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WEST NILE VIRUS VACCINATION: CURRENT THREATS AND FUTURE CONSIDERATIONS

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West Nile Virus Vaccination: Current Threats and Future Considerations

by

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For Harry, the best cat ever. RIP my friend.

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I would simply like to thank my committee members for their guidance.

West Nile Virus Vaccination: Current Threats and Future Considerations

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Since its introduction in the United States in 1999, West Nile virus (WNV) has become an endemic public health problem. Most cases are asymptomatic or manifest as self-limited febrile illnesses. However, the elderly and individuals with certain chronic illnesses have been found to have increased mortality and morbidity for neuroinvasive disease, which can cause permanent disability and death. Much like polio, the sequelae of neuroinvasive West Nile cases make a good argument for vaccination. In this capstone the four candidate vaccines in clinical trials and are reviewed. A stratification scheme for a high risk vaccination strategy is proposed, while focusing on the risk factors for neuroinvasive disease. The role of epidemiologic modeling will also be discussed as to how it might relate to future decision making in public health and be utilized as a potential tool for further risk stratification in a targeted WNV vaccination program.

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CHAPTER 1: INTRODUCTION

Since its introduction in the United States in 1999, West Nile virus (WNV) has become an endemic public health threat. While most cases are self-limited febrile illnesses, individuals at higher risk, such as the chronically ill and elderly, potentially suffer increased mortality and morbidity. The worst outcome is development of neuroinvasive disease, causing permanent disability or death. Recent research from the University of Texas in Houston has demonstrated evidence for the potential development of chronic renal infections with some individuals shedding viral RNA for years after their initial febrile illness has subsided. While more research is needed to understand the mechanisms of chronic infection, this would suggest that WNV is not self-limited in all people. Moreover, much like polio, the sequelae of neuroinvasive cases could make a persuasive argument for vaccination (Martina, et al., 2010).

A. SPECIFIC AIMS:

Four candidate vaccines have progressed to clinical trials. In this capstone the risks and relative advantages and disadvantages of these vaccines are compared. A basic risk stratification scheme for the vaccination of high-risk individuals is proposed based on the assumption that a WNV vaccine will be fully developed in the future, albeit initially cost prohibitive and supply limited. In addition, the utility of some key software tools is reviewed, as this technology can be expected to play a more dominant role in public health risk assessment and allocation of limited public health resources (such as

vaccine) in the future. A detailed account of software modeling and information systems is beyond the scope of this capstone.

B. SIGNIFICANCE:

West Nile Virus is an enveloped single-stranded, positive-sense RNA virus in the family Flaviviridae and is related to other members of the Japanese encephalitis serogroup (Murray, et al., 2011). North American WNV is of genetic lineage I (clade Ia), which can cause severe human neurologic disease (Rossi, et al., 2010). The virus is carried in a mosquito vector, primarily of *Culex* spp., and Paserine avian amplifying hosts (Gyure, 2009). Peak transmission occurs between July and October and is related to seasonal mosquito activity (Gyure, 2009). In order to persist, WNV relies on the mosquito vector and avian amplifying hosts. This situation makes eradication from the human population through vaccination impossible and complicates the epidemiologic picture.

The spread of WNV in the US is primarily attributed to the migration of the avian hosts. Some avian hosts can maintain viremia levels high enough to infect feeding mosquitoes for over 100 days (Reisen & Brault, 2007; Gyure, 2009). Most other mammals (such as horses) and humans are dead-end hosts and do not obtain viremia levels high enough to transmit the virus to uninfected mosquitoes (Gyure, 2009).

West Nile Virus is known to survive the winter season. According to Gyure, "possible mechanisms of overwintering include survival of the virus in hibernating female mosquitoes, vertical passage of the virus from infected females to their progeny,

continued transmission in warmer latitudes, and chronic infections in migratory birds" (Reisen & Brault, 2007; Gyure, 2009).

West Nile virus has become an endemic threat to the health of the US population in the last decade. The first outbreak on US soil occurred in New York City in 1999 and also was the first epidemic outbreak in the western hemisphere (Nash, et al., 2001). The virus appears to be more virulent compared to WNV endemic in the rest of the world prior to the 1990's. The virus had been identified in 3 species of mosquito in America in 1999 compared to 43 species (out of 174 other known species of differing vector competence) in 2003 (Granwehr, et al., 2004). By 2002, WNV appeared in routine mosquito surveillances for St. Louis Encephalitis virus in Houston (Lillibridge, et al., 2004). Increased geographical range, regional epidemics, and increased serologic testing resulted in an increase in reported cases to the CDC in 2002 (Sejvar, et al., 2011). By September 2003 West Nile virus invaded Los Angeles (Kwan, et al., 2010). Spread of the virus is primarily attributed to migratory avian hosts and possible "stow away" mosquitoes via air travel. Spread of WNV since 1999 is illustrated in the map below.

