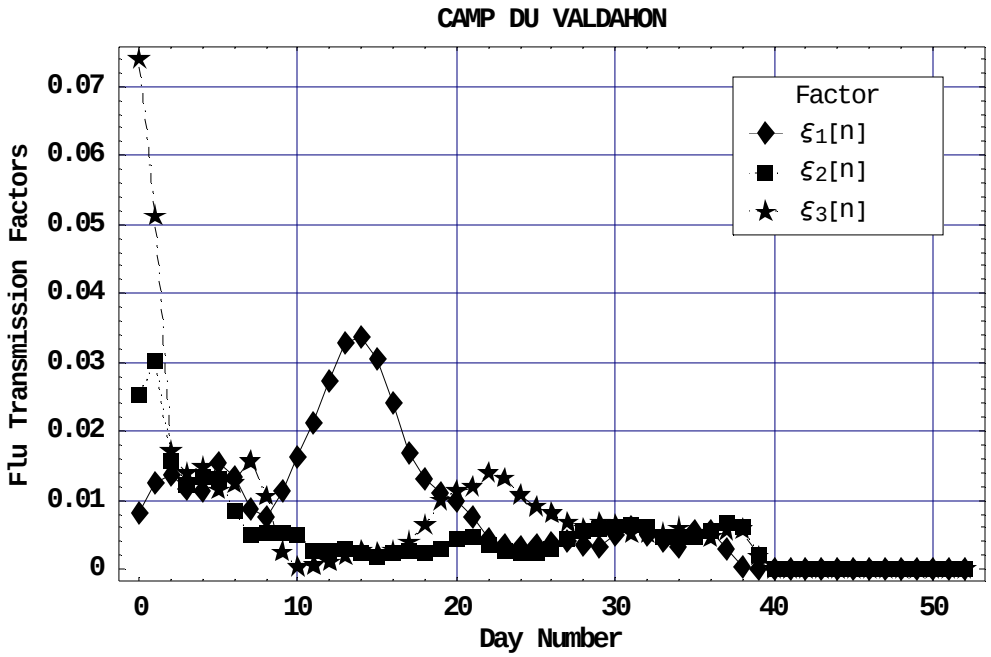

Figure 23. Time Histories of Three Influenza Transmission Factors for the Structured Population at Camp du Valdahon and for the Assumption of Proportionate Mixing

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75 Our calculations of **E** and **I** cohort maxima are consistent with two historical facts: (a) the Camp Custer population was an order of magnitude larger than the Camp du Valdahon population (6th F.A. Brigade) and (b) hospital admissions for each epidemic amounted to 25% of the population.

76 In Figures (24) and (25), we include the overall transmission rate for an unstructured population as a baseline.

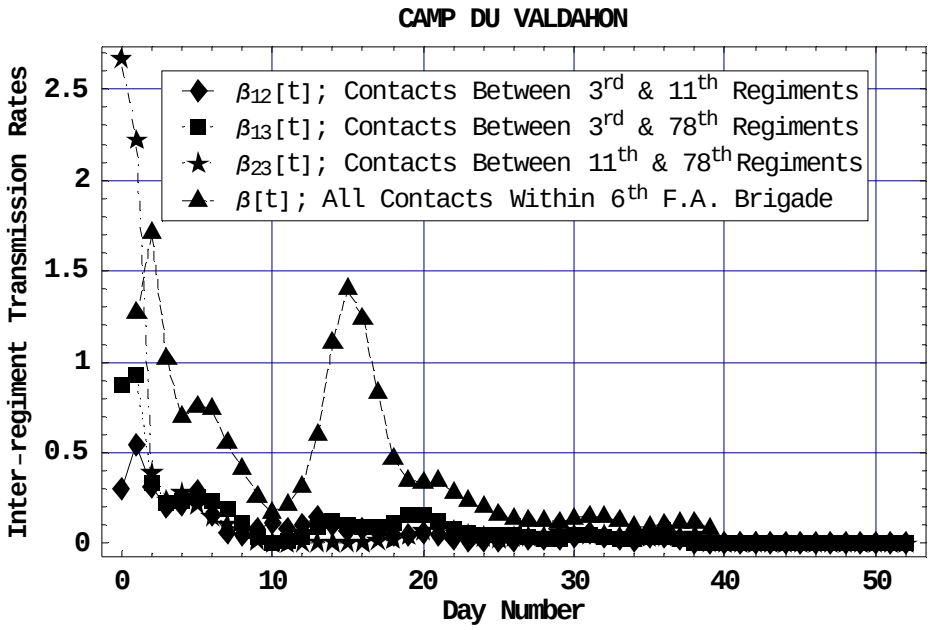

Figure 24. Time-Varying Inter-Regiment Rates of Influenza Transmission for the 6th F.A. Brigade (Proportionate Mixing)

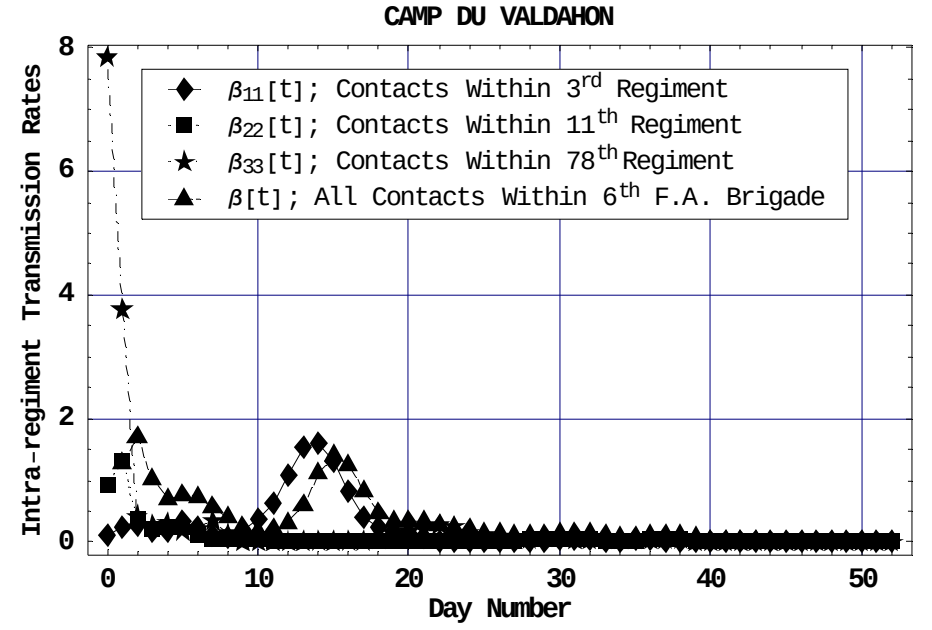

Figure 25. Time-Varying Intra-Regiment Rates of Influenza Transmission for the 6th F.A. Brigade (Proportionate Mixing)

V. ANALYSIS OF POTENTIAL INFLUENZA EFFECTS

A. Predictive Modeling Considerations and Assumptions

Adequate epidemiological data and "natural" rates of influenza transmission are important attributes of the 1918 Camp Custer and Camp du Valdahon epidemics. These transmission rates were natural in the sense that available countermeasures failed to noticeably curtail the spread of influenza within military populations. Natural historical transmission rates facilitate the incorporation of modern countermeasures in our semi-empirical predictive process.

Historical time-varying rates of influenza transmission tend to be somewhat independent of the size of the at-risk population (N_0). Until the total number of infections becomes a significant fraction (> 10%) of N_0, a time-varying transmission rate essentially follows the ratio of the average new infection rate to the **I** cohort. In any event, our assessment of potential influenza effects starts with a derived transmission rate that reproduces an historical epidemic in a modern military population.

Our predictive process accounts for the imposition of current or foreseeable medical countermeasures by either truncating or partially negating historically derived transmission rates. The mathematical truncation of a time-varying transmission rate is a crude characterization of outbreak controls in the aggregate. In other words, the abrupt termination of disease transmission emulates the overarching response time of the military health care system, when various controls completely stop an epidemic.[77] But permanently or temporarily moving uninfected people out of the S cohort and placing them in a virtual (**X**) cohort can partially negate a derived transmission rate, thereby emulating successful pre-attack immunoprophylaxis or post-attack chemoprophylaxis. Likewise, an emulation of successful chemotherapy is achievable by prematurely removing ill people from the **I** cohort and placing them in subdivision $\mathbf{R_x}$ of the **R** cohort.[78]

Figure 26 synopsizes our analytical process for predicting influenza casualties.

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77 *Smallpox Transmission and BW Casualty Assessments*, pp. 44-50. The truncation of a time-varying smallpox transmission rate was a convenient device in the development of casualty contour plots, which graphically summarized results of numerous possible future epidemics spanning various timeframes and a wide range of initial infections. Although casualty contour plots do not appear in this influenza report, the impact of a truncated influenza transmission rate is easy to discern from our graphs of **SEIR** time histories.

78 *Primary Pneumonic Plague Transmission and BW Casualty Assessments*, pp. 76-82. Algorithms and results for primary pneumonic plague epidemics dealt with chemotherapy, but influenza algorithms and results in the present study do not. The inclusion of chemotherapy in our influenza algorithms would not be difficult.

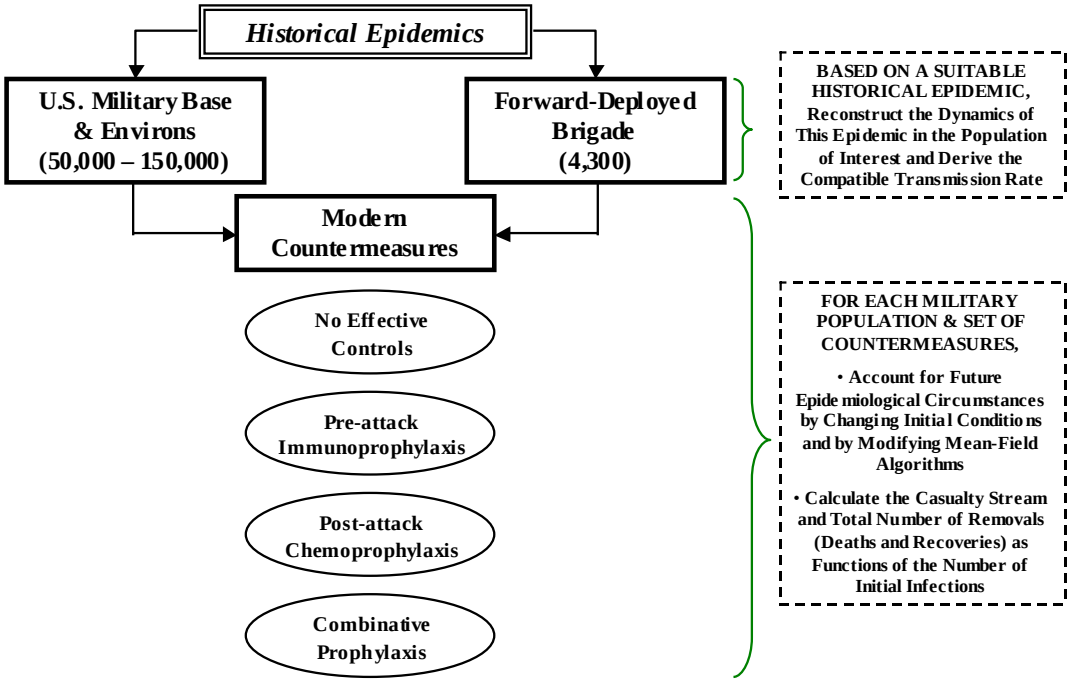

Figure 26. Basic Elements of Influenza Casualty Predictions

Predicting military casualties due to a 1918-like influenza epidemic obviously entails judgments and assumptions with regard to many critical uncertainties. Some important uncertainties are associable with (a) virulent influenza A viruses in the future, (b) natural or unnatural mode of attack and the number of index infections, (c) mixing patterns of uninfected and infected military personnel and (d) future levels of prophylactic efficacy for vaccines and anti-viral drugs.

Four of our fundamental predictive assumptions are transparent. First, the reemergence of a 1918-like influenza virus is not only a long-standing public health concern; it may become a serious bioterrorist or biological warfare threat as well. Second, influenza effects on stateside and overseas military populations in the autumn of 1918 are representative of what could happen to a current U.S. military population anywhere in the world. Third, time-varying rates of influenza transmission within a 1918 stateside training camp or within an overseas unit of the AEF are applicable to today's analogous military populations. And fourth, enough is known about 1918 influenza viruses to make medical plans and preparations for promptly dealing with such a virus in military settings.

B. Estimated Effects for a Military Base in the U.S.

Consider a future influenza epidemic at a military base in the U.S. and suppose the daytime population of this base is 50,000 people, which subsumes a small contingent of civilians. Let's also assume that the surrounding community is mainly composed of civilians and there are 100,000 of them. (These on-base and off-base populations are roughly those of Camp Lejeune in North Carolina.)

If bioterrorists were to infect a certain number of military personnel who live and work on the military base, the resultant epidemic might stay within the confines of this base. On the other hand, initially infected military personnel could mix with people who live in the surrounding community, allowing the at-risk population to quickly grow as large as 150,000 people. In the subsections that follow, we analyze both situations in the manner of Figure 26.

1. Equivalent Past-Future Epidemiological Circumstances

The natural or unnatural emergence of a virulent influenza virus may happen when public and military health officials have neither an effective vaccine nor sufficient anti-viral drugs at their disposal. If so, the ensuing influenza epidemic at a U.S. military base would rapidly overwhelm medical resources and historical (i.e., Camp Custer) epidemiological circumstances could again prevail.

In making our first estimates of potential influenza effects, we invoke two key assumptions: (a) equivalent past-future epidemiological circumstances and (b) an epidemic that (because of quarantine and/or good fortune) stays within the confines of the military base. For an unstructured and fixed military population of 50,000 (vice 39,675) people, the predictive **SEIR** algorithm calls for new $\beta[t]$ calculations that come from Monte Carlo results in Figure 9, historical (29) initial infections, Equation (12) and Equations (14)-(17). The new $\beta[t]$ (for a fixed population of 50,000 people) and the same equations then yield potential influenza effects for an interesting range of initial infections.

Figures (27) through (32) display a recalculated $\beta[t]$ and attendant time histories of **SEIR** cohorts for 100, 300, 500, 800 and 1,000 initial infections. Mass-action transmission rates in Figures (13) and (27) are essentially replicates, though the larger unstructured and fixed population was responsible for a slightly lower transmission rate toward the end of the epidemic (>D+40). The **I** cohorts in Figure (31) contain upwards of 15,000 ill individuals on D+23 and Figure (32) shows that the total number of influenza cases could be as high as 40,000. Further, as the number of initial infections goes from 100 up to 1,000 in Figure (32), saturation effects become apparent.

