West Nile Fever
Summary

Introduction

1. This note summarises an analysis by a DISCONTOOLS group of experts on West Nile Fever (WNF). The group reviewed current knowledge of the disease, considered detection and control tools marketed or in development, identified current gaps in the availability and quality of detection and control tools and determined research necessary to develop new or improved tools. Full details of the analysis can be downloaded from the website at www.discontools.eu

Ecology

2. West Nile Virus (WNV) is an enveloped single-stranded RNA virus which belongs to the genus *Orthoflavivirus* in the family *Flaviviridae*. There are 7-9 distinct lineages described, with lineages 1 and 2 distinctly dominant and associated with human disease. WNV is maintained in nature by cycling between birds as amplifying and reservoir hosts and mosquitoes, generally of the genus *Culex*, which are competent biological vectors. In mosquitoes, the virus must multiply and reach the salivary glands before the mosquito can pass on the infection to another vertebrate host. Mosquitoes also act as a bridge for the transmission of the virus to other susceptible species, such as mammals, amphibians and reptiles. Equids and humans are the most sensitive mammals to WNV infection but are dead-end hosts. Numerous avian and mosquito species support virus replication but not all species of birds are equally competent as reservoir hosts. Historically, WNV infections in Europe were lineage 1 but infections by lineage 2 WNV—previously restricted to sub-Saharan Africa—appeared in Europe in 2004. Since 2010, the majority of human WNV infections in Europe have been lineage 2. The recent re-introduction of WNV Lineage 1 in Italy in 2020 has been associated with a significant increase in human diseases.

Disease Profile

3. The incubation period in vertebrate hosts is typically 3 to 6 days but ranges from 2 to 15 days. In horses, approximately 10–20% of infected animals may develop neurological signs (such as ataxia, limb paresis or paralysis, muscle twitching, teeth grinding, cranial nerve deficits with amaurosis, dysphagia and facial paralysis) as well as general symptoms (fever, depression) and the case fatality rate ranges from 23% to 57%, depending on the outbreak. Infected humans and horses are dead-end hosts, which means that they cannot infect new mosquitoes and that there is no natural spread from them to other people or animals. WNV does not normally spread between people except under special circumstances (e.g. blood transfusion, organ transplantation, transplacental transmission, breastfeeding).

4. When human infection results in clinical disease (20-30% of infected people), a flu-like illness with fever is usually reported. Less than 1% of infected people suffer neurologic disease with potentially fatal meningitis, encephalitis, acute flaccid paralysis, or other neurological symptoms. In humans with neuroinvasive disease, the case fatality rate ranges from 10% to 20% and severe sequelae persist in 20 to 40% of survivors.

Risk

5. WNV is now endemic in the USA, Central Europe and the Mediterranean region. More recently Northern European countries have reported recurring outbreaks. The reporting of high numbers of outbreaks in humans and in horses in Europe particularly in 2018 and 2022 is of concern. The causative virological, ecological and environmental factors that predispose to outbreaks are not fully understood.

6. The speed and extent of WNV spread in affected areas depends on a number of interdependent factors including presence of viremic birds, vectorial capacity (e.g. the ability of the vector to transmit WNV), mosquito biting rate on competent hosts (which is host and vector density dependent) and incubation period (which is temperature dependent). Infection is seasonal in temperate climates.

7. Introduction and spread of WNV in non-affected areas are usually attributed to movement of infected wild birds or importation of infected competent vectors. Climate change may lead to

changes in the distribution of vectors and may increase the opportunity for invasive or bridge mosquito species to establish. Increased temperatures are predicted to increase and accelerate virus replication in the vector, although clear scientific evidence of the effects of climate change to WNV are currently lacking.

8. Several WNV strains belonging to lineages 1 and 2 cause sporadic human and animal disease in central, southern and northern Europe. WNV cases have been reported in at least 22 European countries and the virus is endemic in Romania, Hungary, Serbia, Greece, Spain, Portugal, France, Germany, Austria, Bulgaria, and Italy. Outbreaks in North America and Europe are difficult to predict and the long-term epidemiology of WNV infection in Europe remains uncertain. In Europe, WNV may be evolving towards an endemic state, punctuated by occasional large outbreaks.

