West Nile Fever in Israel 1999–2000
From Geese to Humans

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Abstract: West Nile virus (WNV) caused disease outbreaks in Israel in the 1950s and the late 1970s. In 1998 an outbreak of WNV in goose farms and evidence of infection in dead migratory birds were reported. Consequently, human diagnostic services for WNV were resumed, including virus isolation, serology, and RT-PCR. Risk factors for infection were assessed by a serological survey in 1999, which revealed a seroprevalence of (a) 86% in people who had close contact with sick geese, (b) 28% in people in areas along bird migration routes, and (c) 27% in the general population. Following two fatal cases in Tel Aviv in September 1999 and one encephalitis case in the southern Eilot region, a regional serological survey was initiated there. The survey revealed two more WNV-associated acute encephalitis cases, an IgG seroprevalence of 51%, and an IgM seroprevalence of 22%. In the summer of 2000, acute cases of WN disease were identified in the central and northern parts of Israel, involving 439 people. The outbreak started in mid-August, peaked in September, and declined in October, with 29 fatal cases, primarily in the elderly. During the outbreak, diagnosis was based on IgM detection. Four virus isolates were subsequently obtained from preseroconverted frozen sera. Sequence and phylogenetic analysis of 1662 bases covering the PreM, M, and part of the E genes revealed two lineages. One lineage was closely related to a 1999 Israeli bird (gull) isolate and to a 1999 New York bird (flamingo) isolate, and the other lineage was closely related to a 1997 Romanian mosquito isolate and to a 1999 Russian human brain isolate.

Keywords: West Nile virus; West Nile fever; Israel; geese
INTRODUCTION

West Nile fever (WNF) is caused by a flavivirus and is mainly transmitted by Culex mosquitoes. The virus circulates in nature through a zoonotic cycle. It is capable of infecting many species, including amphibians and reptiles, with birds being the most efficient host for virus amplification. Humans and horses are considered dead-end hosts and are equally susceptible to the virus.

In most cases WN virus (WNV) causes a subclinical or influenza-like disease except for the cases where epidemic outbreaks have been described. In these cases the virus has caused acute encephalitis or meningoencephalitis. The disease is characterized by high fever, rash, swollen glands, sore throat, conjunctivitis, muscle aches, weakness, disorientation, and stiff neck, and pancreatitis and myocarditis have also been associated with WNF. The disease has different manifestations in different age groups; its incidence increases with age, and may have a fatal outcome in the elderly.

WNV was first described in 1937 in Uganda, Africa. The virus is endemic in Africa and Asia, and is characterized by epidemic outbreaks every few years during the late summer/fall. The first descriptions of the disease in Israel, which is located on the migratory route of many bird species from Europe to Africa, dates back to the 1940s. Repeated outbreaks occurred in the central and northern part of the country during the 1950s, when hundreds of cases were recorded, among them encephalitis and meningoencephalitis cases, mainly among the elderly. The Central Virology Laboratory (CVL, Ministry of Health) records showed continuous diagnosis of WNF between 1974 and 1982 (N. Varsano, personal communication). In 1979 and 1980 there were two WNF episodes in the Negev (southern Israel) among soldiers, some with encephalitis, for which WNV was confirmed at the CVL. A serosurvey among army personnel during 1982–1989 showed that immunity increased with age. Thus, groups of 18–20, 21–30, and 40–55 years had 7%, 10.5%, and 42% IgG seroprevalence, respectively.

A cohort study performed in 1989–1990, on hospitalized children aged <1 y–17 y with unexplained encephalitis, meningitis or rash showed evidence of recent exposure to WNV (9.5% had IgM antibodies). The overall seroprevalence was 34% (by either IgG or IgM), with a rate of 20% in the <1 y age group and 45% in the rest of the cohort (Varsano, N., B-E. Lachmi & S. Lustig, 1990, unpublished data).