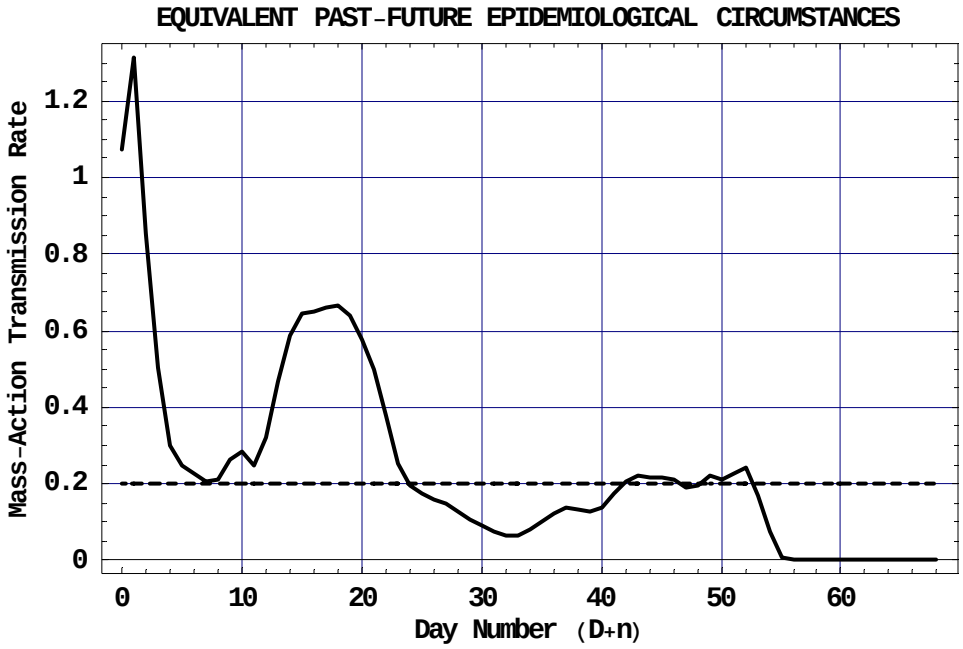

Figure 27. Estimated Time-Varying Rate of Influenza Transmission for a Fixed and Unstructured Total Population of 50,000 People at a U.S. Military Base (Epidemiological Circumstances Like Those at Camp Custer in 1918)

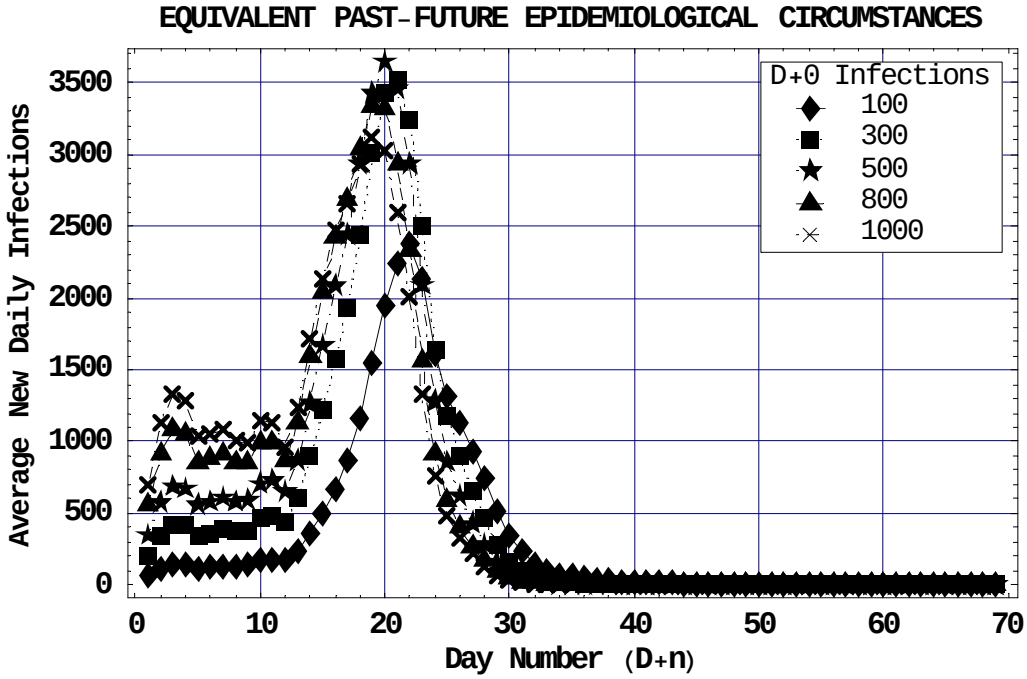

Figure 28. Estimated Average New Daily Infections for a Fixed and Unstructured Total Population of 50,000 People at a U.S. Military Base (Epidemiological Circumstances Like Those at Camp Custer in 1918)

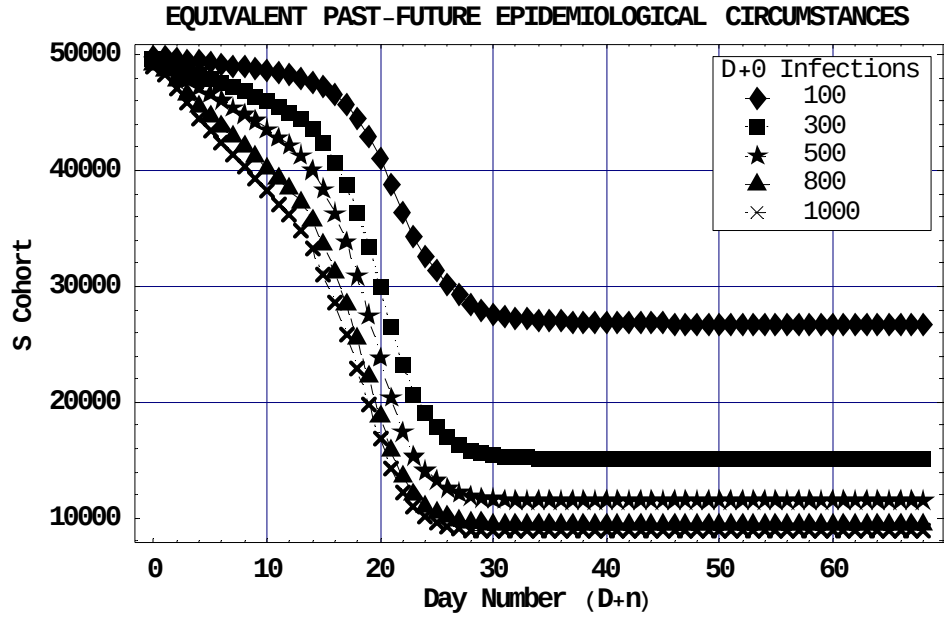

Figure 29. Estimated Susceptible Cohorts for a Fixed and Unstructured Total Population of 50,000 People at a U.S. Military Base (Epidemiological Circumstances Like Those at Camp Custer in 1918)

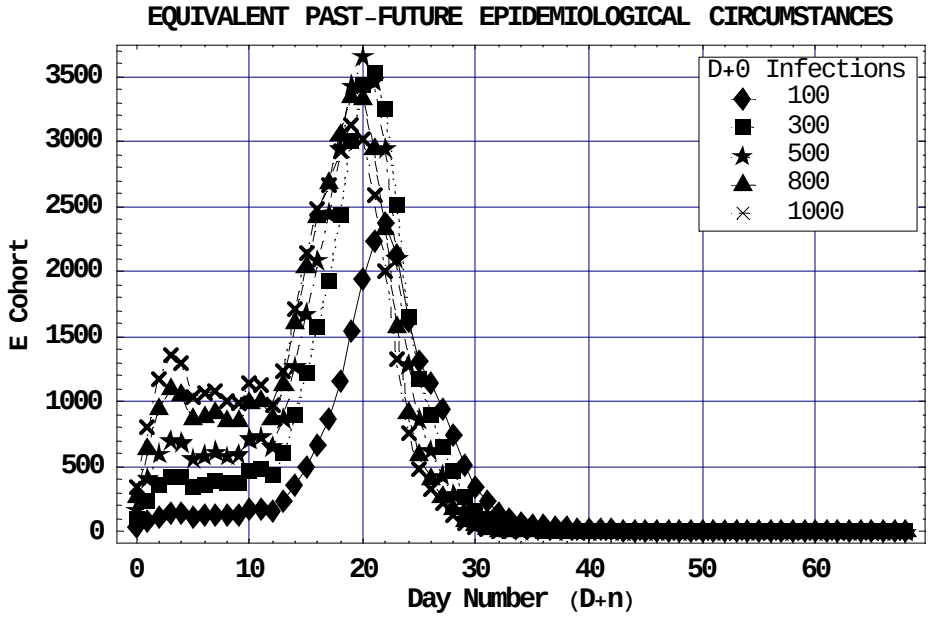

Figure 30. Estimated Exposed (Incubative and Non-Contagious) Cohorts for a Fixed and Unstructured Total Population of 50,000 People at a U.S. Military Base (Epidemiological Circumstances Like Those at Camp Custer in 1918)

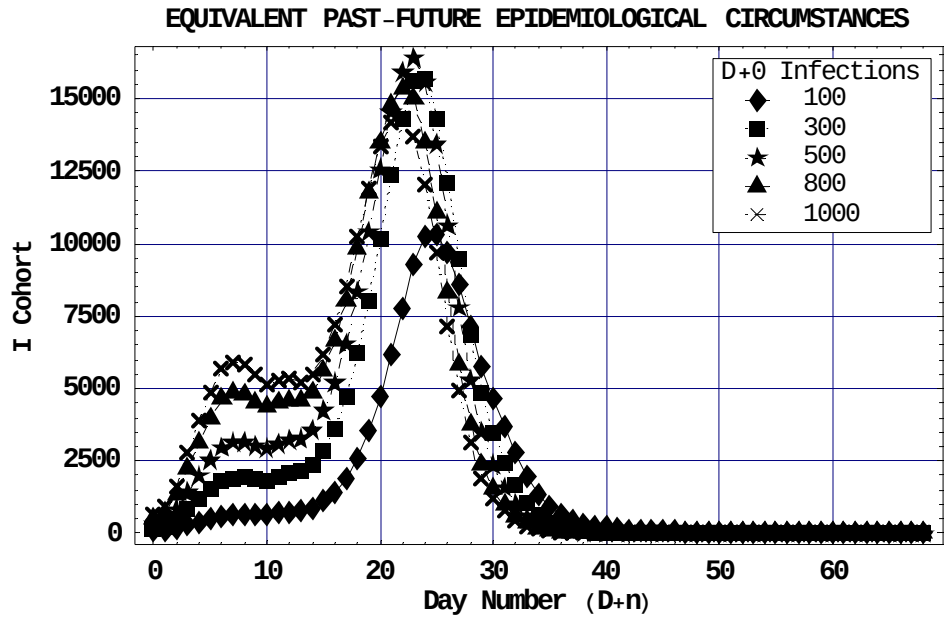

Figure 31. Estimated Infectious (Contagious) Cohorts for a Fixed and Unstructured Total Population of 50,000 People at a U.S. Military Base (Epidemiological Circumstances Like Those at Camp Custer in 1918)

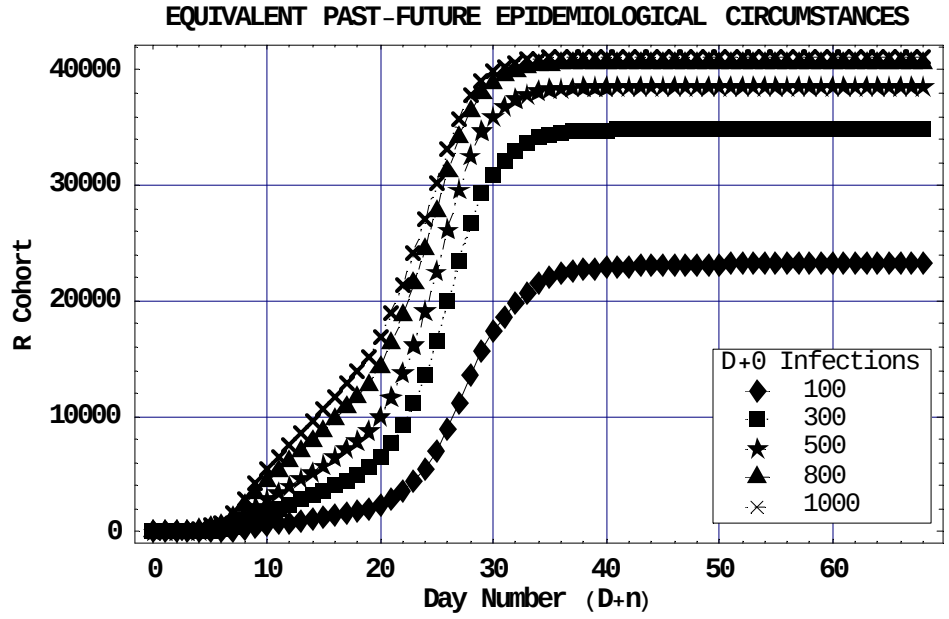

Figure 32. Estimated Removed Cohorts (Recoveries and Deaths) for a Fixed and Unstructured Total Population of 50,000 People at a U.S. Military Base (Epidemiological Circumstances Like Those at Camp Custer in 1918)

Considering a structured and fixed military population of 50,000 people, the predictive network-based **SIR** algorithm requires new $\beta'[t]$ calculations that begin with Monte Carlo results in Figure 9, historical D+0 infections with an inferable (aggregate) **S** cohort, Equation (35) and Equations (38) through (40). The new $\beta'[t]$ and some adaptations of the calculative scheme suffice to estimate network-based SIR cohorts for an arbitrary number of D+0 infections.

For a known $\beta'[t]$, let k stand for the "future" number of D+0 infections and differentiate Equation (34) with respect to t:

(43) $d\alpha[t,k]/dt = \beta'[t]\ \theta[t,k] \div \langle j \rangle$.

The initial value of α also depends on k in that

(44) $N_0 \sum P_c[j]\ \mathrm{Exp}\{- j\ \alpha[0,k]\} = S[0,k] = N_0 - k$.

Equations (36), (38) and (43) now lead to

(45) $d\theta[t,k]/dt = - \theta[t,k] \div (\mu_r - \mu_e) + (\beta'[t] \sum j^2\ P_c[j]\ \mathrm{Exp}\{- j\ \alpha[t,k]\}) \div \langle j \rangle$,

while Equation (39) can be restated as

(46) $\theta[0,k] = \langle j \rangle - \sum j\ P_c[j]\ \mathrm{Exp}\{- j\ \alpha[0,k]\}$.

With $\beta'[t]$ and solutions to Equations (43) through (46) in hand, we are ready to calculate network-based **SIR** cohorts. The defining equations become

(47) $S[t,k] = N_0 \sum P_c[j]\ \mathrm{Exp}\{- j\ \alpha[t,k]\}$,

(48) $I[t,k] = N_0 - S[t,k] - R[t,k]$

and

(49) $dR[t,k]/dt = I[t,k] \div (\mu_r - \mu_e)$.

Initial conditions for these cohorts are $S[0,k] = N_0 - k$, $I[0,k] = k$ and $R[0,k] = 0$.

Figures (33) through (36) display $\beta'[t]$, S[t,100], I[t,100] and R[t,100] for a fixed population of 50,000 people and 3 scale-free networks. Comparing Figure (33) with Figure (16), the larger structured population engenders a slightly smaller transmission rate and, toward the end of the epidemic, the difference between the two rates is about 10%. Network-based **I** cohorts in Figure (35) contain fewer than 5,000 ill individuals on D+23 and network-based **R** cohorts in Figure (36) reach maximum values less than 15,000 cases. In Figures (31) and (32), note that **I** and **R** cohorts for an unstructured population of 50,000 people and for 100 D+0 infections have respective maxima of 10,000 illnesses and 24,000 cases.

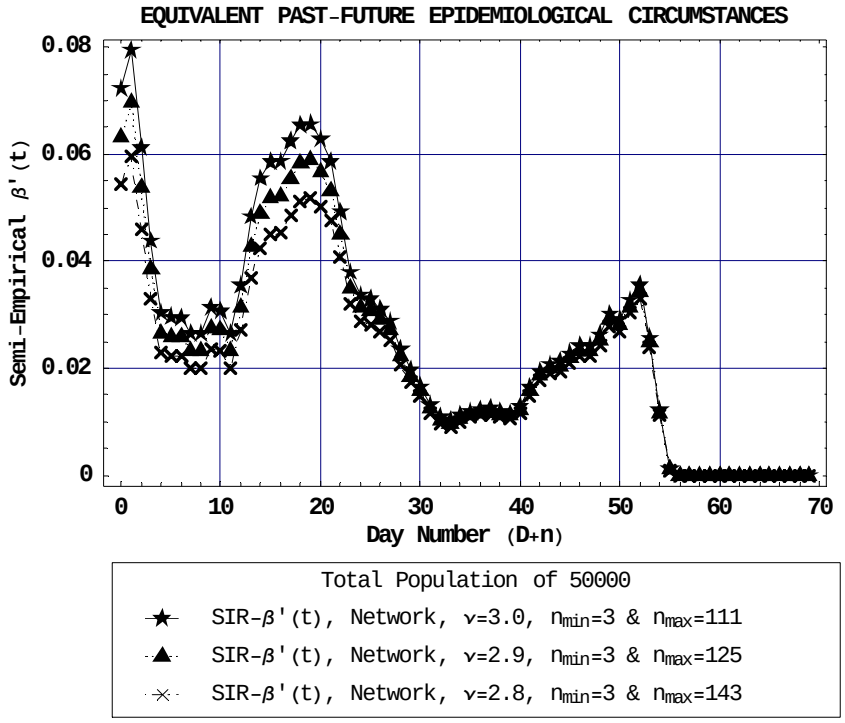

Figure 33. Time Histories of the Transmission Function β′[t] for a Structured Population of 50,000 People and 3 Scale-Free Networks