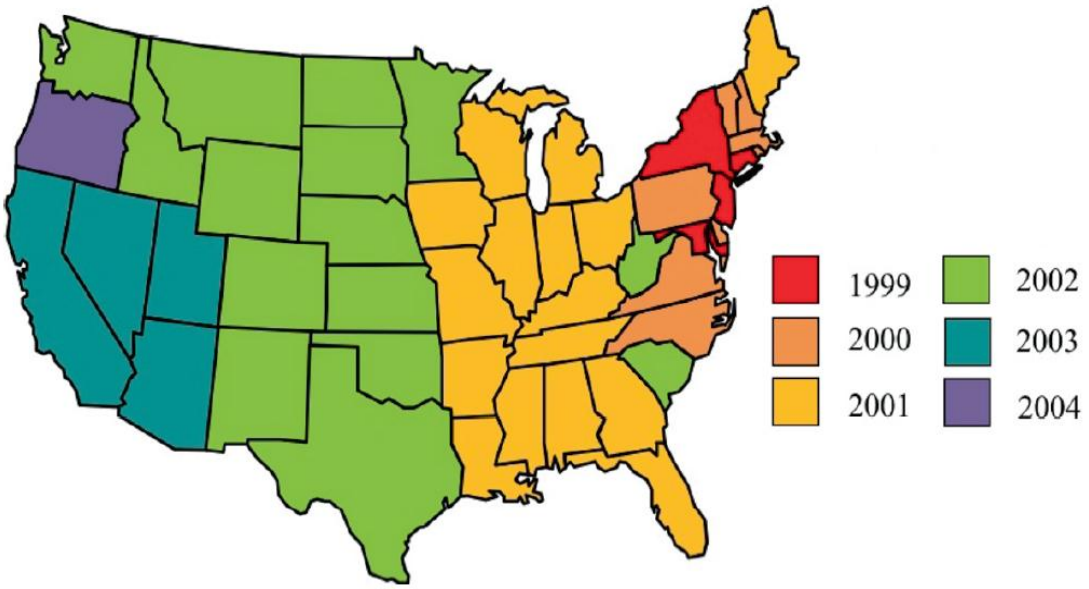

Figure 1: The enzootic spread of WNV across the lower continental USA since its first introduction in Western Hemisphere in 1999. (Available at www.vetres.org; Murray, et al., 2011).

About 80% of WNV infections are asymptomatic with the vast remainder having a mild self-limited illness, much like any other viral infection. Illness is flu-like, occurring 2 to 14 days after infection. Common symptoms include fever, maculopapular or morbilliform rash, headache, muscle weakness, myalgias, anorexia, nausea, vomiting, and difficulty concentrating (Petersen, et al., 2003; Hayes, et al., 2005; Hayes & Gubler, 2006; Gyure, 2009). Recovery is often made in 3 to 6 days. However, 1 in 150 patients develop neuroinvasive disease such as meningitis, encephalitis, and acute flaccid paralysis/poliomyelitis (Davis, et al., 2006; Gyure, 2009), as well as a variety of other neurological abnormalities. Approximately 40% of such patients develop meningitis, while the other 60% develop encephalitis (Gyure, 2009). Approximately 40% to 70% of

MRI imaging is abnormal, demonstrating CNS lesions in patients (Petropoulou, et al., 2005; Debiasi & Tyler, 2006; Gyure, 2009).

Individuals with certain chronic health problems and advanced age are at higher risk for neuroinvasive disease and death. Between 2002 and 2006, a total of 13,482 cases of West Nile Fever (WNF) were reported. In a study looking at these data, median age of all 13,482 was 47 years (Sejvar, et al., 2011). Thirty five fatal cases of West Nile reported to the Centers for disease Control and Prevention were reviewed by the authors and misclassifications were excluded. Of the 23 remaining fatal cases, median age was 78 (range: 54-92) with 78% of victims being older than 70. Leading causes of death in non-neuroinvasive cases were cardiac (8 cases, 47%) and pulmonary (6 cases, 35%). Underlying medical conditions of fatal cases were cardiovascular disease (13; 76%), hypertension (8; 47%), and diabetes (6; 35%). The elderly are at increased risk of death from WNF alone, as well as neuroinvasive disease (O'Leary, et al., 2004; Sejvar, et al., 2011).

In other studies the NY99 strain was shown to have increased morbidity for encephalitis (fatality of 15%), polio-like acute flaccid paralysis (AFP), and less commonly Guillain-Barre-like AFP, with associated neuroinvasive mortality occurring in the elderly and those with chronic health conditions, such as chronic renal failure, diabetes, and hypertension (Nash, et al., 2001; Sejvar, et al., 2003; Murray, et al., 2006; Murray, et al., 2008; Murray, et al., 2011). As described in a review by Gyure, the immunosuppressed are also at higher risk, such as transplant recipients (Iwamoto, et al., 2003; Cushing, et al., 2004; Ravindra, et al., 2004; Hoekstra, 2005), those with

malignancies (chemotherapy), HIV/AIDS patients, alcoholics, and people on corticosteroids (Nash, et al., 2001). Gyure says WNV transmission also has been reported to occur via donor blood products (Pealer, et al., 2003), organ donation (Iwamoto, et al., 2003; Ravindra, et al. 2004; Hoekstra, 2005), breast feeding, and transplacentally (CDC, 2004).

Chronic shedding of WNV NY99 strain RNA in urine occurring years post-illness (suggestive of chronic renal infection) has been documented in a Houston cohort study (Murray, et al., 2010). This would suggest that, in addition to neurological sequelae, WNV infection can potentially have chronic health consequences to the American public beyond a straightforward mortality risk.