After 1990, no clinical cases, seroepidemiological studies, or bird and mosquito isolations were reported until 1998 when Malkinson et al. reported WNV isolation from domestic geese, and migratory and local bird populations. High morbidity in goose flocks was associated with clinical symptoms in goose farmers while the reports of outbreaks in Romania in 1996 and in southern Russia in 1999 which were characterized by high case-fatality rates, prompted us to investigate human infections in Israel, and to prepare for a possible outbreak in humans. This report describes the course of human infections in Israel prior to the outbreak in 2000, and the main features of the 2000 outbreak, including isolation and molecular analysis of four WN viruses from human sera.
MATERIAL AND METHODS

Patients and Sera

Blood samples for seroprevalence studies were collected from volunteers with their informed consent. The volunteers filled out a questionnaire to provide information about their profession, recent clinical symptoms, and contact with sick birds. Additional samples were taken from the CVL serum bank. Preseroconversion sera from patients submitted for diagnosis of WNF just after onset of clinical symptoms, were used for virus isolation, identification and genetic analysis.

WNV Strains

Two Israeli WNV isolates were propagated in Vero cells (ATCC CCL-81). They were derived from a domestic goose in 1998 and from a white-eyed gull in 1999. Both isolations were performed at the Kimron Veterinary Institute (KVI) and their identities confirmed by RT-PCR at the Institut Pasteur (Dr. Deubel, paper in preparation). Virus was grown for 5 days and harvested after showing CPE of 90%.

Antigens for ELISA

Antigen was prepared from the goose or gull WNV isolates. The infected cell slurry was precipitated with polyethylene glycol 6000. We used the current WNV circulating in Israel rather than other strains, in order to improve the sensitivity and specificity of the ELISA for human serology. Uninfected Vero cells were processed in parallel, and were used as mock-infected control antigen.

Serology

Microneutralization Assay

Sera were first analyzed using microneutralization CPE reduction assay. The challenge virus used was the 1998 goose isolate. This assay was used in the early serological surveys and clinical diagnoses and later helped to establish and validate the ELISA assays, with modifications. We found a 96% agreement between the two tests, allowing us to adopt the ELISA as our test of choice for determination of the immune status of humans.

IgG ELISA

The assay consists of five steps starting with coating microtiter plate wells with viral antigen or mock antigen in carbonate-bicarbonate buffer pH 9.6, then blocking with 5% skim milk in phosphate-buffered saline containing Tween 20 (SM-PT). This was followed by incubation with dilutions of human sera and then with horseradish peroxidase (HRP)–conjugated anti-human IgG antibody, both diluted in 3% skim milk in SM-PT. Finally, the substrate O-Phenylenediamine dihydrochloride (OPD, Sigma) was added and the reaction stopped with 1M H₂SO₄ and the optical density (O.D.) at 492 nm was read. The background of nonspecific reactions presented as readings with the control mock antigen and subtracted from the readings of the viral antigen. The cutoff was determined as the average of many negative neutralizing antibody samples plus three standard deviations.
IgM-Capture (CAP) ELISA

The IgM antibody-capture ELISA developed at CVL in 1999, is based on the method described by Tsai et al. (1998), with modifications in the antigen source, and the anti-flavivirus monoclonal antibody, which reacted with Kunjin (KUN) and WN viruses (JCU/KUN/2B2, TropBio, James Cook University, Townsville, Qld, Australia). This antibody targets an epitope in the E protein that is common to both viruses.23,24 KUNV has been recently classified as a subtype of WN virus by the International Committee for the taxonomy of viruses.25,26

During the outbreak, adjustments had to be made to cope with the massive demand for daily testing. Since this test was rapid and sensitive it enabled us to report results within 24 to 48 hours. Patients’ sera or CSF were diluted at 1:100 and 1:2000, or 1:10, and 1:100, respectively. Control mock-antigens were omitted, because the background readings were very low. Nonetheless, the cutoff was adjusted to a point higher than 3 SD above the mean of the negative controls to prevent detection of false positives. An equivocal zone (“gray-zone”) was defined at 20% above and below the mean O.D. values of the negative controls.