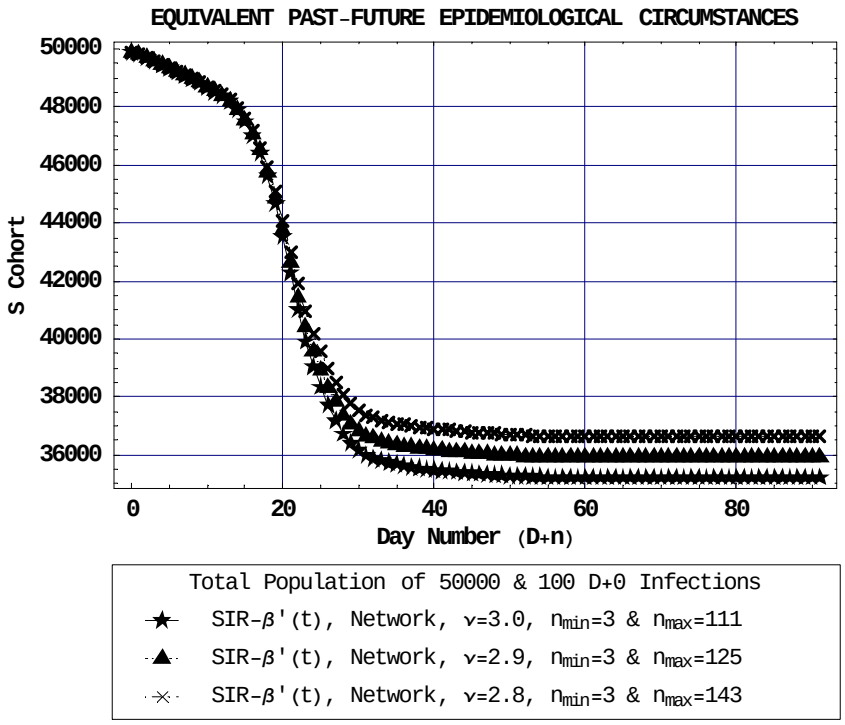

Figure 34. Susceptible Cohorts for a Structured Population of 50,000 People, 100 D+0 Infections and 3 Scale-Free Networks

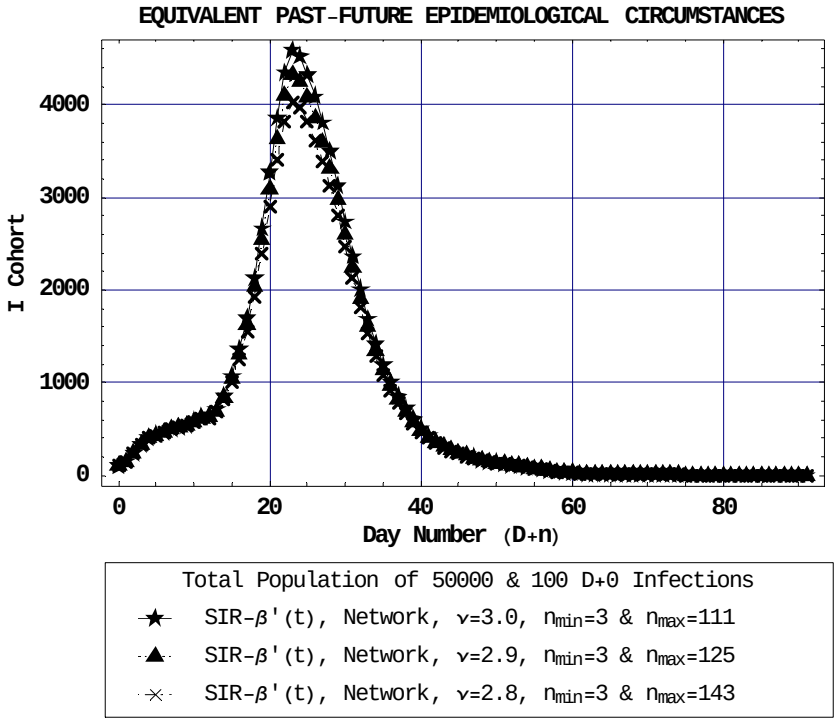

Figure 35. Infectious Cohorts for a Structured Population of 50,000 People, 100 D+0 Infections and 3 Scale-Free Networks

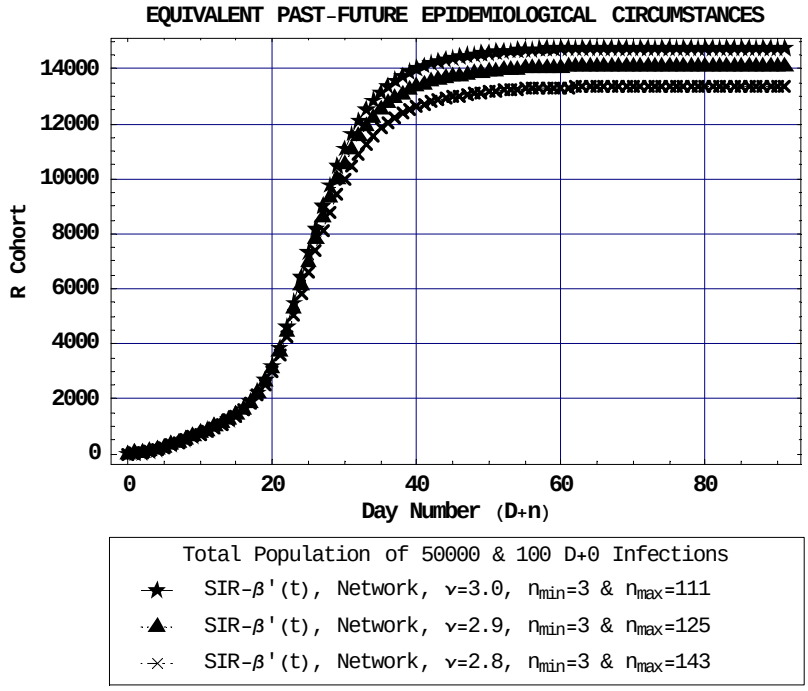

Figure 36. Removed Cohorts for a Structured Population of 50,000 People, 100 D+0 Infections and 3 Scale-Free Networks

The final number of secondary infections (or total influenza cases due to transmission) can be viewed as a function of primary (or D+0) infections. Figure 37 summarizes this functional relationship for a broad spectrum of epidemics occurring in an unstructured or a structured fixed population. Mixing more and more primary infections with remaining susceptible individuals eventually saturates the fixed population. As D+0 infections surpass the "saturation turning point," a further increase in D+0 infections reduces secondary infections.[79] Evidently, the size and structure of a population, as well as the time-varying transmission rate, determine the upper limit on secondary infections and the saturation turning point.

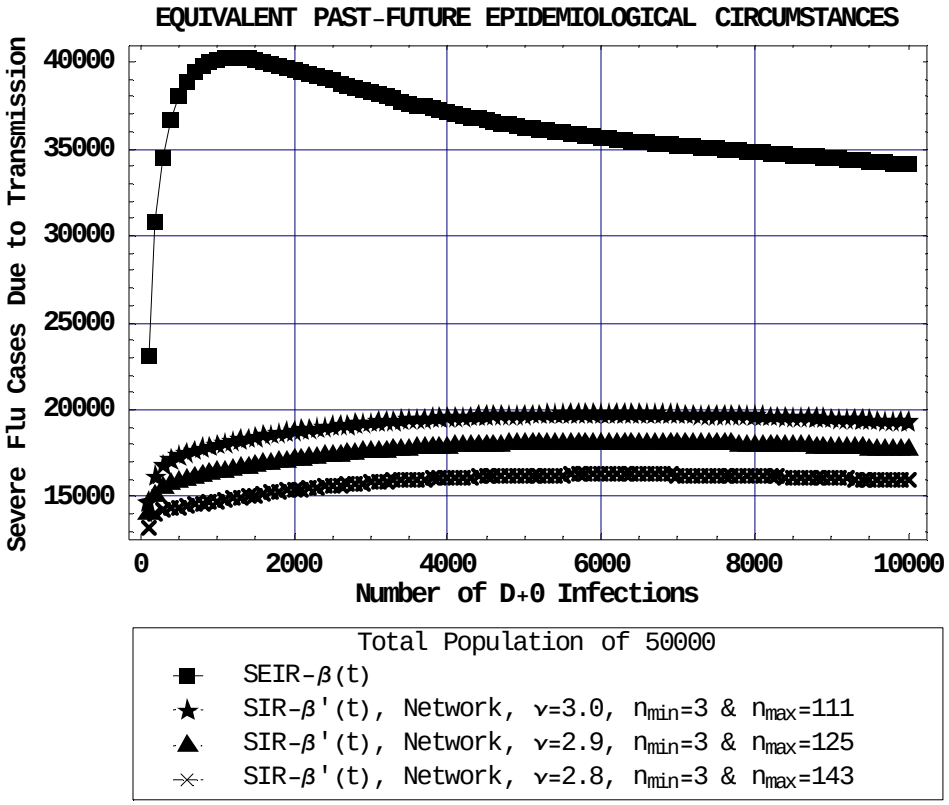

Figure 37. Influenza Transmission Casualties Versus the Number of D+0 Infections for Unstructured and Structured Populations with 50,000 People

Secondary infections in the structured populations of Figure 37 are roughly a factor of two smaller than those in the unstructured population. In our implementation of the May-Lloyd network-based **SIR** model, we've made no attempt to maximize secondary infections by optimally allocating primary infections among connectivity

79 *Primary Pneumonic Plague Transmission and BW Casualty Assessments*, pp. 119-125. This reference introduces the concept of a saturation turning point and discusses it in connection with both primary pneumonic plague and influenza epidemics in brigade and airbase populations.

classes ($j = 3,4\ldots n_{max}$). Optimal allocations of primary infections within a network-based **SIR** model are beyond the scope of the present study.

2. Immunoprophylaxis Before the Epidemic

In analyzing benefits of foreseeable medical countermeasures, we define a growing total population that allows an explosive epidemic at a U.S. military base to affect the surrounding civilian community. Incorporating a time-dependent unstructured population in our **SEIR** algorithm is straightforward, but appropriate adaptations of the May-Lloyd network-based **SIR** model are not evident. This means that our remaining investigations of possible future epidemics at U.S. military bases will focus entirely on growing unstructured populations.

We assume the total population at risk will grow in the following manner:

(50) $N[t] = N_\infty + (N_0 - N_\infty)\,\mathrm{Exp}[-v_{mix}\,t]$,

wherein $N_0 = 50{,}000$, $N_\infty = 150{,}000$ and v_{mix} is an arbitrary growth rate. Figure 38 indicates how the ratio $N[t] \div N_\infty$ changes with t and v_{mix}.

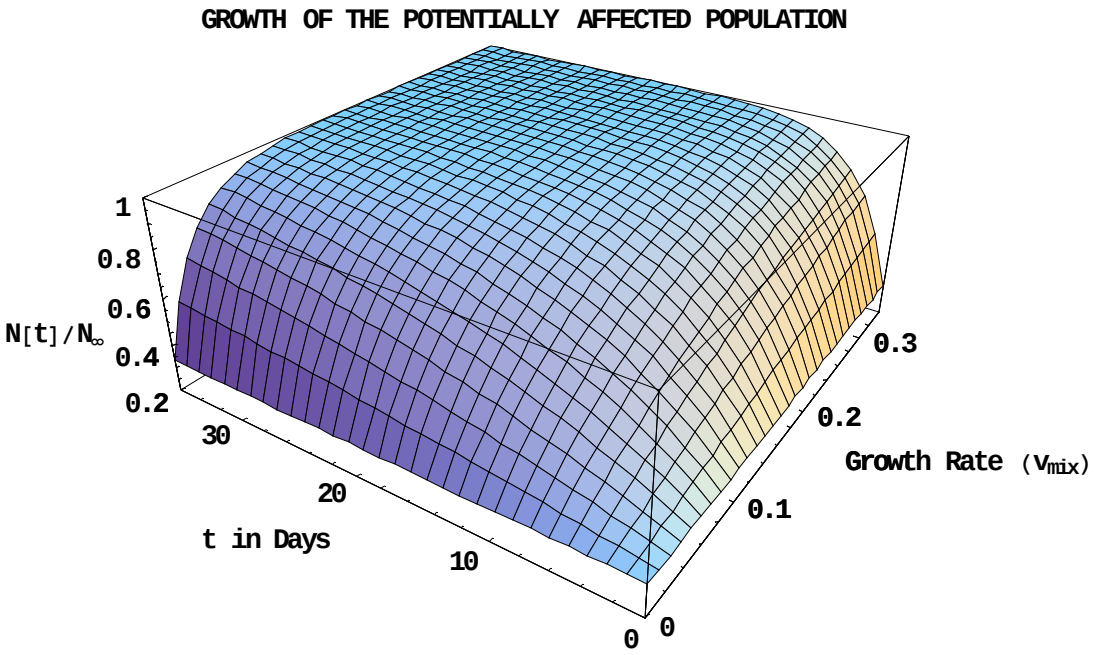

Figure 38. Growth of the Potentially Affected Population According to Equation (5)

When $v_{mix} = 0.1$, the at-risk population N[t] is close to 89,000 on D+5 and it approaches 128,000 on D+10. This value of v_{mix} and the resultant N[t] seem reasonable, if the on-base military population and surrounding civilian community are close-knit.

The incorporation of a time-dependent total population in our **SEIR** algorithm starts with replacements for Equations (7), (8) and (12); namely,

(51) $N[t] = S[t] + E[t] + I[t] + R[t]$,

(52) $dS[t]/dt = dN[t]/dt - p[t]$

and

(53) $p[t] = \beta[t]\, S[t]\, I[t] \div N[t]$.

Our replacement for Equation (13) is

$$(54)\ S[t] = N[t] - \{N[0] - S[0]\}\, u[t] - \int_0^t p[v]dv\,.$$

As before, the integral in Equation (54) makes it possible to integrate Equations (9), (10) and (11) and to express E[t], I[t] and R[t] as functions of S[t] and N[t].

Our discrete **SEIR** algorithm encompassing a time-dependent unstructured population thus replaces Equations (14) through (17) with

(55) $S[m] - S[m-1] = N[m] - N[m-1] - \beta[m-1]\, S[m-1]\, I[m-1] / N[m-1]$,

(56) $E[m] = E[0]u[m] - (N_0 - S[0])\{(g[m] - g[0]u[m]) + (u[m] - u[m-\mu_e])\} + N[m] - N[m-\mu_e] + S[m-\mu_e] - S[m]$,

(57) $I[m] = I[0]u[m] + (N_0 - S[0])\{(g[m] - h[m]) - (g[0] - h[0])u[m] + (u[m-\mu_r] - u[m-\mu_e])\} + N[m-\mu_e] - N[m-\mu_r] + S[m-\mu_r] - S[m-\mu_e]$

and

(58) $R[m] = R[0]u[m] + (N_0 - S[0])(h[m] - h[0]u[m] - u[m-\mu_r]) + N[m-\mu_r] - S[m-\mu_r]$.

The previous initial conditions ($I[0] = R[0] = 0$ and $N_0 - S[0] = E[0]$) are again applicable.

In the event that pre-attack influenza vaccinations protect some fraction (ε_s) of the total population, we can multiply the right-hand side of Equation (50) by $(1 - \varepsilon_s)$ and subsequently employ Equations (55) through (58). The derived rate of influenza transmission in Figure 27 appears to be an adequate approximation for present purposes, since it is basically unaffected by a total population of more than 50,000 people.

Numerical results from Equations (55) through (58) are in Figures 39 through 44. We chose the overarching effectiveness of the pre-attack vaccination program to be 80% ($\varepsilon_s = 0.8$), assuming the vaccine and viruses in circulation are “antigenically similar.” Note that the rise and fall of the susceptible cohort (Figure 40) reflects population growth and the depletion due to influenza transmission in the surrounding (off-base) community.