CHAPTER 2: METHODS

Candidate vaccines were searched for on clinicaltrials.gov and eight referenced articles were retrieved from PubMed. Five hundred thirty two general WNV review articles were retrieved from PubMed. Of these, the selection was narrowed down to nine (published since 1999 pertaining to the United States) that best served the purpose of this capstone. Of the 107 WNV vaccine review articles retrieved from PubMed, four were used in this capstone. Of nine chosen articles concerning vaccination development, seven were limited to human studies, while two animal studies were cited where immunogenicity information needed to be supplemented (such as with the DNA and recombinant subunit vaccines). Articles concerning human subjects for the dengue-based vaccine could not be found. Health risk factors were well-cited in all review articles. Two articles involving the work of Dr. Kristy O. Murray, whose data concerning comorbid health conditions and odds ratios for development of WNV encephalitis were particularly useful for this capstone, were cited in the results section. Only one study assessing the economics of West Nile virus vaccination could be found and is cited in this capstone. One article was found that gave a conceptual overview of Geographic Information Systems (GIS) and other related information systems without cumbersome modeling details. One article was found covering the Models of Infectious Disease Agent Study (MIDAS) and modeling repository.

CHAPTER 3: RESULTS

A. DEMOGRAPHICS AND RISK FACTORS FOR NEUROINVASIVE DISEASE:

Below are results from a 2006 nested case-control study based on data in Houston, TX 2002 to 2004 (Murray, et al., 2008). The odds ratio for developing encephalitis after initial WNV infection increases with age and is higher for males, Caucasians, and the homeless (presumably due to vector exposure). Thus, age greater than 65 years significantly increases the risk of poor outcome in individuals infected by WNV.

Case Characteristic	All Cases (n=172)	Attack Rate	WNE Deaths (n=17) No.	OR (95% CI)	All WNE (n=113)	WNM/WNF (n=59)	WNE OR (95% CI)
Sex:							
Female	56 (33%)	3.28	7 (41%)	1.5 (0.5-4.7)	33 (29%)	23 (39%)	Reference
Male	116 (67)	6.85	10 (59)	0.7 (0.2-2.2)	80 (71)	36 (61)	1.5 (0.8-3.0)
Age:							
0-19	7 (4)	0.65	0	0	4 (4)	3 (5)	Reference
20-44	41 (24)	2.95	0	0	8 (7)	33 (56)	0.2 (0.03-0.2)*
45-64	64 (37)	9.48	5 (29)	0.3 (0.1-1.1)*	45 (40)	19 (32)	1.8 (0.4-8.7)
65+	60 (35)	23.73	12 (71)	Reference	56 (50)	4 (7)	10.5 (1.7-64.1)*
Race:							
Caucasian	95 (55)	6.56	7 (41)	Reference	62 (55)	32 (54)	Reference
Black	36 (21)	5.73	8 (47)	3.6 (1.2-11.1)*	25 (22)	11 (19)	1.2 (0.5-2.6)
Hispanic	39 (23)	3.48	2 (12)	0.7 (0.1-3.5)	24 (21)	15 (25)	0.8 (0.4-1.8)
Asian/Asian Indian	2 (1)	1.15	0	0	1 (1)	1 (2)	0.5 (0.03-8.4)
Homeless	10 (6)	100.0	2 (12)	2.5 (0.2-13.9)	9 (8)	1 (2)	5.0 (0.7-223.7)
West Nile encephalitis (WNE), West Nile Meningitis (WNM), West Nile Fever (WNF), odds ratio (OR), confidence interval (CI). Attack Rate per 100,000 population (Harris County 2000 census data). * Means significant at α=0.05							

Table 1: West Nile virus-positive patient demographics, Houston, 2002-2004. Original data from article (Murray, et al., 2008).

Below are the data for comorbidities, many of which have been mentioned in the Background section. Many of these comorbidities have increasing likelihood with age. For example, an individual at age 65 will be more likely to have chronic conditions such as hypertension, cardiovascular disease, diabetes, cancer, and chronic lung disease (Murray, et al., 2008).