Virus Isolation and Identification

Virus isolation was performed on Vero cell monolayers using the tube method. Infected cells that showed CPE were evaluated with RT-PCR and a sample of the supernatant was passed on another Vero cell monolayer to confirm the presence of WNV. In addition, infected cells that showed CPE were also evaluated by indirect immunofluorescent assay (IFA) using the monoclonal antibody JCU/KUN/2B2. Cells from monolayers that did not show CPE were passed onto fresh Vero cell monolayers and monitored for another 7 days. Cells that did not show CPE after a total of 14 days incubation were reported as negative for WNV only after confirmation that the cells were also negative by IFA.

Phylogenetic Analysis of WNV Isolates from Humans

Patient samples were analyzed for WNV by RT-PCR using primer sequences for the envelope gene generously provided by Drs. L. Kramer, K. Bernard, and P-y. Shi from the Wadsworth Center, Arbovirus Laboratories, New York State Department of Health, Slingerlands, as described by Lanciotti et al. and Shi et al.27,41 The primers Kun 108, Kun 848, Kun 998c and Kun 1830c were used in RT-PCR for sequence analysis.28 Sequence analysis was performed on a 1662bp fragment of the WN virus genome encoding 309 nt upstream from the premembrane protein (prM), the entire prM and membrane protein (M) genes and 855 nt of the 5’ portion of the envelope glycoprotein (E) gene. Purification of the RT-PCR product and sequence and phylogenetic analyses were as described.29 Both strands of the amplified PCR products were sequenced.
RESULTS

Early Serological Surveys in 1998–1999

Morbidity in domestic geese due to WNV was reported in 1998 by the veterinary services, Ministry of Agriculture. Thereafter we initiated a study among goose farmers and poultry veterinarians to detect human infections following contact with sick geese. Sera were collected from volunteer goose farmers and veterinarians working with sick geese (study group, \(N = 37\)) or healthy geese (control group, \(N = 39\)), between December 1998 and October 1999. The sera were tested initially by neutralization assays and later by IgG ELISA for antibodies to WNV. The results shown in Figure 1 indicated a strong association between positive serology and contact with flocks of sick geese. Several farmers reported having a flu-like illness when their geese were sick. Interestingly, although sick and healthy flocks of geese were almost always found in different villages, in one village both sick and healthy flocks were found concomitantly. The veterinarians and farmers working with these flocks presented with correlated serological status. This finding is of particular interest because whether bird to bird or bird to human transmission of WNV occurs is still an open question.

Study in Rural Populations Living along Bird Migration Routes

During 1998, WNV was isolated from different bird species, in particular migratory storks, near Eilot, in the most southern part of Israel. The birds were reported to be sick or dead. By contrast, storks captured in northeast Israel were seropositive,
but WNV was not isolated from them. To study whether human infections were associated with the infected birds without reports of unusual morbidity in the general population, we conducted a serological survey in northern communities located along bird migration routes and feeding areas. Fish farming in open ponds near these communities attract hundreds of migratory birds during migration. Sera were collected from 90 volunteers from three communities in the Jordan Valley and were tested for WNV IgG by ELISA. Sixty serum samples from the CVL bank, collected in the summer of 1998 from males and females aged 30–50 years in other parts of the country (unconnected with migration) were used as controls. The seroprevalence found in the rural communities in the Jordan Valley was 28% (average of the three communities) ranging from 21–43% (Fig. 2), whereas the prevalence in the control group was 22%. However, 58–100% of the individuals in the three rural communities had high antibody titers (1:6400–1:48,000) whereas in the control group only 25% of the positives had high antibody titers; mostly the titers were less than 1:6400. These findings suggest that individuals in the rural communities may have been repeatedly exposed to WNV, apparently owing to their residence and work in close proximity to large numbers of migratory birds.