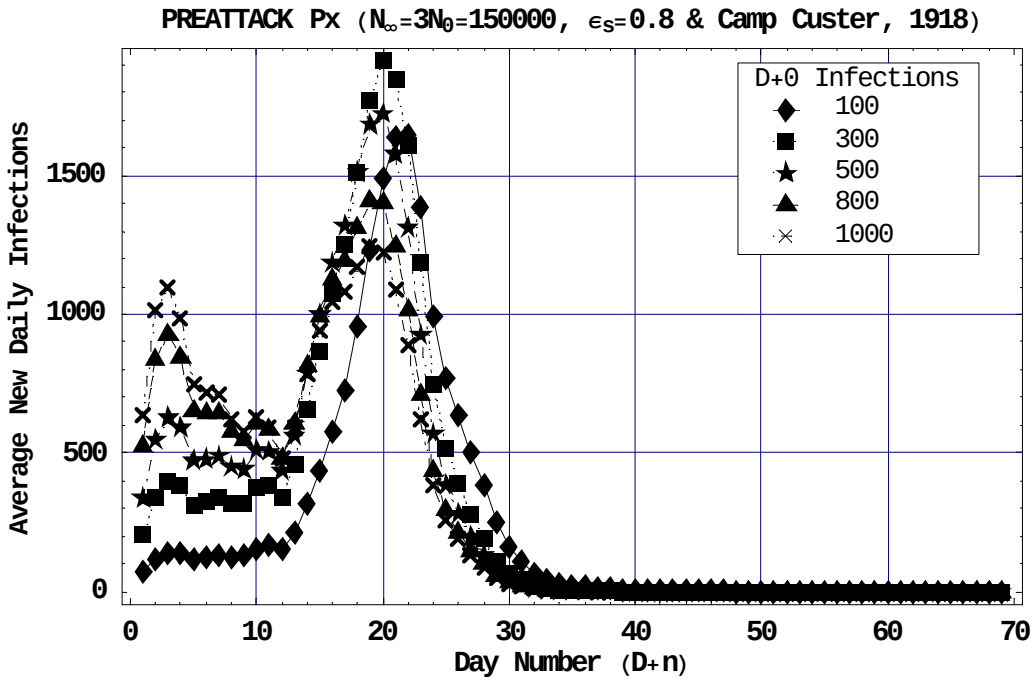

Figure 39. Estimated Average New Daily Infections for a Time-Dependent Vaccinated Population Emulating the Spread of Influenza from a U.S. Military Base into the Surrounding Civilian Community

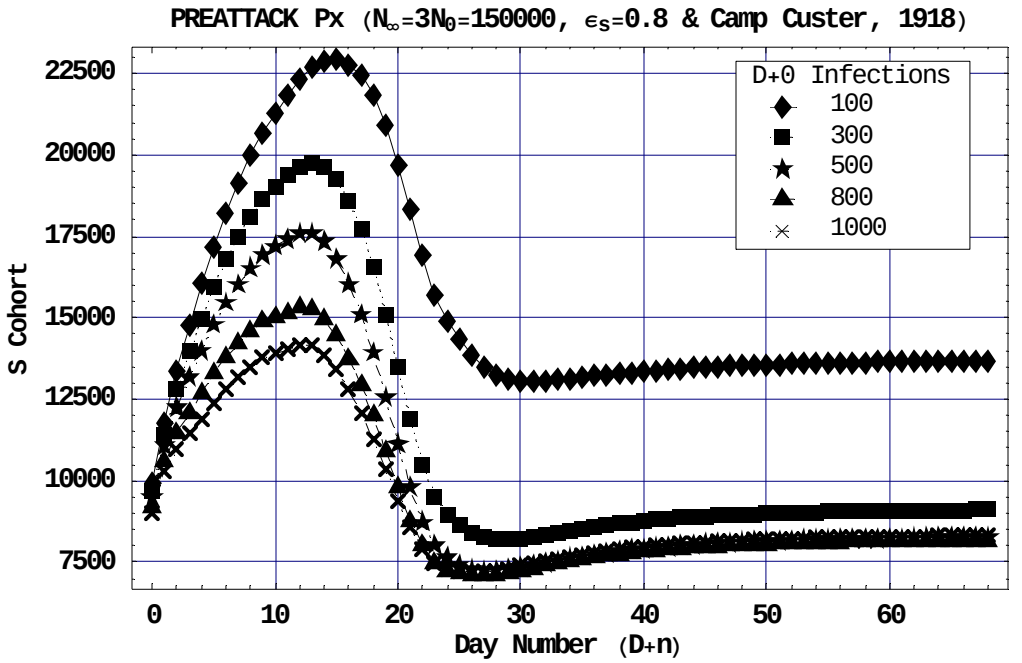

Figure 40. Estimated Susceptible Cohort for a Time-Dependent Vaccinated Population Emulating the Spread of Influenza from a U.S. Military Base into the Surrounding Civilian Community

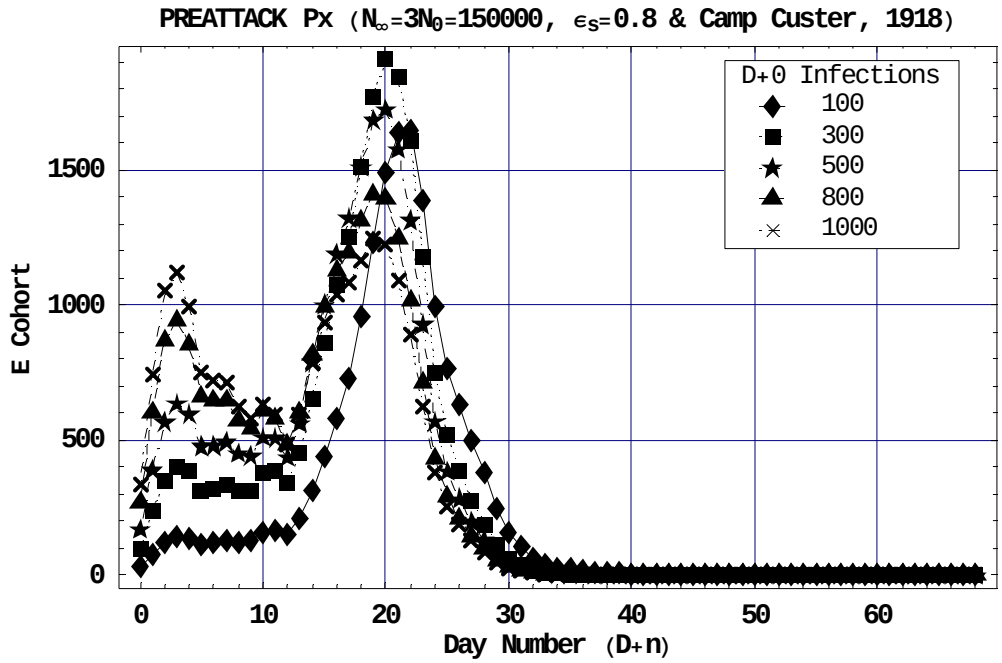

Figure 41. Estimated Exposed Cohort for a Time-Dependent Vaccinated Population Emulating the Spread of Influenza from a U.S. Military Base into the Surrounding Civilian Community

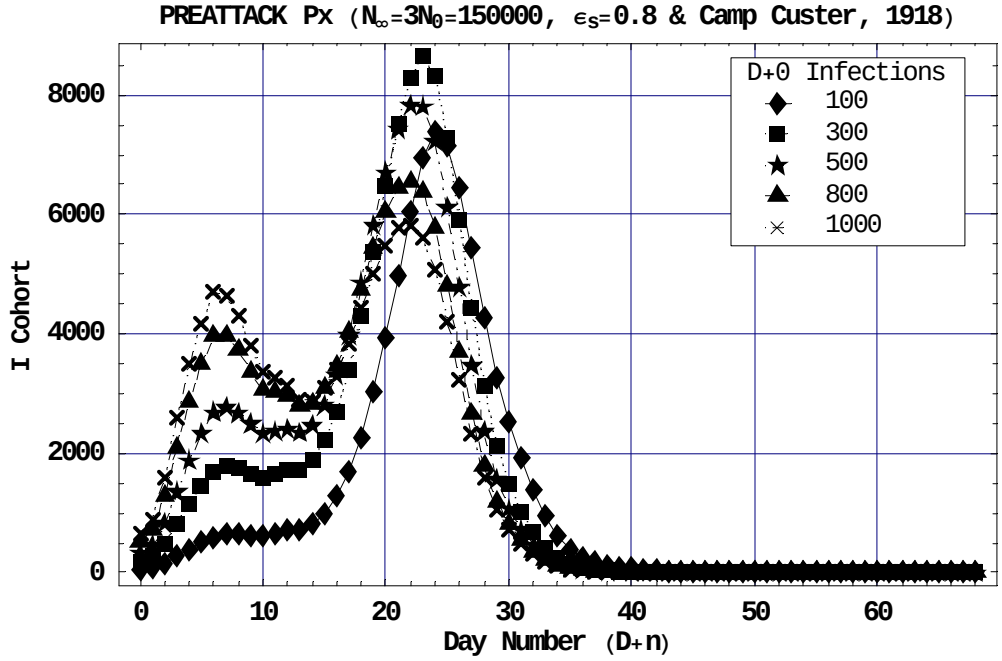

Figure 42. Estimated Infectious (Contagious) Cohort for a Time-Dependent Vaccinated Population Emulating the Spread of Influenza from a U.S. Military Base into the Surrounding Civilian Community

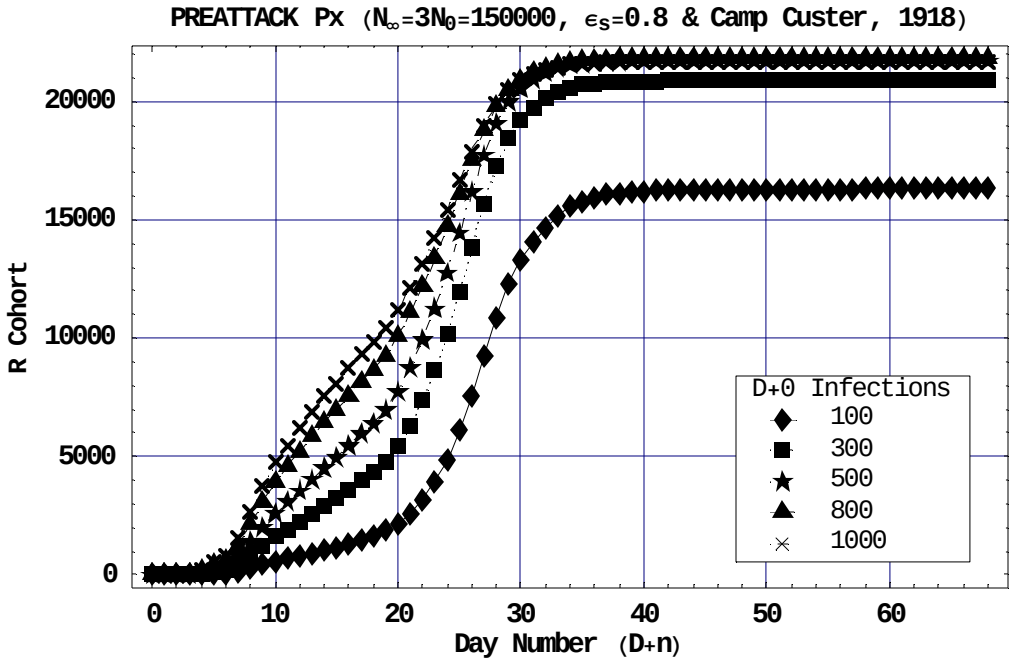

Figure 43. Estimated Removed Cohort for a Time-Dependent Vaccinated Population Emulating the Spread of Influenza from a U.S. Military Base into the Surrounding Civilian Community

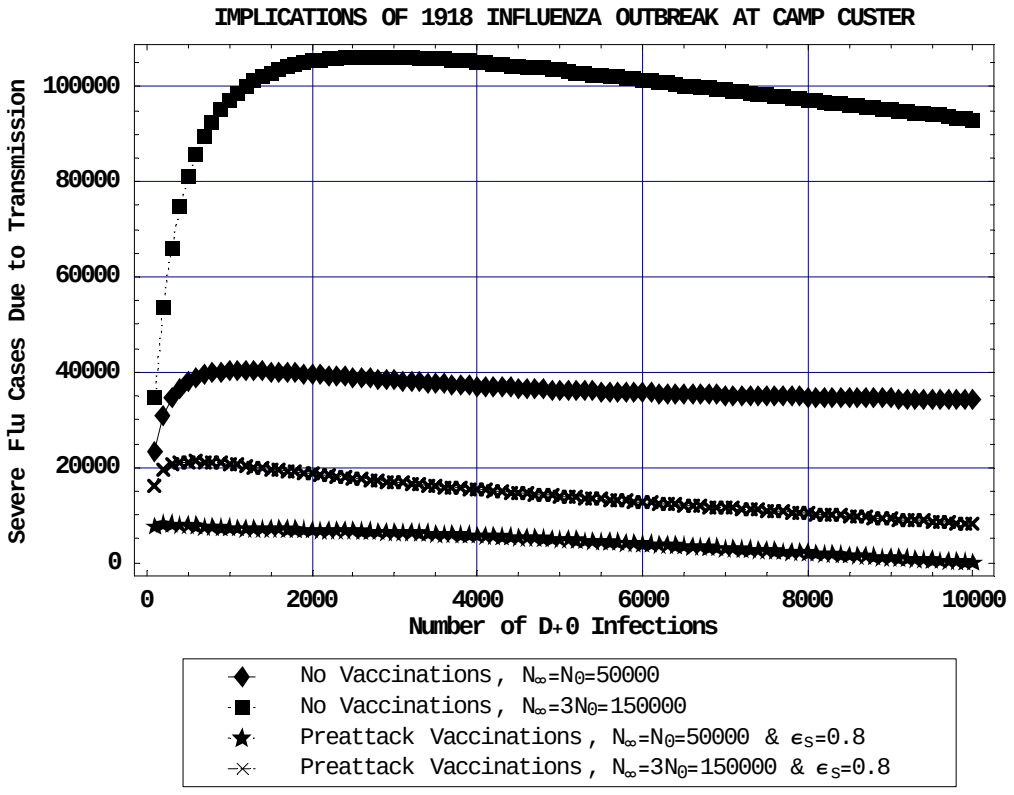

Figure 44. Influenza Transmission Casualties Versus the Number of D+0 Infections for Unstructured Populations That Are Fixed or Time-Dependent and Vaccinated or Unvaccinated

Figure 44 tells us that a threefold growth in an unvaccinated total population increases influenza transmission casualties by slightly less than a factor of 3 at saturation turning points. As a consequence, confining the epidemic to the military base could prevent as many as 70,000 infections in the surrounding civilian community. And a threefold growth in a vaccinated total population increases influenza transmission casualties by a little more than a factor of 2 (at saturation turning points), preventing upwards of 10,000 off-base infections. Obviously, the combination of an effective vaccine and a strict quarantine could keep the number of on-base infections under 10,000 (0.2×50,000).

3. Chemoprophylaxis During the Epidemic

Defining X[t] as the post-attack chemoprophylaxis cohort, an **SEIRX** algorithm for a time-dependent unstructured population follows from

(59) $N[t] = S[t] + E[t] + I[t] + R[t] + X[t]$,

(60) $dS[t]/dt = d(N[t] - X[t])/dt - p[t]$

and Equations (56) through (58). Writing Equation (60) as a difference equation and substituting (N[t] – X[t]) for N[t] in Equations (56) through (58) yield

(61) $S[m] - S[m-1] = N[m] - N[m-1] - X[m] + X[m-1] - \beta[m-1]\, S[m-1]\, I[m-1] / N[m-1]$,

(62) $E[m] = E[0]u[m] - (N_0 - S[0])\{(g[m] - g[0]u[m]) + (u[m] - u[m-\mu_e])\} + N[m] - N[m-\mu_e] - X[m] + X[m-\mu_e] + S[m-\mu_e] - S[m]$,

(63) $I[m] = I[0]u[m] + (N_0 - S[0])\{(g[m] - h[m]) - (g[0] - h[0])u[m] + (u[m-\mu_r] - u[m-\mu_e])\} + N[m-\mu_e] - N[m-\mu_r] - X[m-\mu_e] + X[m-\mu_r] + S[m-\mu_r] - S[m-\mu_e]$

and

(64) $R[m] = R[0]u[m] + (N_0 - S[0])(h[m] - h[0]u[m] - u[m-\mu_r]) + N[m-\mu_r] - X[m-\mu_r] - S[m-\mu_r]$.

We complete the algorithm by adding our definition of X[t], i.e.,

(65) $X[m] = If[m \geq \tau_{on} \,\&\, m < \tau_{off},\ \varepsilon_x \{(N[\tau_{on}] - N[\tau_{on}-1]) + (S[\tau_{on}-1] - p[\tau_{on}-1])\},\ 0]$.

In the foregoing algorithm, individuals in the **S** cohort simultaneously begin post-attack chemoprophylactic regimens and the general level of effectiveness is ε_x. These regimens become effective on $D+\tau_{on}$ and then lose all effectiveness on $D+\tau_{off}$.

Figures 45 through 50 depict numerical results for a post-attack chemoprophylaxis program and growing at-risk population. In these figures, post-attack 30-day chemoprophylactic regimens are effective in the timeframe from D+3 through D+32 and the level of effectiveness is 80% (oseltamivir and zanamivir, preferably).