Case Characteristic	All Cases (n=172)	WNE Deaths (n=17) No.	OR (95% CI)	All WNE (n=113)	WNM/WNF (n=59)	WNE OR (95% CI)
Social History:						
Tobacco Use	63 (37%)	9 (53%)	2.1 (0.7-6.6)	42 (37%)	21 (36%)	1.1 (0.5-2.2)
Alcohol Abuse	35 (20)	11 (65)	10.0 (3.0-35.6)**	27 (24)	8 (14)	2.0 (0.8-5.5)
Illicit Drug Use	25 (15)	4 (24)	2.0 (0.4-7.2)	16 (14)	9 (15)	0.9 (0.4-2.5)
Cocaine/Amphetamine	14 (8)	2 (12)	1.6 (0.2-8.2)	10 (9)	4 (7)	1.3 (0.4-6.1)
Heroine/Opiates	5 (3)	2 (12)	6.8 (0.5-62.7)	3 (3)	2 (3)	0.8 (0.1-9.6)
Marijuana	11 (6)	2 (12)	2.2 (0.2-11.9)	4 (4)	7 (12)	0.3 (0.1-1.0)***
IV Drug Abuse	5 (3)	2 (12)	6.8 (0.5-62.7)	4 (4)	1 (2)	2.1 (0.2-106.6)
Comorbidity:						
Hypertension	86 (50)	14 (82)	5.4 (1.4-30.1)**	74 (65)	12 (20)	7.4 (3.4-17.1)**
History of Drug-induced Hypertension	94 (55)	14 (82)	4.4 (1.2-24.5)*	79 (70)	15 (25)	6.8 (3.2-14.9)**
Cardiovascular Disease	39 (23)	8 (47)	3.6 (1.1-11.3)*	36 (32)	3 (5)	8.7 (2.5-46.1)**
Diabetes	47 (27)	9 (53)	3.5 (1.1-11.0)*	36 (32)	11 (19)	2.0 (0.9-4.9)
Immunosuppressing Condition	88 (51)	13 (76)	3.5 (1.0-15.1)*	66 (58)	22 (37)	2.4 (1.2-4.8)**
Chronic Lung Disease	19 (11)	4 (24)	2.9 (0.6-10.9)	16 (14)	3 (5)	3.1 (0.8-17.1)
Cancer past 5 years	16 (9)	6 (35)	7.9 (1.9-29.4)**	14 (12)	2 (3)	4.0 (0.9-37.6)
Stroke	12 (7)	2 (12)	1.9 (0.2-10.4)	11 (10)	1 (2)	6.3 (0.9-273.8)
Chronic Renal Disease	14 (8)	6 (35)	10.0 (2.4-39.4)**	14 (12)	0	OR undefined**
Hypothyroidism	14 (8)	4 (24)	4.5 (1.0-18.7)*	11 (10)	3 (5)	2.0 (0.5-11.7)
Hepatitis C	7 (4)	3 (18)	8.1 (1.1-52.1)*	6 (5)	1 (2)	3.3 (0.4-152.1)
Hepatitis B	4 (2)	1 (6)	3.2 (0.1-41.5)	3 (3)	1 (2)	1.6 (0.1-84.5)
HIV	4 (2)	1 (6)	3.2 (0.1-41.5)	2 (2)	2 (3)	0.5 (0.04-7.3)
History of Head Trauma	4 (2)	0	0.0 (0.0-14.4)	4 (4)	0	OR undefined
Pregnancy	3 (2)	0	0.0 (0.0-22.8)	0	3 (5)	0.0 (0.0-1.2)

West Nile encephalitis (WNE), West Nile Meningitis (WNM), West Nile Fever (WNF), odds ratio (OR), confidence interval (CI). * Significant at α=0.05; ** Significant at α=0.01; *** Significant at α=0.05 but does not retain significance after controlling for age (P=0.47)

Table 2: Findings from social and medical histories, 2002-2004, Houston. Original data from article (Murray, et al., 2008).

In Table 3 data are presented from a 2009 case-control study conducted in Houston. In this study the odds ratio for chronic renal disease (a comorbidity also more prevalent in the elderly) is reported.

Case Characteristic	Cases (n=113)	Controls (n=113)	OR (95% CI)	P-value
Social History:				
Tobacco Use	42 (37%)	23 (20%)	1.7 (0.8-3.4)	0.16
Alcohol Abuse	27 (24)	6 (5)	6.3 (2.2-18.0)	0.001
Illicit Drug Use	17 (15)	3 (3)	6.0 (0.7-49.8)	0.10
Cocaine/Amphetamine	10 (9)	2 (2)	5.0 (0.6-42.8)	0.14
Comorbidity:				
Hypertension	74 (65)	37 (33)	5.1 (2.5-10.4)	<0.001
History of Drug-induced Hypertension	79 (70)	39 (35)	5.0 (2.5-9.9)	<0.001
Cardiovascular Disease	36 (32)	4 (4)	17.0 (4.1-70.8)	<0.001
Diabetes	36 (32)	21 (19)	2.0 (1.1-3.7)	0.03
Immunosuppressing Condition*	66 (58)	28 (25)	4.2 (2.2-7.8)	<0.001
Cancer past 5 years	19 (17)	6 (5)	3.2 (1.3-7.9)	0.01
Stroke	11 (10)	5 (4)	2.5 (0.8-8.0)	0.12
Chronic Renal Insufficiency	14 (12)	1 (1)	14.0 (1.8-106.5)	0.01
Hypothyroidism	11 (10)	4 (4)	4.5 (0.97-20.8)	0.05
Hepatitis C	6 (5)	0 (0)	Undefined	0.03**
Hepatitis B	3 (3)	0 (0)	Undefined	0.25**
HIV	2 (2)	0 (0)	Undefined	0.97**
Odds ratio (OR), confidence interval (CI). * One or more: cancer within 5 years, recent chemotherapy or radiation therapy, diabetes, steroid use or other immunosuppressing drugs, organ transplant recipient, HIV, chronic alcohol use; ** Fischer exact two-tailed P-value				

Table 3: Comorbid conditions among West Nile encephalitis cases and age, gender, and race/ethnicity matched hospitalized controls, Houston. Original data from article (Murray, et al., 2009).