Diagnostics

9. Virus isolation from horses is problematical as viraemia is short lived and viral titres are low. Virus isolation should be attempted on tissue samples, primarily nervous tissue, from dead animals, as well as on urine samples in humans.
10. Several test kits are available in Europe but are generally for use in laboratories. Most are based on competitive and IgM-capture ELISAs. Sensitivity and specificity of WNV IgM and IgG ELISAs for use in humans and animals are variable among tests. The specificity and sensitivity of competitive assays are uncertain if used in species other than species for which test was developed, due to species-specific reagents in the test or lack of data on test performance in such species. A major problem for WNV serological assays is the high degree of cross-reactivity between antibodies against WNV and other flaviviruses and, in humans, the longevity of IgM.
11. New tests and kits are being developed but improved specificity, cost, and practicality are needed. Fast and practical tests, such as penside tests and Point-Of-Care Testing, are required for the detection of infection in both horses and birds.
12. The main purpose of diagnostic tests is to confirm clinical infection. DIVA serological tests based on non-structural proteins of WNV would be useful to discriminate antibodies arising from natural infection from those arising from vaccination both in the clinical setting and during surveillance.
13. Molecular tests that can differentiate between WNV lineage 1 and WNV lineage 2 are needed, with the objective to monitor outbreaks.
14. There is a limited market in Europe for diagnostic tests. Opportunities for development of diagnostic kits are increasing as the number of outbreaks increases but it remains questionable whether there is incentive to develop new diagnostic kits for commercial use.

Vaccines

15. WNV vaccines currently sold in the EU for horses have good safety and efficacy profiles. Horse owners are likely to use different registered vaccines for prime-boost and annual booster immunization depending on the availability of vaccines and costs. Thus, duration of immunity and long-term protective efficacy should be established for prime-boost with different combinations of registered vaccines. The protective status of post-vaccination exposure should be established that will allow horse owners to determine if the annual revaccination is essential to protect their horses against re-exposure. Improvement to existing vaccines would include a single dose vaccine with early onset of immunity and long duration of immunity.
16. As a result of recent outbreaks in EU Countries, potential for commercial vaccine usage in horses has increased. In principle, if WNF becomes a problem in any country, vaccination can be used as a preventive measure. Eradication of disease is impossible due to the extensive wildlife reservoir, i.e. birds, and bird migration.
17. No WNV vaccines have been approved for use in humans. The development and validation of new WNV vaccines in animals may make the development of a human vaccine cheaper and more attractive for vaccine companies to take up this important need.

Pharmaceuticals

18. There is an urgent need for effective antiviral drugs or monoclonal antibodies to treat patients and animals with West Nile Neuroinvasive Disease. Broad-acting antiviral drugs would be preferable. No major funding is available for such research since West Nile infection in the horse and in humans is perceived as self-limiting.

Knowledge

19. There is still a lack of knowledge about the pathogenesis, immunology, ecology and epidemiology of WNF. Gaining knowledge on the epidemiology, ecology and pathology will facilitate development of monitoring and control strategies.

20. Further research is needed to develop more effective tools for the detection and control of WNF. Details on knowledge gaps are shown in the Disease and Product Analysis for West Nile Fever on the DISCONTOOLS website.

Conclusions

21. Further elucidation of the ecology, epidemiology, pathogenesis and evaluation of factors that predispose to disease outbreaks in the EU or in other endemic regions are required. Strengthening and integrating animal, vector and human surveillance and developing preparedness plans and capacity for detection and response to outbreaks are essential to benefit public and veterinary health, in regions with increased WNV incidence such as the EU.

22. Climate change may influence vector distribution, behaviour and virus transmission, as well as bird migration and, as a result, alter patterns of WNV spread and transmission and change its burden on animal and human health.

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