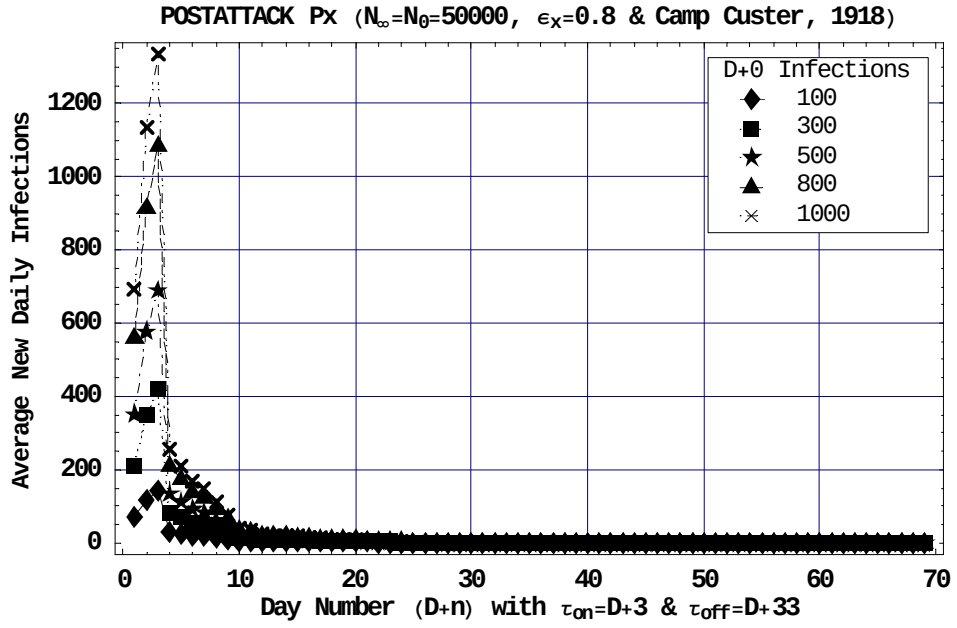

Figure 45. Estimated Average New Daily Infections for a Post-Attack Chemoprophylaxis Program and Time-Dependent Population Emulating the Spread of Influenza from a U.S. Military Base into a Surrounding Civilian Community

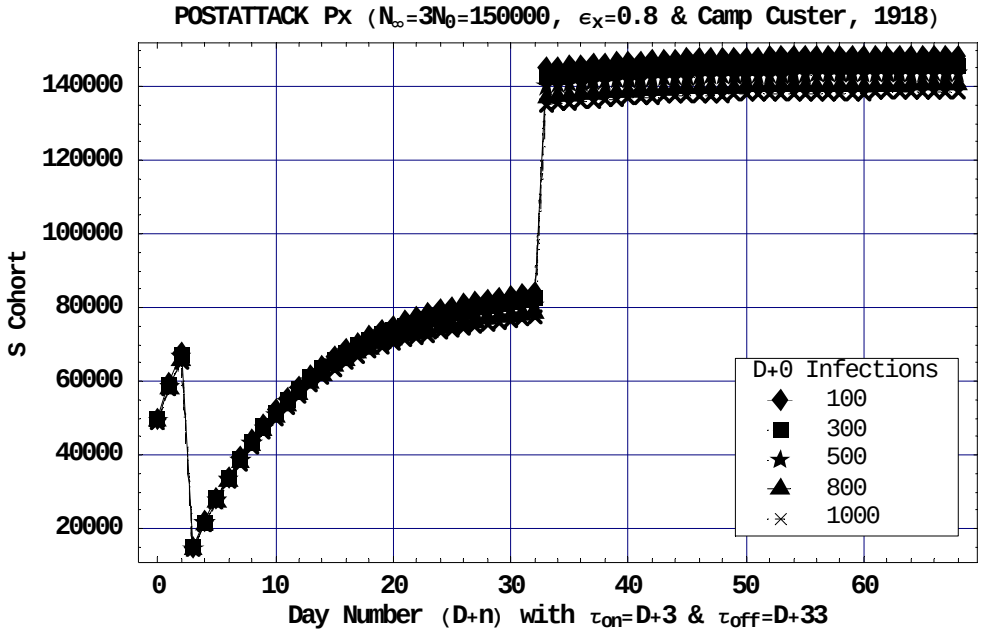

Figure 46. Estimated Susceptible Cohort for a Post-Attack Chemoprophylaxis Program and Time-Dependent Population Emulating the Spread of Influenza from a U.S. Military Base into a Surrounding Civilian Community

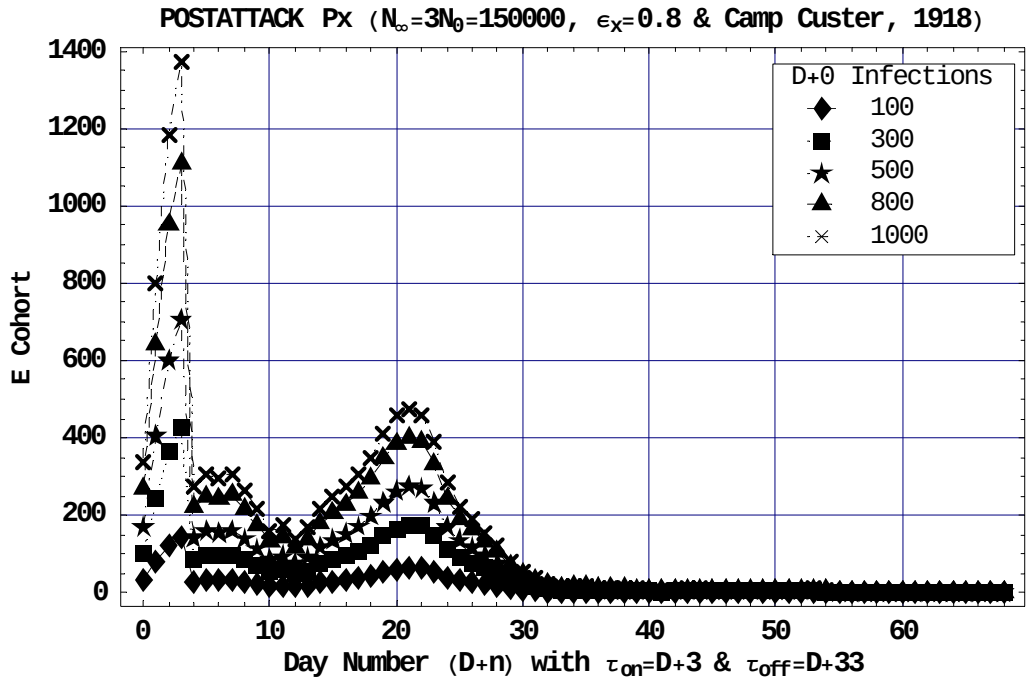

Figure 47. Estimated Exposed (Incubative and Non-Contagious) Cohort for a Post-Attack Chemoprophylaxis Program and Time-Dependent Population Emulating the Spread of Influenza from a U.S. Military Base into a Surrounding Civilian Community

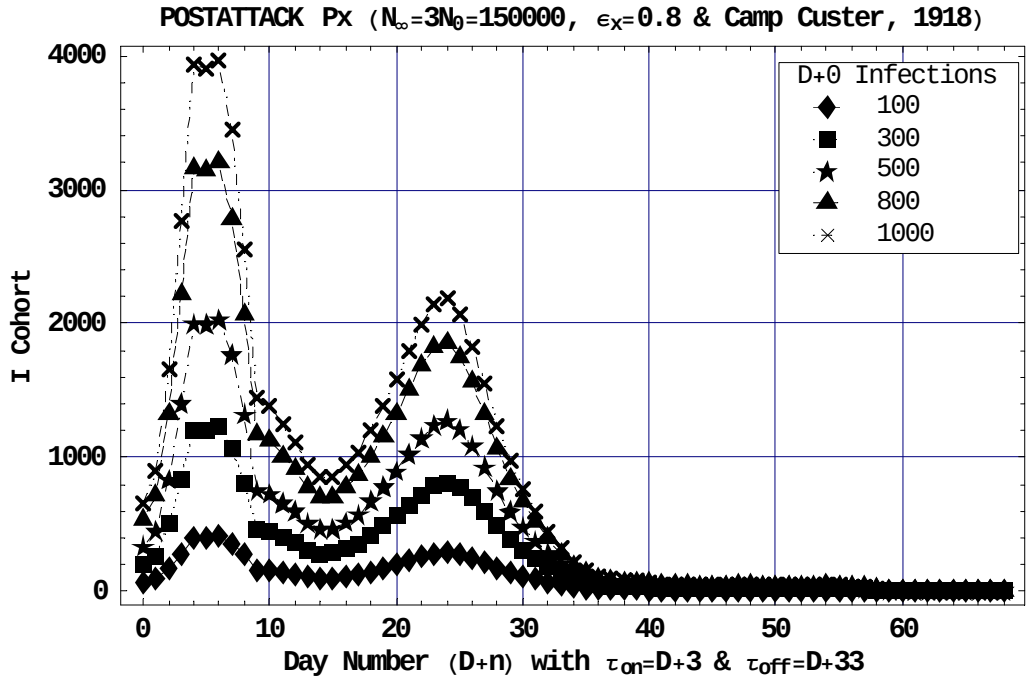

Figure 48. Estimated Infectious (Contagious) Cohort for a Post-Attack Chemoprophylaxis Program and Time-Dependent Population Emulating the Spread of Influenza from a U.S. Military Base into a Surrounding Civilian Community

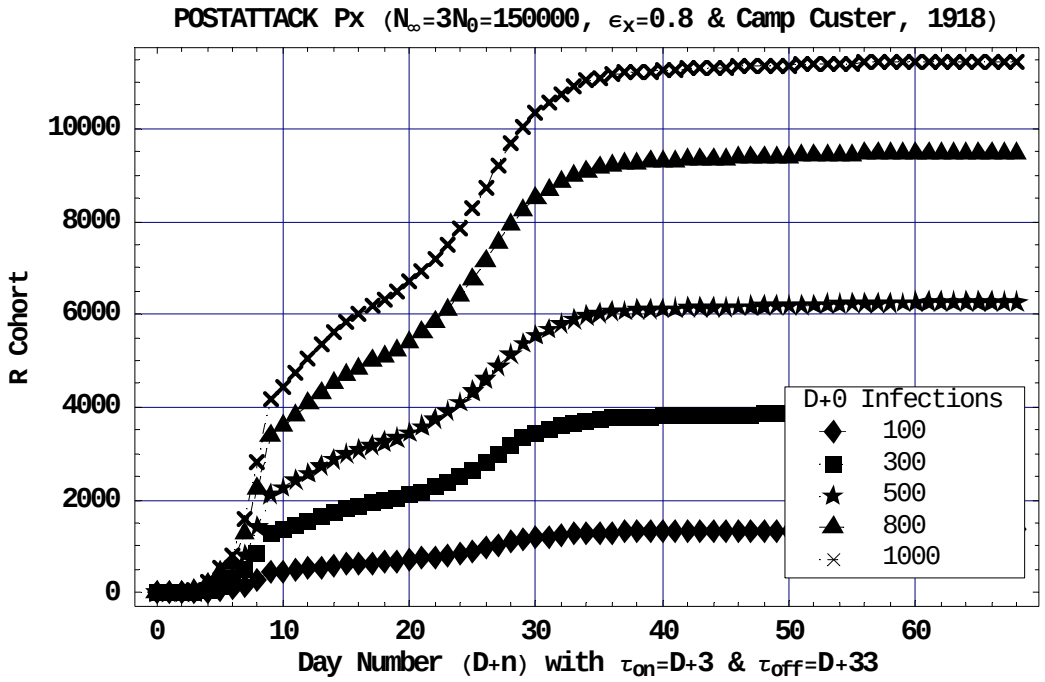

Figure 49. Estimated Removed Cohort for a Post-Attack Chemoprophylaxis Program and Time-Dependent Population Emulating the Spread of Influenza from a U.S. Military Base into a Surrounding Civilian Community

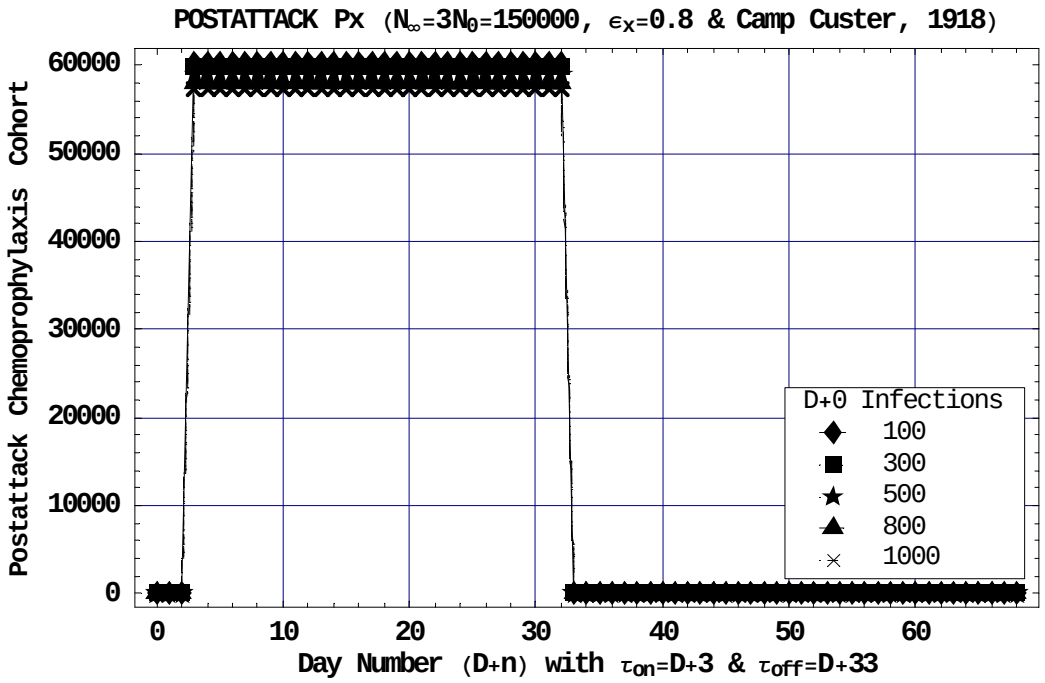

Figure 50. Estimated "X" Cohort for a Post-Attack Chemoprophylaxis Program and Time-Dependent Population Emulating the Spread of Influenza from a U.S. Military Base into a Surrounding Civilian Community

4. Combinative Prophylaxis

The combination of pre-attack vaccinations and prompt post-attack chemoprophylactic regimens reduces influenza transmission to the greatest extent possible using foreseeable medical countermeasures. Adding a strict quarantine to prophylaxis reduces influenza transmission by an additional factor of 2 or so. For example, consider 3,000 D+0 infections and accompanying estimates in Figure 51: (a) ~10,000 severe influenza cases due to transmission for a time-dependent vaccinated population and post-attack chemoprophylactic regimens and (b) ~5,000 cases due to transmission for a fixed at-risk population (or strict quarantine) and combinative prophylaxis. In passing, recall that ~30 D+0 infections produced over 10,000 hospital admissions at Camp Custer in 1918.

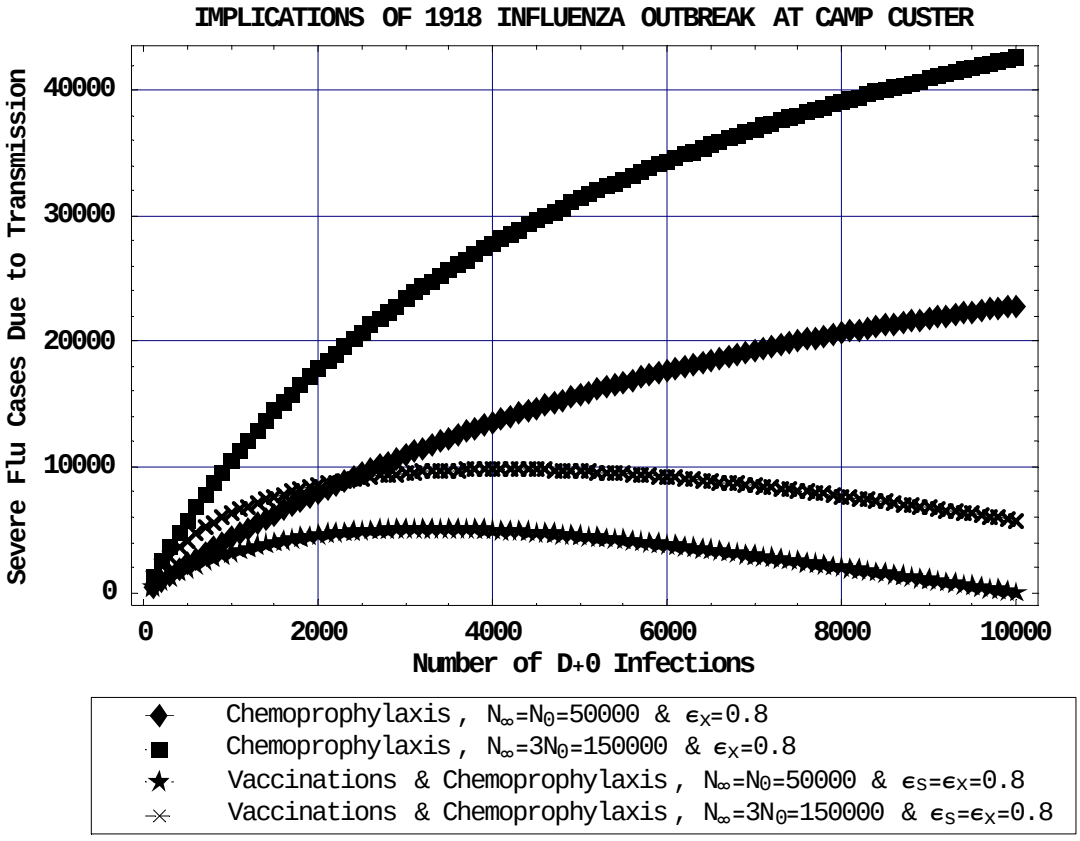

Figure 51. Influenza Transmission Casualties Versus the Number of D+0 Infections for Unstructured Fixed or Time-Dependent Populations and Pre-Attack Immunoprophylaxis and/or Post-Attack Chemoprophylaxis

C. Estimated Effects for a Forward-Deployed Military Unit

The second and last series of numerical results deals with a forward-deployed U.S. military unit: e.g., a U.S. infantry contingent on the move or a U.S. military population at a foreign fixed facility. This military unit is composed of 4,300 personnel (N_0) in 3 equal subunits (~1,430 people per subunit). We suppose that the at-risk unit is isolated from either civilians or other military units, because military operations preclude external contacts early in an influenza epidemic and because military commanders impose a strict quarantine upon recognition of a serious health threat.