B. COMPARISON OF VACCINES:

Of the four human vaccine candidates two structural proteins are targeted for vaccine design: precursor membrane (preM) and envelope (E) proteins (Martina, et al., 2010). E-protein contains three domains. Domain II elicits more antibody response, producing antibodies that are cross-reactive with other flavivirus species (Martina, et al., 2010). Though less of a response is generated against domain III, the antibodies are more potent at neutralizing virus and are more type-specific (Beasley & Barrett, 2002; Volk, et

al., 2004; Oliphant, et al., 2006; Pierson, et al., 2007; Martina, et al., 2010). Epitopes in preM and E-proteins are also recognized by T-cells (McMurtrey, et al., 2008; Parsons, et al., 2008). Antibody-mediated responses are thought to limit viral dissemination and patients are possibly at greater risk for neuroinvasive disease as a consequence of an insufficient IgM response during initial infection (Diamond, et al., 2003; Samuel & Diamond, 2006; Klein & Diamond, 2008). CD8 T-cell response is also thought to play a role in neurological protection (Shrestha & Diamond, 2004).

Four criteria define an effective WNV vaccine. First, the vaccine should be able to exhibit the physiochemical features of viruses (*i.e.* mimic the virus in the host). Second, the vaccine should elicit an optimal B-cell response (neutralizing antibodies). Third, clonal expansion should be optimized during initial and subsequent antigenic exposure. Finally, stimulation of the innate immune system should occur for a long-lasting adaptive response (Spohn & Bachmann, 2008; Martina, et al., 2010). For these reasons killed and recombinant subunit vaccines require an adjuvant to enhance the immune response and provide longer lasting immunity. Only live-attenuated and vectored (or chimeric) vaccines fulfill all four criteria but carry the theoretical risk of reversion to virulence (Martina, et al., 2010).

Three different types of vaccines have made it into Phase 1 clinical trials (ClinicalTrials.gov; Martina, et al., 2010):

Vaccine	Type	Advantages	Disadvantages	Trial Phase
WN-80E	Recombinant Subunit	No risk of reversion to virulence	Weak immunogenicity Requires adjuvant Does not provide long-term immunity No T-cell stimulation Does not mimic viral replication DIII escape mutants	Phase I-complete
WNVDNA017-00-VP	DNA Plasmid	No risk of reversion to virulence Some designs can be used to make VLPs	Theoretical risk of plasmid integration Weak immunogenicity: requires cytokine expression or promoter modification Theoretical risk of VLP virulence Does not mimic viral replication	Phase I-complete
WNVDNA020-00-VP				Phase I-complete
WN/DEN4-3'Δ30	Chimeric (vectored)	Mimics viral process for increased immunogenicity: Humoral and T-cell responses More likely to induce long-term immunity	Anti-vector immunity Theoretical risk of virulence or reversion Viremia symptoms	Phase I-complete
WN/DEN4Δ30				Phase I-unknown*
ChimeriVax-WN02 (2 trials)				Phase II-complete
Virus-like particle (VLP). * WN/DEN4Δ30 status not updated on clinicaltrials.gov for over 2 years.				

Table 4: Comparison of relative advantages/disadvantage of vaccines in clinical trials (adapted from Martina, et al., 2010).

Of these candidate vaccines the most promising appears to be ChimeriVax-WN02, which has completed Phase 2 trials as well. The ChimeriVax is generated from a Yellow Fever genetic 17D vaccine virus genetic backbone with the preM and E-protein genes replaced by those for West Nile virus. Thus, the safety record of yellow fever

vaccine strain 17D is conveniently exploited while conferring immunity to WNV. In a recent phase 2 trial, neutralizing antibodies were induced in >96% of subjects in a 65 and older cohort and 93% of the 41-64 year old cohort with no serious adverse events (Biedenbender, et al., 2011). In another study of subjects immunized with ChimeriVax, CD8+ T-cell responses were detected up to a year post-immunization in 7 of 10 individuals tested (Smith, et al., 2011).

The WN/DEN4-3'Δ30 and WN/DEN4Δ30 are also chimeric: the difference being the preM and E-protein genes of WNV are substituted onto a dengue-4 virus vector instead of yellow fever 17D vaccine virus. However, literature is lacking beyond the phase 1 trial information on ClinicalTrials.gov. Moreover, the status has not been updated in over two years for the WN/DEN4Δ30 trial (ClinicaTrials.gov). Whether the dengue-based vaccines will continue to progress through clinical trials is not clear.

The phase I trial for the VRC-WNVDNA017-00-VP vaccine induced neutralizing antibodies in the 12 subjects who completed the 3-dose schedule, 53% of whom developed T-cell specific responses. The trial was completed without significant side-effects (Martin, et al., 2007; Martina, et al., 2010). However, no phase II trial has been initiated. Since plasmids do not replicate, the immunogenicity of traditional DNA vaccines is weak and must be enhanced by genetic means, such as co-expressing cytokine or enhancing promoter expression of antigenic protein (Martina, et al., 2010). A theoretical risk of integration of the plasmid into host DNA also exists (Martina, et al., 2010). In 2008, a DNA vaccine was modified such that virus-like particles (VLPs) were produced which lacked the infectivity of chimeric virus, yet enhanced immunogenicity in

mice and horses (Chang, et al., 2008). The most recent study published for the VRC-WNVDNA0200-00-VP showed enhanced immunogenicity in humans with greater humoral and T-cell immune responses owing to a cytomegalovirus-derived promoter (CMV/R) used to enhance protein expression (Ledgerwood, et al., 2011).

