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Combating West Nile Virus Disease — Time to Revisit Vaccination

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It is time to revisit the need for human West Nile virus (WNV) vaccines. Since its initial detection in the United States in 1999, WNV has become the leading cause of domestic arthropod-borne viral (arboviral) disease. Spread by infected culex-species mosquitoes, WNV has caused more than 55,000 reported cases of human disease, more than 27,000 of them neuroinvasive, and 2600 deaths between 1999 and 2021, according to data from the Centers for Disease Control and Prevention (CDC). WNV is also an ongoing public health threat in many areas of the world; the largest recorded outbreak in Europe occurred in 2018.

Despite development and expansion of WNV-specific mosquito surveillance and control programs over the past two decades, a consistently high burden of disease is reported each year in the United States.¹ At a subnational level, the occurrence of WNV is both geographically focal and sporadic, making it difficult to predict outbreaks and leading to regional and temporal variation in disease burden; for example, in Maricopa County, Arizona, more than 1400 WNV disease cases and 100 resulting deaths were reported in 2021, as compared with only 3 cases the previous year.

In addition to morbidity and mortality, WNV disease results in substantial costs to patients and society. Between 2004 and 2017, a total of 3109 California residents were hospitalized with WNV, with estimated hospital costs averaging \$59.9 million per year.²

Primary prevention of WNV and other domestic arboviral diseases currently includes personal protective measures to reduce vector exposure and community-based mosquito control programs. But these approaches have limitations. Adherence to personal protective measures, such as wearing long sleeves and long pants, avoiding outdoor activities during periods of high vector activity, and using insect repellent, is often low. Intensive, reactive vector-management programs have been effective in reducing the size of WNV outbreaks but are costly and typically initiated only after many cases have already occurred.¹ Proactive strategies, such as larvicide application and intensive, early-season adult mosquito control,

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are preferable but are challenging to implement because of complexities in establishing evidence-based vector indexes and action thresholds and variability in jurisdictional vector surveillance and resources.¹

Although several veterinary vaccines have been licensed, WNV vaccines for humans have not progressed beyond phase 1 or 2 clinical trials.³ Human clinical studies have been conducted with several vaccine candidates, including two live attenuated chimeric, one DNA (first and second generation), one recombinant subunit, and two inactivated whole-virus vaccines (see table). All were associated with minimal adverse events, and most were shown to have favorable immunogenicity, although the inactivated virus vaccine elicited only moderate immune responses. In phase 2 trials, the live attenuated recombinant yellow fever vaccine strain expressing the premembrane and envelope (prM-E) genes of WNV (ChimeriVax-WN02) was found to have a good safety profile and immunogenicity even in older age groups after a single dose.³

Several factors have hindered WNV vaccines from moving forward into later stages of clinical development, including challenges with designing and implementing efficacy studies, potential vaccine safety concerns, and anticipated costs of WNV vaccine programs. Traditionally, large-scale phase 3, randomized clinical trials are needed to show efficacy; however, the sporadic and unpredictable nature of WNV disease outbreaks makes it challenging to select geographic areas and prepare (e.g., obtain ethics approval) for vaccine efficacy trials before WNV activity is detected during a given season. In addition, severe disease is observed primarily in a subset of the population (i.e., persons 50 years of age or older or those with certain underlying medical conditions). If case counts are low in areas chosen for clinical trials, enrollment might take years to complete. A trial's end points, such as preventing neuroinvasive disease, preventing all disease, or preventing infections, would also affect its feasibility. Infection prevention would be difficult to assess because viremia is short-lived, and measurement of the WNV-specific antibodies required to confirm infection would need to differentiate between vaccine- and infection-induced immunity.

Concerns have also been raised over vaccine safety, particularly with live attenuated virus vaccine candidates. The risk of prolonged viremia and adverse events from live vaccines is highest in the same populations for which vaccination would be recommended. Although early clinical trials with WNV chimeric vaccines did not find that older participants had serious vaccine-associated adverse events, the number of participants vaccinated was limited. Another potential safety concern is antibody-dependent enhancement (ADE), which has been observed with other flaviviruses and related vaccines; however, ADE has not been observed with WNV infections in persons with previous flavivirus exposure.

Finally, costs associated with WNV vaccine programs have been noted as a potential obstacle to vaccine development. This concern is based on cost-effectiveness models evaluating theoretical national and age-based WNV vaccine programs.^{2,4}

The challenges to WNV vaccine development are not unique and could be addressed with approaches similar to those used for other vaccines. Given the unpredictability of outbreaks and the related challenges of conducting vaccine efficacy trials, alternative

licensing pathways using surrogate end points, such as immune protection in animal models of disease (which is being used for chikungunya vaccines) and immunologic markers, could be considered.

Work already performed for WNV indicates that a reasonable surrogate end point could be established.⁵ There are animal models relevant to human disease or infection that could be used to conduct passive immune transfer studies to determine whether the human immune response to WNV vaccination can protect animals from clinical illness or viral replication. Because the presence of neutralizing antibodies has been established as a correlate of protection for other neuroinvasive flavivirus vaccines for humans (e.g., Japanese encephalitis vaccine), it would probably be one of the most useful immunologic markers for WNV vaccine efficacy.

As with Zika virus vaccines, other potential options could be considered, such as making WNV vaccines available before licensure under an investigational new drug application with an expanded access mechanism, or under an emergency use authorization. Some alternative pathways being considered for Zika vaccines, however, such as use of a human challenge model, would not be appropriate because of the potential severity of WNV disease. With a nontraditional pathway to licensure, regulators would have to consider vaccines' safety, feasibility, and acceptability, as well as postmarketing requirements for studies or clinical trials that could show clinical benefit.