All primary or index influenza infections occur within a single subunit ("Subunit 1") of the forward-deployed military unit and, therefore, every influenza infection within Subunits 2 and 3 is a consequence of transmission. Although a distribution of primary infections ($E_j[0]$) among subunits is within our modeling capabilities, we confine primary infections to Subunit 1 in this document to emphasize the influence of military organizational structure.

Epidemic modeling tools are already in hand to deal with medical countermeasures in Figure 26 and a fixed (somewhat) structured population. For a particular military subunit (j = 1, 2 or 3), we rewrite Equation (59),

(66) $N_j = S_j[t] + E_j[t] + I_j[t] + R_j[t] + X_j[t] = N_0 \div 3,$

and then incorporate the **X** cohort in equations (18) through (21):

(67) $S_j[m] - S_j[m-1] = - X_j[m] + X_j[m-1] - p_j[m-1],$

(68) $E_j[m] = E_j[0]\,(1 - g[m]) + \{(1 - \varepsilon_s)N_j - E_j[0]\}(1 - u[m-\mu_e]) - X_j[m] + X_j[m-\mu_e] + S_j[m-\mu_e] - S_j[m],$

(69) $I_j[m] = E_j[0](g[m] - h[m]) + \{(1 - \varepsilon_s)N_j - E_j[0]\}(u[m-\mu_e] - u[m-\mu_r])\} - X_j[m-\mu_e] + X_j[m-\mu_r] + S_j[m-\mu_r] - S_j[m-\mu_e],$

(70) $R_j[m] = E_j[0]h[m] + \{(1 - \varepsilon_s)N_j - E_j[0]\}u[m-\mu_r]) - X_j[m-\mu_r] - S_j[m-\mu_r]$

with

(71) $X_j[m] = \text{If}[m \geq \tau_{on}\ \&\ m < \tau_{off},\ \varepsilon_x\,(S_j[\tau_{on}-1] - p_j[\tau_{on}-1],\ 0].$

Equation (26) and the transmission factors in Figure 23 are necessary to achieve a complete model that spans pre-attack vaccinations and post-attack chemoprophylaxis.

1. Equivalent Past-Future Epidemiological Circumstances

In the above model, setting $\varepsilon_s = \varepsilon_x = 0$, $E_2[0] = E_3[0] = 0$ and $E_1[0]>1$ supports the estimation of potential influenza effects that are based on the epidemiological

circumstances surrounding Camp du Valdahon in 1918. Figures (52) and (53) constitute a summary of results for numerous possible epidemics arising from 1 to 1,000 index infections.

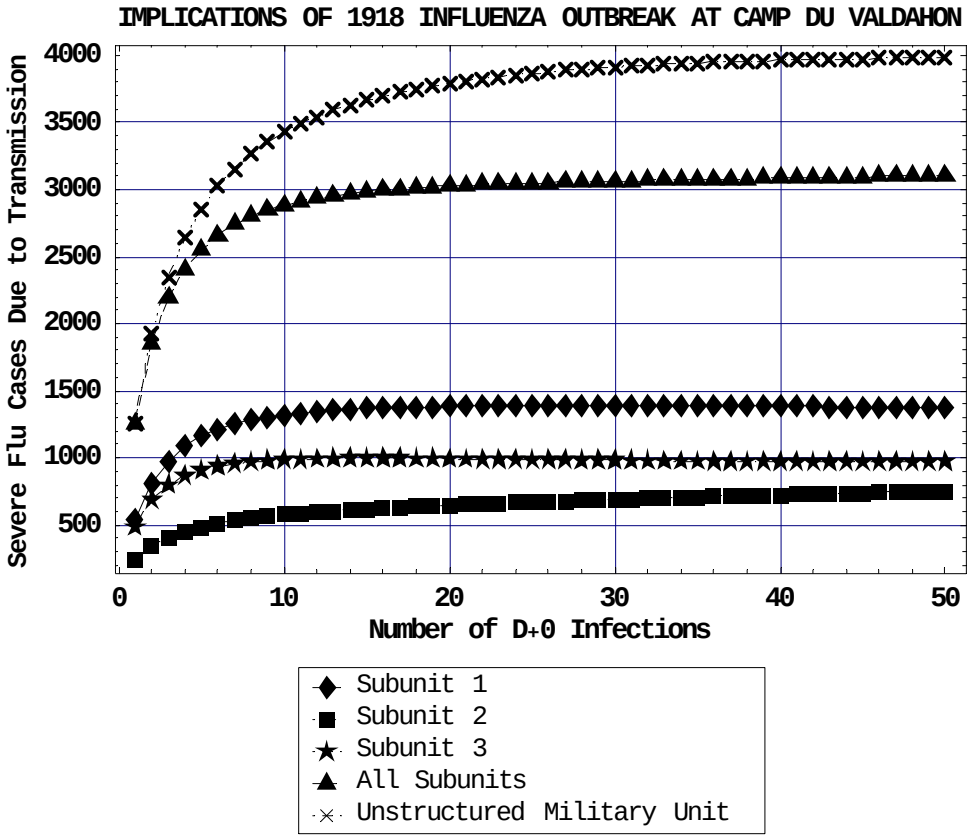

Figure 52. Influenza Transmission Casualties for up to 50 D+0 Infections in an Unstructured or a Structured Military Unit with 4,300 Personnel

Beyond 20 D+0 infections in Figure 52, the number of influenza transmission casualties for an unstructured military unit approaches 4,000 and is approximately 25% greater than the corresponding number for the structured unit. All but a few personnel in Subunit 1 come down with severe influenza cases and Subunit 2 fares the best.

Values along the x and y axes in Figure 53 are ratios and N_0 is the common denominator; for instance, x = 0.1 and y = 0.85 respectively imply 430 D+0 infections and 3,655 influenza transmission casualties. And above 430 D+0 infections, results for the unstructured population become indistinguishable from matching calculations for the structured population. The upshot is that, given equivalent past-future epidemiological circumstances, the structure of a military unit matters most when the number of D+0 infections is relatively small (less than 10% of N_0). Even then, the number of cases for the structured unit is at least 75% of the number of cases for the unstructured unit.

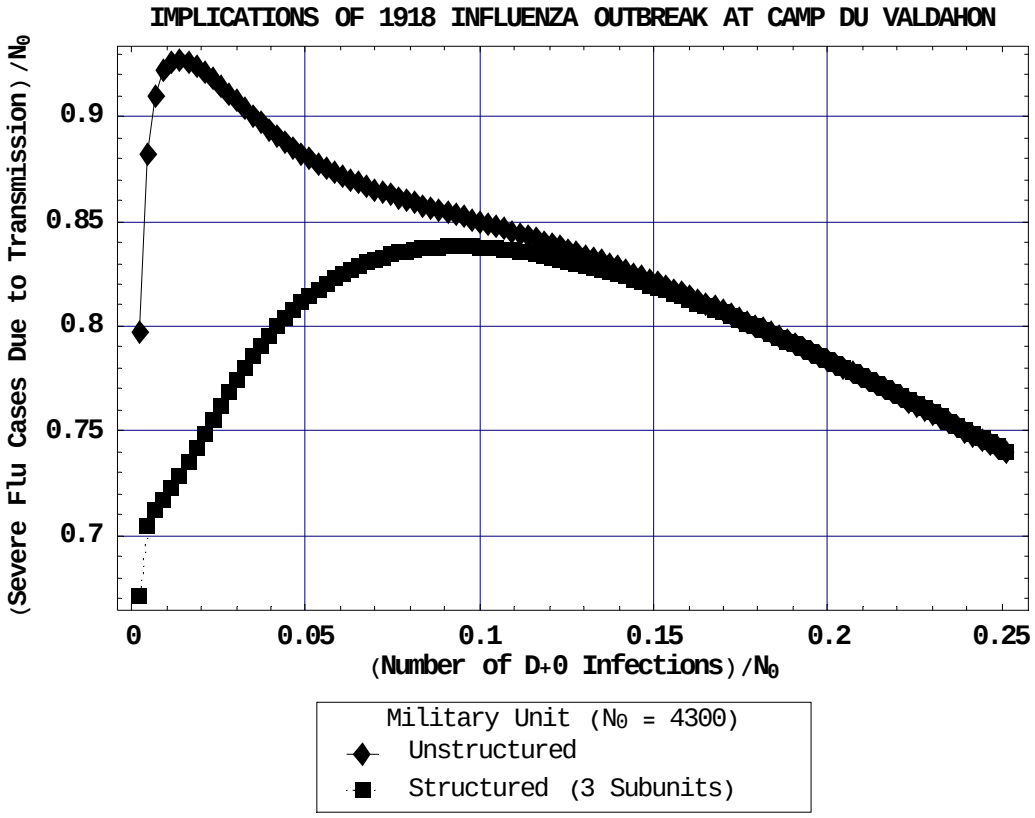

Figure 53. Relative Number of Influenza Transmission Casualties Versus the Relative Number of D+0 Infections in an Unstructured or a Structured Military Unit

2. Immunoprophylaxis Before the Epidemic

The general level of effectiveness for influenza vaccinations varies from year to year, depending on the composition of the vaccine and circulating viruses. Here, we employ 3 different levels of effectiveness (ε_s = 0.8, 0.65 and 0.5) and calculate potential influenza effects for each of those levels. Figures 54-56 display our calculations of influenza transmission casualties.

In Figure 54, ε_s = 0.8 and the maximum number of D+0 infections is 860 (since 0.2 × 4,300 = 860). As many as 860 D+0 infections are possible in the unstructured military unit but, in the structured population, the confinement of all D+0 infections within Subunit 1 forces us to terminate calculations at ~285 D+0 infections. Similar limits on D+0 infections are apparent in Figure 55 (ε_s = 0.65) and Figure 56 (ε_s = 0.5).

Influenza transmission casualty estimates for structured and unstructured populations agree very well up to the D+0 infection limit for the structured population. Most importantly, in dropping the value of ε_s from 0.8 to 0.5, the maximum number of influenza transmission casualties jumps from ~300 to ~700 and then to ~1,200.

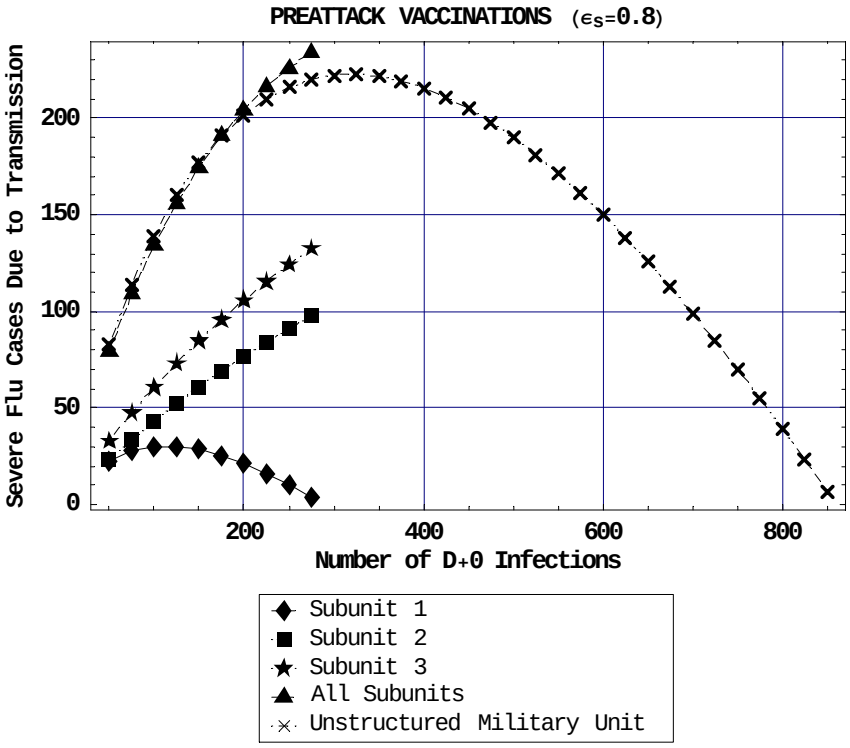

Figure 54. Influenza Transmission Casualties Versus the Number of D+0 Infections in an Unstructured or a Structured Vaccinated Military Population (ε_s = 0.8)

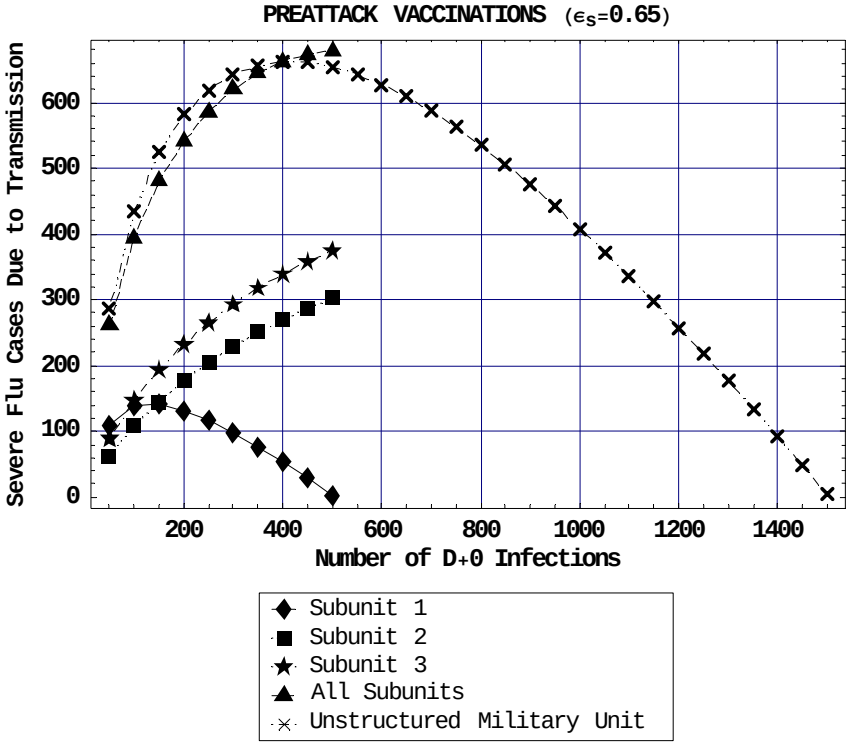

Figure 55. Influenza Transmission Casualties Versus the Number of D+0 Infections in an Unstructured or a Structured Vaccinated Military Population (ε_s = 0.65)

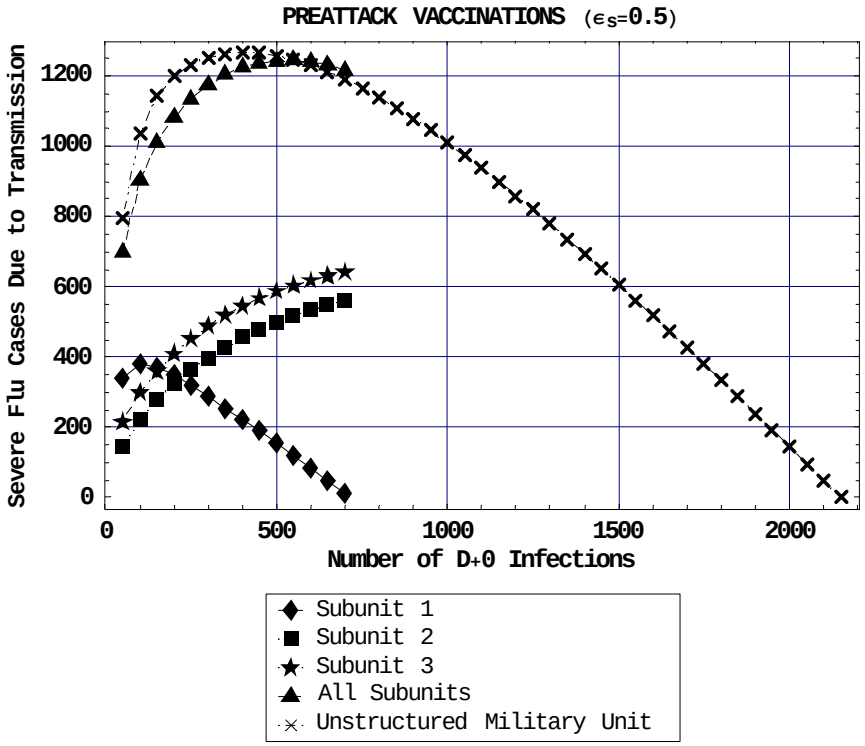

Figure 56. Influenza Transmission Casualties Versus the Number of D+0 Infections in an Unstructured or a Structured Vaccinated Military Population (ε_s = 0.5)

3. Chemoprophylaxis During the Epidemic

In this subsection, we again posit post-attack chemoprophylactic regimens (with ε_x = 0.8 and τ_{on} = 3) for all at-risk personnel. This time, however, these regimens are not limited to 30 days; they continue until the epidemic is over.