A single phase 1 trial was completed for the WN-80E vaccine. As previously stated, domain III of the E-protein contains the most potent neutralizing epitopes but is weakly immunogenic (Martina, et al., 2010). Therefore the 80E vaccine is based on the N-terminal 80% portion of the E protein (and also represents the soluble ectodomain). For this reason, the vaccine is administered with an adjuvant to bolster immunogenicity. In a 2009 study, WN-80E was administered to macaques with GPI-0100 adjuvant (Lieberman, et al., 2009). About half of the primates immunized had evidence of cell-mediated immunity, while all immunized tolerated WNV challenge and had adequate neutralizing antibody titers. In the human phase 1 trial the vaccine was tolerated without serious safety concerns but information about the immunogenicity and subject immune responses are lacking (ClinicalTrials.gov).

C. ECONOMICS:

In 2006, a study was conducted to explore the cost-effectiveness of WNV vaccination (Zohrabian, et al., 2006). Outcomes included in the analysis were: asymptomatic infection, uncomplicated illness with recovery (5 day productivity loss), neuroinvasive illness with full recovery, neuroinvasive illness with disability, and death. Estimates for the life-time cost of acute stroke were used as a proxy for neuroinvasive

disease with disability. A baseline cost of $100 was assumed for vaccination. Other assumptions were made for the probability of infection and risk of certain disease outcomes based on preexisting data on WNV. The results of this analysis indicated that a universal vaccination program would not result in societal monetary savings unless the cumulative 10-year incidence were to increase substantially (to 1.4%), the cost of vaccination per person were to drop below $12.80, or the cost of lifelong disability were to rise to $3.2 million (15 times higher than the baseline estimate) (Zohrabian, et al., 2006). The risk for infection, probability of symptomatic illness, and cost of vaccine had the greatest influence on cost-effectiveness outcome in this study. The authors of this study did not explore a high-risk vaccination strategy which, as opposed to a universal strategy, would only target those individuals possessing risk factors of a strong predictive value for developing West Nile encephalitis post-infection in the population.

D. EPIDEMIOLOGIC MODELING AND FURTHER RISK STRATIFICATION:

If a universal vaccination program is undesirable, or simply impossible, further stratification of at-risk human populations will be necessary. Though WNV is considered endemic in the United States, outbreaks are difficult to predict. The major challenge in developing a targeted approach to vaccination against WNV lies in attempting to understand the temporal and spatial behavior of the disease in the human population as a function of the epidemiology of the vector and avian host. The risk of human exposure to WNV cannot be separated from the multitude of factors influencing the behavior of the virus in populations of mosquitoes and birds. Given the volume and complexity of data

relating to WNV transmission, analysis of the epidemiology can be daunting without the aid of computer-based software techniques. An in-depth treatment of this subject is beyond the scope of this paper. However, presented here are some key concepts of modeling and how it applies as a tool to understand the behavior of West Nile in the human population and risks to public health.

Relevant terms:

- *Spatial Risk Model:* a statistical model used to estimate or predict vector presence or abundance, or case presence or incidence within a particular geographical area (Eisen & Eisen, 2011).

- *Geographic Information System (GIS):* software with database, mapping, and data analysis capacity (Eisen & Eisen, 2011).

- *Decision Support System (DSS):* an interactive system that aids the process of gathering, storing, and analyzing data; presenting data outputs; gaining new insights; generating alternatives; and making decisions (Eisen & Eisen, 2011).

- *Models of Infectious Disease Agent Study (MIDAS):* a research partnership between the NIH and scientific community to develop computational models for policymakers, public health workers, and researchers to help them make better-informed decisions about emerging infectious diseases and respond to outbreaks and epidemics (Cooley, et al., 2008).

- *Model Repository (MREP):* organizes and categorizes the MIDAS models and results and makes them accessible to users for research purposes (Cooley, et al., 2008).

A spatial risk model is a software program designed to analyze data with a particular purpose in mind: in this case studying a vector-borne disease such as WNV (Eisen & Eisen, 2011). Input (raw data) can take the form of many variables of interest that affect (or reflect) the behavior of disease transmission. This information can take the

form of surveillance data, such as WNV-positive mosquito trapping locations or human cases, or variables such as land cover and climate characteristics (typically estimated via satellite measurements). Within the GIS framework, modeling data are cross-linked to location coordinates on a scale dictated by data quality and study design. This is necessary to produce meaningful spatial output (usually in the form of a map) by the modeling system. GIS models can also be used to analyze data and draw conclusions about data that may not have been apparent to the researcher initially and help to identify other risk factors. GIS modeling can also be further integrated into DSS where the use of administrative data can be correlated with GIS outputs to aid in the decision-making process with regard to the allocation of public health resources (Eisen & Eisen, 2011).

The MIDAS seeks to develop models for the study of infectious disease while centralizing the models with all associated information inputs, outputs, and study designs into a modeling repository for future retrieval, study replication, and model improvements (Cooley, et al., 2008). Projects such as this will serve as a valuable tool in DSS development for mitigation of disease and allocation of limited resources (such as vaccine).