Although serious adverse events were not reported in early clinical trials, potential safety concerns need to be addressed in future WNV vaccine development efforts. The benefits of live vaccines, including durability of immunity and need for only one dose, will need to be weighed against potential safety concerns, particularly for the principal age group that would be targeted. Although inactivated vaccines might have a better safety profile, the likely need for multiple doses and the limited sustainability of immunity could affect vaccine uptake. For example, all four approved veterinary vaccines have a two-dose primary series and annual booster schedules.³

To address the issue of cost barriers, an age- and incidence-based vaccine program could substantially improve cost-effectiveness while still leading to disease reduction.⁴ Such a strategy was used successfully for initial implementation of the hepatitis A vaccine. Although WNV disease incidence is difficult to predict, many areas of the United States are known to have sustained high incidence and could be targeted for vaccine programs and longer-term postmarketing studies. Geographic targeting could result in more predictable and consistent vaccine demand. Furthermore, recent estimates of WNV-associated hospitalization costs in California indicate that updated cost-effectiveness ratios would be more favorable than previous estimates.²

Our experience over the past two decades has demonstrated that current prevention strategies are not enough to reduce the ongoing WNV disease burden. WNV vaccination would be more effective in preventing WNV disease and related deaths. Lessons from the development of other vaccines can be applied to move WNV vaccine candidates further

through development to ensure the availability of safe and effective vaccines for people at risk.

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West Nile Virus Vaccine Candidates Tested in Clinical Trials.*

Vaccine Type, Name, and Trial	Age of Participants (yr)	No. of Participants Enrolled	No. and Timing of Doses	Immunogenicity	Serious Adverse Events Attributed to Vaccine	ClinicalTrials.gov Number
Live attenuated chimeric						
WN/DEN4-3'Δ30 (NIAID, NIH)						
Phase 1 trial, completed in 2005	18–50	56	1 Dose	55–75% Seroconversion (increase in PRNT ₆₀ by a factor of ≥4 at day 28 or 42)	None	NCT00094718
Phase 1 trial, completed in 2009	18–50	26	2 Doses, 6 mo apart	89% Seroconversion after second dose (increase in PRNT ₆₀ by a factor of ≥4 at day 28 or 42)	None	NCT00537147
Phase 1 trial, completed in 2016	50–65	28	2 Doses, 6 mo apart	95% Seroconversion after first dose by day 90 (PRNT ₅₀ ≥1:10)	None	NCT02186626
ChimeriVax-WN02, YFV 17D backbone (Sanofi Pasteur)						
Phase 2 trial, completed in 2009						
Part 1	18–40	112	1 Dose	>96% Seroconversion (increase in PRNT ₅₀ by a factor of ≥4 at day 28)	None	NCT00442169
Part 2	≥41	96	1 Dose	Approximately 96% seroconversion (increase in PRNT ₅₀ by a factor of ≥4 at day 28); GMT and viremia tended to be higher among persons ≥65 yr of age	None	NCT00442169
Phase 2 trial, completed in 2009	≥50	479	1 Dose	92–95% Seroconversion (increase in PRNT ₅₀ by a factor of ≥4 at day 28)	None	NCT00746798
DNA						
VRC-WNVDNA017-00-VP, first generation (NIAID, NIH, DVBID, CDC)						
Phase 1 trial, completed in 2008	18–50	15	3 Doses, 4 wk apart	100% Had neutralizing antibodies detected (PRNT ₅₀) at 4 wk and 24 wk after third dose; titers were similar to those elicited in horses 3 wk after 1 dose of WNV DNA vaccine	None	NCT00106769
VRC-WNVDNA020-00-VP second generation (NIAID, NIH)						
Phase 1 trial, completed in 2007	18–65	30	3 Doses, 4 wk apart	>96% Had neutralizing antibodies detected (EC ₅₀) at 4 wk after third dose	None	NCT00300417
Recombinant subunit						
WN-80E (Hawaii Biotech)						
Phase 1 trial, completed in 2009	18–45	25	3 Doses, 4 wk apart	Unpublished	Unpublished	NCT00707642
Inactivated whole virus						
HydroVax-001, hydrogen peroxide inactivated (Najit Technologies)						

Vaccine Type, Name, and Trial	Age of Participants (yr)	No. of Participants Enrolled	No. and Timing of Doses	Immunogenicity	Serious Adverse Events Attributed to Vaccine	ClinicalTrials.gov Number
Phase 1 trial, completed in 2016	18–49	51	2 Doses (1 μ g or 4 μ g), 4 wk apart	31–50% Seroconversion at 15 days after second dose (PRNT ₅₀ $\geq$ 20 with or without complement enhancement)	None	NCT02337868
Formalin inactivated (Nanotherapeutics)						
Phase 1–2 trial, completion date unknown	$\geq$ 18	320	2 Doses, 3 wk apart; booster on day 180	All doses elicited immune response, with peak antibody responses after booster dose (microneutralization)	None	None

* PRNT (plaque reduction neutralization test) titers are expressed as the reciprocal of the last serum dilution showing the given reduction in plaque counts (50% or 60%). For the WN-80E vaccine, the patent number is US20120141520 A1. CDC denotes Centers for Disease Control and Prevention, DVBID Division of Vector-Borne Diseases, EC effective concentration, GMT geometric mean titer, NIAID National Institute of Allergy and Infectious Diseases, NIH National Institutes of Health, WNV West Nile virus, and YFV yellow fever virus.