Estimates of influenza transmission casualties, in the presence of post-attack chemoprophylaxis, are in Figure 57. In the absence of pre-attack vaccinations, the only limitation on D+0 infections within the structured population is the size of Subunit 1 (~1430).

The agreement between results for structured and unstructured populations is quite good in Figure 57. Perhaps the most interesting aspect of these results is the failure of prompt post-attack chemoprophylactic regimens (with ε_x = 0.8) to prevent a thousand or more influenza transmission casualties. Because the D+0 infections develop for 3 full days (D+0, D+1 and D+2) before those regimens become effective (D+3), the fast progression of influenza makes it possible for a considerable number of secondary infections to occur. Of course, a faster adoption of chemoprophylactic regimens (τ_{on} = 2, for example) should partially close the window of opportunity for secondary infections.

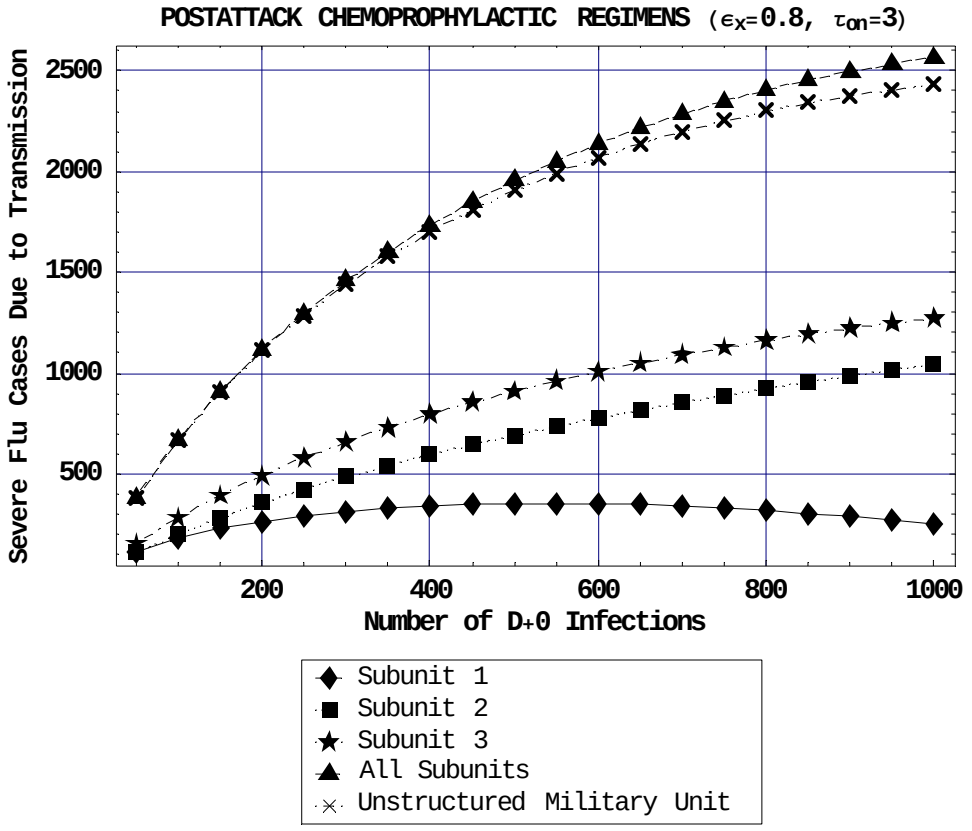

Figure 57. Influenza Transmission Casualties Versus the Number of D+0 Infections for a Vaccinated Military Unit (with or without Structure) and Prompt Post-Attack Chemoprophylactic Regimens

4. Combinative Prophylaxis

Figure 58 brings our quantitative analyses to a close. The combination of pre-attack vaccinations (ε_s = 0.8) and prompt post-attack chemoprophylactic regimens (ε_x = 0.8 and τ_{on} = 3) seems to cap secondary infections in the neighborhood of 150. These pre-attack vaccinations greatly reduce the size of the at-risk population and thereby limit the number of D+0 infections, while the chemoprophylactic regimens further reduce the number of susceptible individuals on D+τ_{on}.

A comparison of Figures 52 and 58 is informative. An ineffective vaccine and ineffective antiviral drugs could eventuate in 1918-like epidemiological circumstances and Figure 52 tells us, for example, that only 50 D+0 infections in a military unit of 4,300 would lead to upwards of 3,000 secondary infections. But if the military setting and epidemiological circumstances are comparable to those behind Figure 58, the number of secondary infections could be as low as 40.

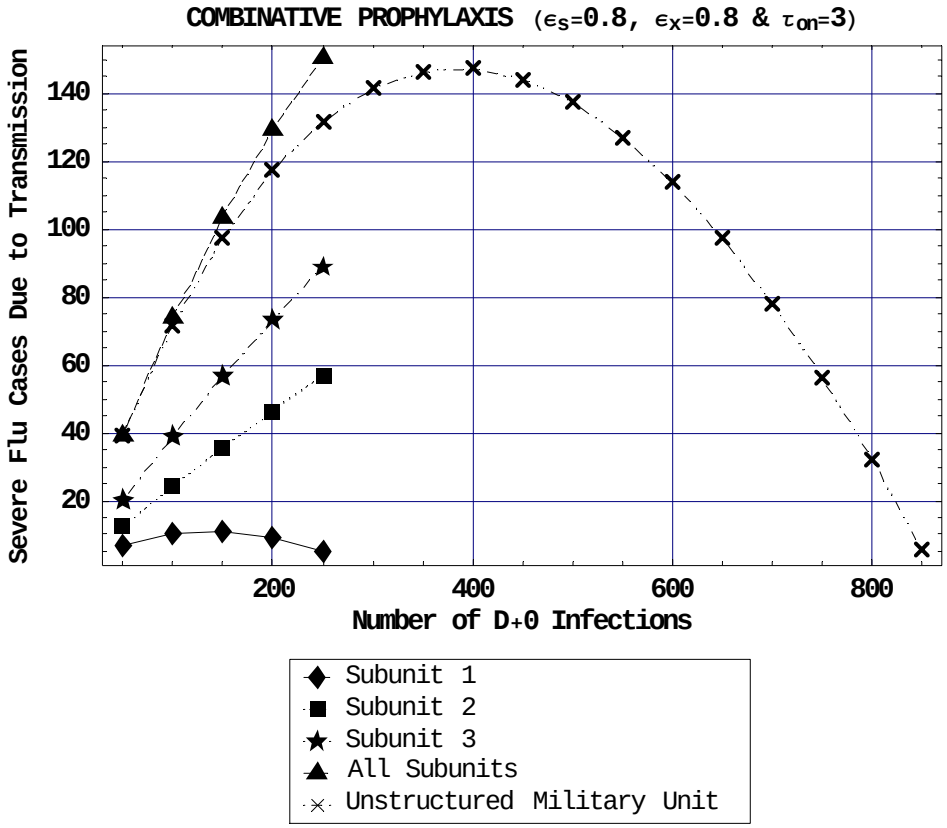

Figure 58. Influenza Transmission Casualties Versus the Number of D+0 Infections for Prompt Post-Attack Chemoprophylactic Regimens and for an Unstructured or a Structured Vaccinated Military Unit

5. Variations of Prophylaxis Parameters

To be sure, levels of prophylactic effectiveness for an influenza vaccine and anti-viral drugs are rather uncertain. The strain of an influenza virus, timeliness of vaccinations or drug regimens, health status of at-risk individuals and other factors can affect the performance of a vaccine or an anti-viral drug in a particular setting. We conclude our quantitative analysis of a structured forward-deployed military unit by systematically varying prophylaxis parameters and by examining the impact of these parameter variations on influenza transmission.

In Figures 59 through 62, we restrict our attention to (a) 100 D+0 infections in Subunit 1 (1,433 personnel) and (b) the relative total number of severe influenza cases arising from person-to-person transmission. The prophylaxis parameters under consideration are levels of effectiveness for pre-attack vaccinations (ε_s) and post-attack anti-viral drug regimens (ε_x); characteristic times (τ_{on} and τ_{off}) for simultaneous unit-wide drug regimens are also subject to variation.

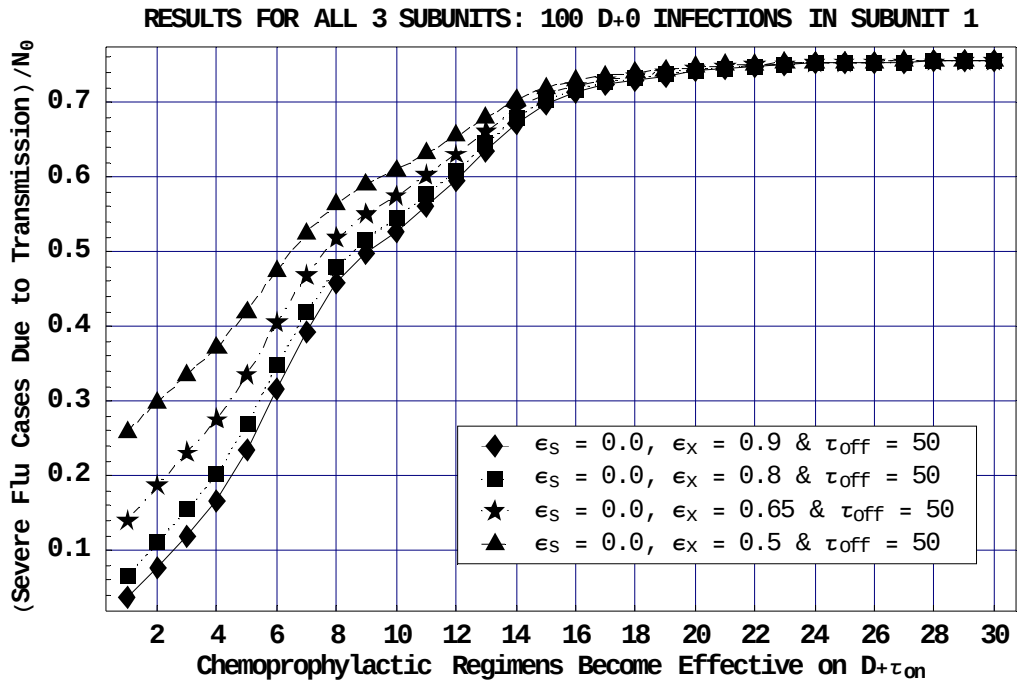

Figure 59. Transmission-Related Impact of Post-Attack Chemoprophylaxis at Various Levels of Effectiveness Versus First Day ($D+\tau_{on}$) of Protection (No Effective Vaccinations)

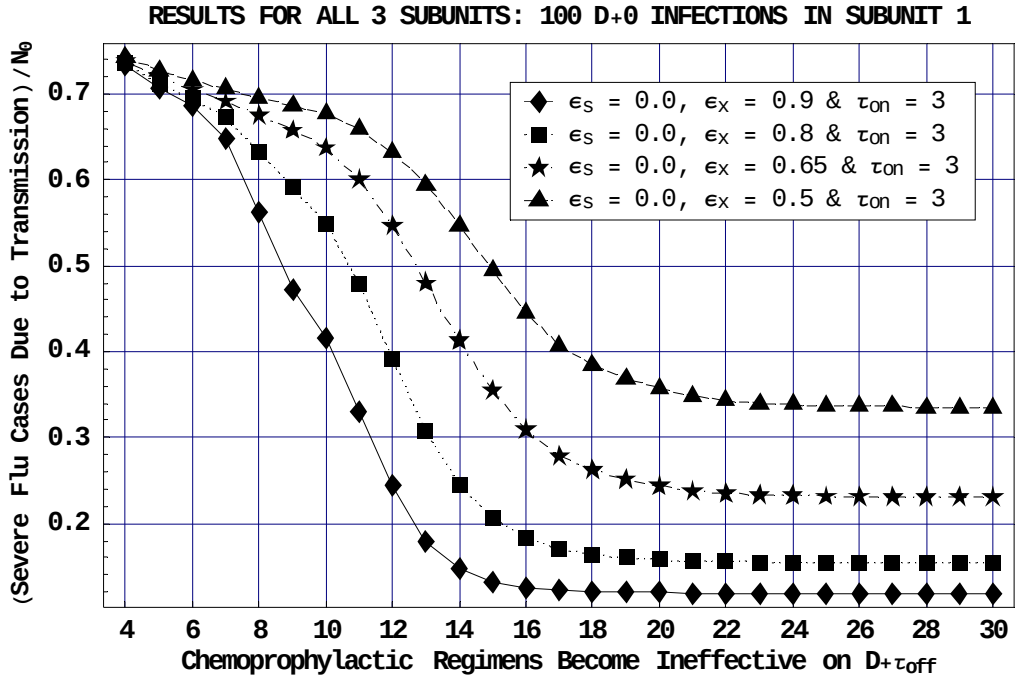

Figure 60. Transmission-Related Impact of Post-Attack Chemoprophylaxis at Various Levels of Effectiveness Versus Expiration Day ($D+\tau_{off}$) of Protection (No Effective Vaccinations)

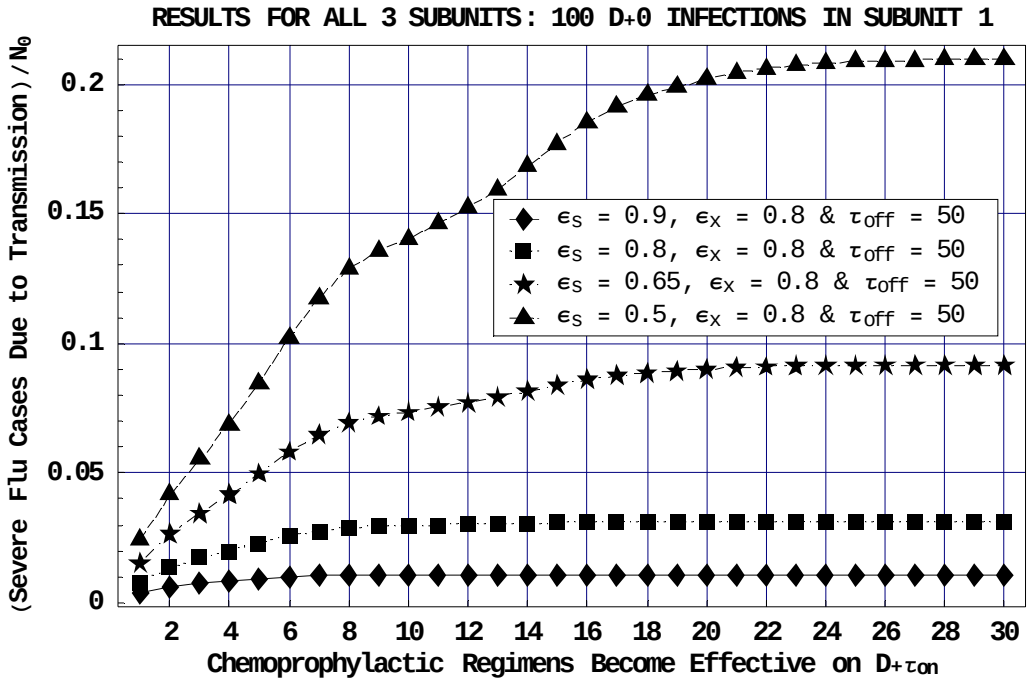

Figure 61. Transmission-Related Impact of Combinative Prophylaxis (Various Levels of Pre-Attack Vaccinal Effectiveness and Fixed Level of Chemoprophylactic Effectiveness) Versus $D+\tau_{on}$