CHAPTER 4: DISCUSSION

Of the vaccines in clinical trials the likely candidates for progression to licensure are the DNA vaccine and ChimeriVax. Ideally the vaccine should mimic the virus in the host, elicit the induction of neutralizing antibodies, establish immune memory response, and also establish a long-lasting adaptive response. Of the two, ChimeriVax appears to be closest to meeting these objectives, although it carries the theoretical risk of reversion to virulence. The DNA vaccine does not carry this risk since it does not replicate. However, it is less immunogenic and must rely on genetic enhancements to boost effectiveness. One potential advantage of the DNA vaccine is that it would be theoretically safer in immunosuppressed individuals.

As noted in the previous section, the 2006 economic study suggested that a universal vaccination program for WNV would not be cost-effective. While cost is not the sole determinant of protecting public health, having a cost-effective vaccination program would be ideal (Zohrabian, et al., 2006). Once a vaccine theoretically completes all phases of clinical trials and is produced for clinical use, it is expected that the vaccine will be expensive and in limited supply. If a WNV vaccination program were to be implemented in the future, a high-risk strategy for vaccination would be desirable because narrowing the target population to those most at risk will serve to improve cost-effectiveness. Thus, an economic study evaluating the cost-effectiveness of a high-risk vaccination strategy could lend further justification of WNV vaccination program.

In lieu of the data in Table 2, a starting point for risk stratification of individuals to receive WNV vaccine would be to first impose an age cutoff criterion at 65 and older, since this group is most at risk for neuroinvasive disease. Thus, automatically providing vaccine to those individuals aged 65+ and living in areas of high risk is rationally justified (determination of area risk discussed later).

Moving from the 65+ group to the age stratum 45-64 years of age, the odds ratio for neuroencephalitis drops significantly (10.5 to 1.8 respectively), but this still represents higher risk compared to the 20-44 group (OR=0.2, which suggests protection). If the goal is to target only those most at risk for vaccination, based on these data not vaccinating individuals in the 45-64 age group seems reasonable unless they possess a comorbid risk factor that will elevate their risk of encephalitis. In other words, an OR=1.8 could constitute "acceptable risk" for a healthy individual of age 45-64. Of the comorbid conditions that elevate the odds ratio, cardiovascular disease and chronic renal disease appear to elevate it the most. These two conditions could reasonably serve as criteria for vaccination in and of themselves, regardless of age. (See Table 3; Figure 5) Otherwise, being in the 45-64 age stratum, one should possess at least one of the remaining risk factors in Table 2 and three to justify vaccination. Individuals younger than 45, who may have extenuating circumstances (perhaps a young patient with a debilitating condition), can receive the vaccine at the discretion of a physician.

Theoretically, immunosuppressed individuals are more susceptible to infections and could possibly receive vaccine for protection against neuroinvasive disease. However, in clinical practice live-attenuated vaccines generally are not administered to

individuals with altered immune function. If the vaccine is proven safe to use in these individuals, a qualified clinician can make the decision to administer the treatment. Similar caution applies to pregnant women.

Current trends in the population demographics of the United States predict significant increases in the elderly population. A logical consequence of a growing elderly population is an increase in prevalence of the comorbidities that increase risk for neuroinvasive disease from WNV in the general population. Given the concerns addressed about cost and supply of vaccine, it follows that an additional stratum for risk evaluation is required. This stratum would be based on location. The question then becomes: How do you define an area at risk, where an individual might receive vaccine, verses an area where the same person would not? Moreover, how do you adjust for the risk as it fluctuates over time? As previously discussed this would have to be defined by the epidemiology of WNV, which is not a simple matter. Understanding this epidemiology becomes possible though the application of software technology.

While a disease spread by person-to-person or point-source contact follows a relatively simple transmission pattern, a disease like West Nile (involving a vector and amplifying host) is more complex with regard to assessing risk of transmission to humans. Variables influencing transmission must be taken into account for all three corners of the epidemiologic triad: insect, bird, and human. For example, variables such as climate, land cover, and presence of standing water can influence the mosquito population; a variable such as migratory flight patterns applies to the avian host; and variables such as residence location, occupation, socioeconomic status, etc. apply to

humans. Fortunately, software models are under constant development to help researchers, epidemiologists, and the public health worker understand how these variables relate to WNV transmission and how they influence disease risk in the human population. These variables, along with surveillance data and relevant administrative data, are entered as location-specific input into GIS models in order to produce output in the form of a map illustrating risk density. This gives the scientific community the ability to design time and cost-saving programs. However, in order to obtain effective modeling output, quality data must be available and must be used with the appropriate model.

Ambitious projects such as the MIDAS and MREP will be useful in the future to develop reliable models to analyze risk to the public health and aid in the development of Decision Support System for efficient allocation of limited resources to protect the public health, such as WNV vaccine. This process is represented in Figure 5 as a continuous loop that theoretically can evaluate the risk of any human population at any time. This would be a dynamic process, as risk can change. For example, a cutoff criterion (such as a threshold risk score) may be reached following data analysis, which can designate an area as "at risk" and trigger the implementation of vaccination of high-risk individuals in the geographic location of interest. With ever improving technological advances, GIS modeling and DSS will likely play a role in future vaccination decisions by public health workers.

In summary, WNV has become a threat to public health since the initial epidemic in New York in 1999. Since it is a vector-borne disease utilizing an avian host, its presence will likely persist as a threat to public health for quite some time. Eradication is

not possible by contemporary means and a universal vaccination plan is not economically feasible (at least at this time). Thus, a stratification scheme must be employed if an efficient and cost-effective vaccination program is to be developed. The scheme proposed in these pages relies on demographic factors, such as age and chronic disease status. Other factors of interest are population location with respect to time and diverse predictors represented in data collected by the public health sector. The next tier of stratification is complicated by the fact that the epidemiology of WNV is ever changing in the human, insect, and avian populations, phenomena of which must also be taken into account as WNV behavior in all populations is interdependent. In order to utilize data representing such diverse and dynamic phenomena, software modeling will increasingly have to be used with the objective of assessing risk and predicting WNV behavior so that public health interventions might be allocated in an efficient and cost-effective manner. For the purpose of this capstone, this would presumptively apply to a future vaccine presumed to initially be in short supply.

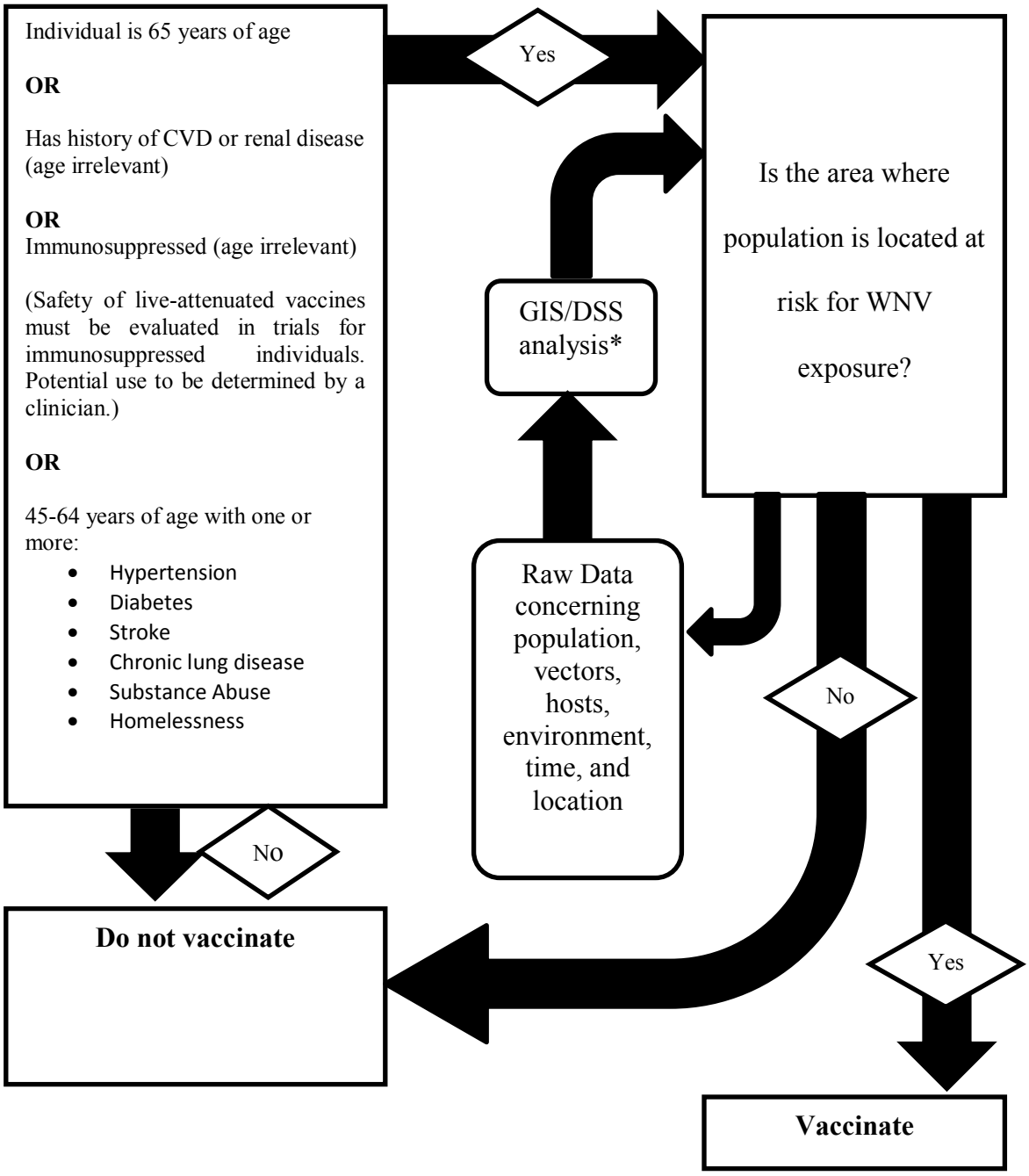

Figure 2: Risk Stratification and Decision Making Scheme for WNV Vaccination.

*Note that GIS data analysis is a continuous loop as risk may change over time.

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