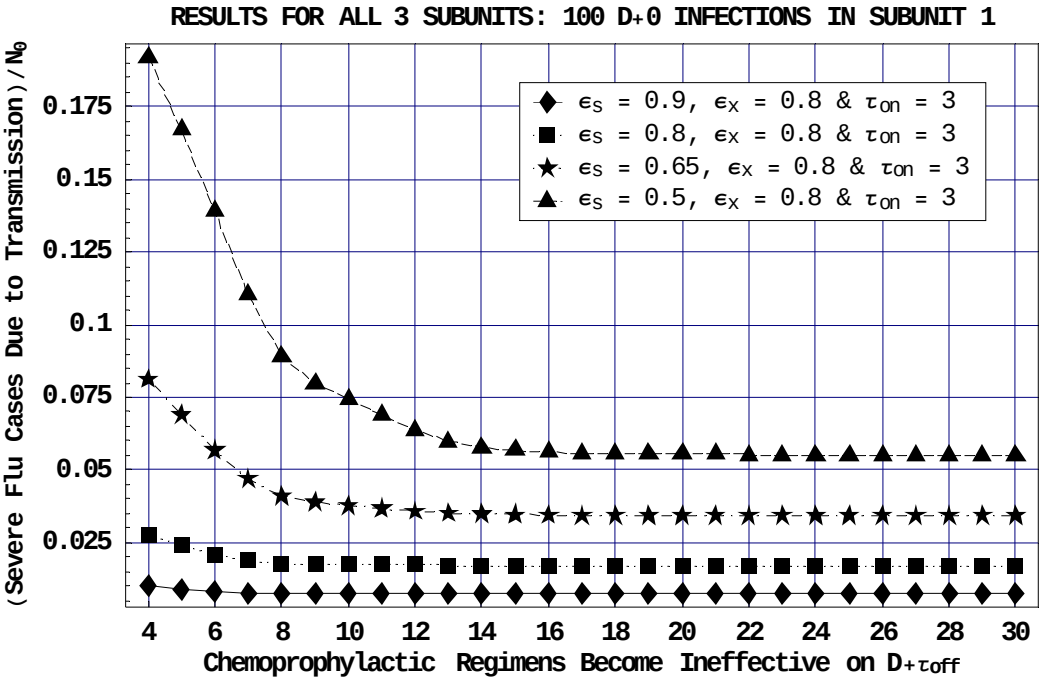

Figure 62. Transmission-Related Impact of Combinative Prophylaxis (Various Levels of Pre-Attack Vaccinal Effectiveness and Fixed Level of Chemoprophylactic Effectiveness) Versus $D+\tau_{off}$

In the complete absence of pre-attack vaccinations (or in the presence of completely ineffective vaccinations), Figure 59 describes the relative total number of transmission-related influenza cases versus $D+\tau_{on}$ (the first day that unit-wide anti-viral drug regimens are effective). Drug regimens remain effective from τ_{on} through $\tau_{off}-1$ (D+49) and, during this period, the effectiveness can be at one of four levels (0.5, 0.65, 0.8 or 0.9). A high level of effectiveness (0.8 or 0.9) is especially beneficial when drug regimens begin early (before D+10 or D+12). Moreover, according to our model, initiating drug regimens after D+20 fails to substantially alter the "natural" course of the outbreak.[80]

Figure 60 displays the relative total number of transmission-related severe cases as a function of $D+\tau_{off}$, where $D+\tau_{off}-1$ is the last day of effectiveness for the simultaneous unit-wide drug regimens. In this figure, we assume that (a) $\varepsilon_s = 0$, (b) drug regimens always become effective on D+3 ($\tau_{on} = 3$) and (c) ε_x varies from 0.5 up to 0.9 (as in Figure 59). If drug regimens last longer than a few days, a high level of effectiveness tends to be quite important. For example, comparing results at $\tau_{off} = 14$, it's apparent that the relative total number of transmission-related cases for $\varepsilon_x = 0.5$ is a factor-of-three larger than the matching number for $\varepsilon_x = 0.9$.

Figure 61 is analogous to Figure 59 in that the relative total number of transmission-related severe cases is again displayed as a function of $D+\tau_{on}$. But in Figure 61, we vary the effectiveness of pre-attack vaccinations from 0.5 up to 0.9 and keep the effectiveness of post-attack anti-viral drug regimens fixed at 0.8. The synergy of pre-attack vaccinations and post-attack drug regimens is noteworthy, particularly when levels of effectiveness are high for both types of protection. Given that $\varepsilon_s = 0.9$ and $\varepsilon_x = 0.8$, then 100 D+0 infections (in a structured military unit with 4,300 personnel) would eventuate in no more than about 50 transmission-related cases.

The effectiveness of vaccinations is again subject to variation in Figure 62, which shows the relative total number of transmission-related severe cases versus τ_{off}. (Values of ε_x and τ_{on} are fixed at 0.8 and 3, respectively.) It's not surprising that the duration of the drug regimens matters most at lower levels (0.5 or 0.65) of vaccinal effectiveness.[81] Furthermore, Figure 62 does not justify drug regimens lasting longer than about 14 days.

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80 A value of 0.023 along the x-axis of Figure 53 represents 100 D+0 infections and the matching y-axis value for the structured military unit is about 0.75. Returning to Figure 59, we see that the relative total number of transmission-related influenza cases also approaches 0.75 for $\tau_{on} = 20$.

81 If it takes 1 day for an anti-viral drug regimen to become effective, and if this regimen ceases to provide protection one day after the last dose, then the period of effectiveness ($\tau_{off} - \tau_{on} - 1$) is also the regimen's duration.

VI. CONCLUDING COMMENTS

A. General Findings

This study was designed to answer two basic questions. First, how did the 1918 influenza pandemic affect military trainees in stateside camps and the American Expeditionary Forces in Europe? Second, given the natural or unnatural emergence of 1918-like influenza viruses, what potential influenza effects on military populations would follow from historically derived transmission rates and modern medical countermeasures?

The second or autumnal epidemic wave of 1918 hit the stateside training camps very hard, forcing substantial reductions in training time or even camp closures. These reductions in training time undoubtedly led to less proficiency with military equipment and less indoctrination, but wartime needs generally prevailed over concerns about poor training. And efforts to manage epidemics in the camps (quarantine and restriction of movement), as well as ineffectual medical treatment, tended to lower the morale of trainees. Once out of the camps and on their way to the front lines, fresh troops in new military units could still be victimized by influenza at ports of embarkation, on troopships and at ports of debarkation.

American combat troops in Europe were less susceptible to influenza than the trainees in stateside camps, though debilitating influenza effects appear to have constrained the tempo of military operations. The prevalence of influenza within the ranks degraded the integrity of front-line military units, congested the supply routes with evacuating patients and made advances or retreats more difficult to execute. Moreover, as the war progressed and more seasoned soldiers became injured or ill with influenza, they were replaced with inexperienced military personnel who just arrived from U.S. training camps, further degrading unit integrity or cohesion.

The fall 1918 epidemics at Camp Custer (stateside exemplar) and Camp du Valdahon (overseas exemplar) were driven by epidemiogical circumstances that seem pertinent to today's military settings. In analytically reconstructing these two epidemics, we derived time-varying rates of influenza transmission for structured as well as unstructured populations. We used either a scale-free network (Camp Custer) or a simple regimental organization (Camp du Valdahon) to account for social structure in our epidemic models.

Under the assumption of equivalent past-future epidemiological circumstances, modern medical countermeasures can provide little or no protection against emergent virulent influenza viruses. The only real barriers to influenza transmission in this

situation are levels of natural immunity and mixing patterns. Our estimates of potential influenza effects show that, for populations of the same size, an unstructured population may accommodate twice as many secondary infections as a population with a high degree of structure (e.g., a scale-free network with >100 subgroups or connectivity classes). But as we steadily increase the number of primary infections, secondary infection estimates for a structured population get closer and closer to larger limiting estimates for the unstructured population. A low degree of structure (say, 3 subgroups) assures that corresponding secondary infection estimates for structured and unstructured populations converge at a "small" number of primary infections (e.g., 430 out of a total population of 4,300).

Pre-attack influenza vaccinations in our analyses simply reduce the size of the at-risk population. Given 100 primary infections in a forward-deployed structured military unit of 4,300, calculated secondary infections for vaccination success rates of 80% (860 susceptible personnel), 65% (~1,500 susceptible personnel) and 50% (~2,200 susceptible personnel) are 135, 400 and 900. Dropping the level of vaccinal effectiveness from 80% to 65% or from 80% to 50% thus multiplies the number of secondary infections by a factor of ~3 or ~7. Even 235 serious influenza cases (100 primary infections plus 135 secondary infections) in a battlefield unit with 4,300 personnel raise difficult operational and medical response issues. An effective vaccine is surely a stepping-stone toward a robust medical defense against influenza, but other medical preparations and careful military planning could be equally important.

Post-attack chemoprophylactic regimens are not as productive as pre-attack vaccinations in reducing the size of the at-risk population, especially since primary and some secondary influenza infections occur before the administration of anti-viral drugs. We've considered prompt post-attack drug regimens that protect 80% of the uninfected recipients and that extend throughout the epidemic. With regard to our forward-deployed structured military unit and 100 primary infections, we find that D+3 chemoprophylactic regimens would allow roughly 650 secondary infections.[82] Our calculations concerning the benefits of post-attack chemoprophylaxis certainly support findings of the Advisory Committee on Immunization Practices.[83]

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82 In the absence of any medical countermeasures, we calculated that 100 primary infections would generate approximately 3,200 secondary infections. See the results for the structured military unit in Figure 53.

83 *Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (SCIP),* p. 18.

"Chemoprophylactic drugs are not a substitute for vaccination, although they are critical adjuncts in the prevention and control of influenza."

In principle, the combination of pre-attack vaccinations and prompt post-attack chemoprophylactic regimens places upper limits on both the number of primary infections ($\leq 0.2 \times N_0$) and the number of secondary infections ($\leq 0.2 \times N_0$ minus primary infections). Returning one more time to our example of 100 primary infections in a structured military unit with 4,300 personnel, combinative prophylaxis and Figure 58 indicate about 75 secondary infections.

Lastly, we previously mentioned that our present influenza models do not account for anti-viral drug therapy. If the accessible anti-viral drugs were insufficient to sustain necessary prophylactic regimens, these drugs would probably be used to treat victims. Anti-viral drug therapy could significantly reduce the number of severe influenza cases (hospitalizations and deaths). Additionally, the early therapeutic use of anti-viral drugs should shorten contagious periods and correspondingly decrease disease-causing contacts. An in-depth quantitative investigation of influenza chemotherapy in a military setting would complement, and enhance the utility of, the present study.

B. Biodefense Implications

There are several biodefense implications of our study. First, from the standpoint of person-to-person transmission, today's military populations at U.S. bases may be more vulnerable to a 1918-like influenza attack than today's forward-deployed military units. Robust and responsive influenza surveillance, detection and identification capabilities for both stateside military bases and overseas units are imperatives. Second, because the level of effectiveness for vaccinations against virulent influenza viruses may be no better than that for vaccinations against circulating viruses of the last 50 years, the wide utilization of anti-viral drugs in a complementary preventive role would enhance the chances of rapidly terminating a deadly outbreak. Third, preparing for "special" force-wide influenza vaccinations and assuring the availability of sufficient anti-viral drugs are critical planning activities. And finally, given the transmissibility of 1918 influenza viruses, even extraordinary military and civil efforts might not be enough to control virulent influenza viruses and prevent a nationwide epidemic or pandemic. More research emphasis on specific therapy for influenza could yield ameliorative or life-saving drugs for the last line of medical defense.

C. A Cautionary Note

Antigenic shifts led to three influenza pandemics in the 20th century: (a) Spanish flu (A/H1N1) of 1918–19, (b) Asian flu (A/H2N2) of 1957–58 and (c) Hong Kong flu (A/H3N2) of 1968–69. We've emphasized the importance of the Spanish influenza virus because of its lethality and potential reproducibility in the laboratory. The Asian flu

spread from China to the U.S. in June of 1957 and caused the deaths of ~ 70,000 Americans. Similarly, the Hong Kong flu probably arrived in the U.S. during the summer or fall of 1968 and was responsible for the deaths of ~ 30,000 Americans.

The next influenza pandemic could have a much greater or lesser impact on U.S. military populations than did the 1918 influenza pandemic. An understanding of 1918 influenza effects may indeed help us prepare for future natural or man-made outbreaks, but the unpredictability of influenza viruses will remain a fact of life in the foreseeable future.

REFERENCES

Albert, Reka, and Albert–Laszlo Barabasi, "Statistical Mechanics of Complex Networks," *Reviews of Modern Physics*, Vol. 74, January 2002, pp. 47–97.

Billings, J. S., "Influenza in Camp Custer," *Journal of Laboratory and Clinical Medicine*, Vol. 4, 1919, pp. 225–228.

Bloomfield, Arthur, and George A. Harrop, Jr., "Clinical Observations on Epidemic Influenza," *Bulletin of the Johns Hopkins Hospital*, Vol. XXX (No. 335), January 1919, p. 3.

Bombardt, John N., Jr., *Contagious Disease Dynamics for Biological Warfare and Bioterrorism Casualty Assessments*, IDA Paper P-3488, Alexandria, VA: Institute for Defense Analyses, February 2000.

———, *Primary Pneumonic Plague Transmission and BW Casualty Assessments*, IDA Paper P-3657, Alexandria, VA: December 2001, For Official Use Only.

———, *Smallpox Transmission and BW Casualty Assessments*, Institute for Defense Analyses, IDA Paper P-3488, October 2000, For Official Use Only.

Braim, Paul F., *The Test of Battle: the American Expeditionary Forces in the Meuse-Argonne Campaign*, 2nd Edition, Shippenburg, PA: White Mane Books, 1998, p. 105.

Burch, M., "I Don't Know Only What We Hear: the Soldiers' View of the 1918 Influenza Epidemic," *Indiana Medical History Quarterly*, Vol. 9 (No. 4), 1983, pp. 25–26.

Chesney, Alan M., and Frank W. Snow, "A Report of an Epidemic of Influenza in an Army Post of the American Expeditionary Forces in France," *The Journal of Laboratory and Clinical Medicine*, Vol. 6, 1920–21, pp. 78–95.

Coffman, E. M., *The War to End All Wars*, Madison, WI: The University of Wisconsin Press 1986.

Cox, Nancy J., and Kanta Subbarao, "Influenza," *The Lancet*, Volume 354 (9186), October 9, 1999, pp. 1277–1282.

Crosby, Alfred E., *America's Forgotten Pandemic: The Influenza of 1918*, Cambridge University Press, 1989.

Department of Defense Dictionary of Military and Associated Terms, Joint Publication 1-02, 12 April 2001 (As Amended Through June 5, 2003), p. 387.

Irons, Ernest E., "Pneumonia Following Influenza in the Camps in the United States," *The Military Surgeon*, March 1921, pp. 275–305.

Isham, Valerie, and Graham Medley (Editors), *Models for Infectious Human Diseases*, Cambridge University Press, 1996, pp. 215–238.

Kolata, Gina, *Flu*, New York: Farrar, Straus and Giroux, 1999.

MacNeal, Ward J., "The Influenza Epidemic of 1918 in the American Expeditionary Forces in France and England," *Archives of Internal Medicine*, Vol. 23 (No. 6), June 1919, p. 681.

May, Robert M., and Alun L. Lloyd, "Infection Dynamics on Scale–Free Networks," *Physical Review E*, Vol. 64, 2001.

McGinnis, Janice P. Dickin, "The Impact of Epidemic Influenza: Canada, 1918–1919," in *Medicine in Canadian Society*, S. E. D. Shortt (Editor), McGill–Queen's University Press, 1981, pp. 470–471.

Parkinson, R., *Tormented Warrior*, London: Holder and Staughton Ltd., 1978, p.163.

"Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (SCIP)," *Morbidity and Mortality Weekly Report*, Centers for Disease Control and Prevention, Vol. 52 (No. RR–8), April 25, 2003, p. 5.

Sanford, W. L., "The Influenza Epidemic of 1918 and its Effects on the Military," *Indiana Medical History Quarterly*, Vol. 9 (No. 4), 1983, p. 16.

Taubenberger, Jeffery K., "Seeking the 1918 Spanish Influenza Virus," ASM News, Vol. 65 (No. 7), July 1999.

Top, Franklin H., Jr. and Philip K. Russell, "Swine Influenza A at Fort Dix, New Jersey (January–February 1976): IV. Summary and Speculation," *The Journal of Infectious Disease*, Vol. 136 (Supplement), December 1977, pp. S376–S380

Tumpey, Terrence M., Adolfo Garcia–Sastre, Andrea Mikulasova et al., "Existing Antivirals Are Effective against Influenza Viruses with Genes from the 1918 Pandemic Virus," *Proceedings of the National Academy of Sciences*, Vol. 99 (No. 21) October 15, 2002, pp. 13849–13854.

U.S. Surgeon General Office, *MEDICAL DEPARTMENT OF U.S. ARMY IN WWI*, Volume IX: *Communicable and Other Diseases*, 1928.

Woolley, Paul B., "The Epidemic of Influenza at Camp Devens, Massachusetts," *Journal of Laboratory and Clinical Medicine*, Vol. 4, March 1919, pp. 330–343.

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14. ABSTRACT

This paper begins with an historical review of the 1918 "Spanish" influenza pandemic as it affected military populations and operations. Next is the analytical reconstruction of selected Spanish influenza outbreaks in stateside training camps and overseas units of the American Expeditionary Forces in World War I. Derived time-varying rates of Spanish influenza transmission for unstructured and structured historical military populations are then used to analyze potential natural or unnatural influenza outbreaks in modern military populations. A summary of findings and a discussion of biodefense implications bring the paper to a close.

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