**Seroprevalence by Age in a Control Group**

To assess the seroprevalence of WNV IgG in different age groups in Israel we used sera from the CVL bank (kindly provided by N. Varsano and R. Handcher). Sera from 56 infants aged 12–18 months and 33 serum samples from 14-year-old
children collected in 1998 were tested alongside the adult group described above. The results depicted in FIGURE 3 show that the seroprevalence increases with age from 0% in the age group 12–18 months, to 7% in 14-year-olds, to 22% in the age group 30–50.

**The First Human Clinical Cases in Urban Areas**

In August 1999, a married couple (75/76 years old) from Tel Aviv were hospitalized with high fever and respiratory distress. Both patients later developed encephalitis and coma. The wife died three weeks after hospitalization and the husband survived for six months and died of multiorgan failure. Both tested positive for IgG and IgM in the serum and CSF. The initial diagnosis was done by Dr. R. Swanepoel, National Institute for Virology, South Africa, and later confirmed by Dr. Grant L. Campbell, CDC, Fort Collins, CO (Prof. S. Berger, Tel Aviv Medical Center, personal communication).

**Morbidity in Rural Eilot District**

In December 1999, a 34-year-old female from a southern rural community was hospitalized in the Chaim Sheba Medical Center Tel-Hashomer with neurological symptoms compatible with encephalitis. In view of concurrent reports on WNF in Tel Aviv and the lack of any other diagnosis of the causative agent, the patient’s serum was tested for WNV IgG and were found to be high positive (>1:48,000) and IgM positive. The patient’s residence in the Eilot region, where birds infected with WNV were previously found, suggested that human infections might be prevalent in

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**FIGURE 3. Seroprevalence of antibodies to WNV in the general population according to age.** Sera were collected in 1998 and chosen from areas with no reports of WNV. Screening was done by IgG ELISA.
the area. The patient’s community physician and nurse were then contacted for information on unusual morbidity in the area and for collection of serum specimens. Of 37 sera collected in the patient’s community (Ktura), 33% were positive for WNV IgG, half of them with high titers (>1:6400). Some of the people reported having recent clinical symptoms resembling WNF. An expanded serosurvey which included most of the rural communities in the Eilot district is shown in Figure 4. The IgG prevalence ranged from 21% to 82%. The IgM prevalence ranged from 0% to 73% with direct correlation to the IgG prevalence. Since this small cohort comprised various age groups and a mixture of healthy and symptomatic individuals, a thorough epidemiological analysis was not pursued. However, the average 67% IgG prevalence and 30% IgM prevalence in the Eilot district were strong indications of active WNV circulation in this region during and preceding the study period (January–April, 2000). A retrospective investigation revealed two cases of encephalitis and meningoencephalitis in young adults from two adjacent communities, whose IgM were positive and IgG titers were 1:12,000 and 1:100,000. These data suggest that an outbreak in the Eilot district preceded by several months the outbreak in the central and northern regions of Israel.

**WNF Outbreak, August–October 2000**

Starting in mid-August and lasting until the end of October high morbidity from WNF was recorded throughout the entire country (Fig. 5). The total number of cases, including sporadic cases in July and November 2000, was 439, with 29 fatal cases (4 additional patients with WNV IgM died from complications of other diseases). The outbreak started in central Israel and spread north and south. The highest attack
rates were in the center and the lowest were in the South. During the outbreak, laboratory diagnosis was based on the capture IgM ELISA assay, which was done at 1:100 and 1:2000 serum dilutions and 1:10 and 1:100 in CSF samples. The turnaround time for reporting results to physicians and to the Epidemiology Department of the Ministry of Health was 24–48 hours. The outbreak dynamics, reflected by the weekly cases tested and the percentage of positive patients, are shown in Figure 6. Interestingly, the percentage of positive cases was the highest at the beginning of the outbreak and declined gradually. This reflects the increasing awareness of physicians and perhaps also the public panic, which was augmented by media reports.
Clinical data available for 233 hospitalized and 37 ambulatory patients revealed that 73% of the hospitalized patients had some form of CNS involvement, while only 8% of the ambulatory patients had mild encephalitis. Morbidity increased significantly over age 45 (69% of the cases, Fig. 7) and mortality increased dramatically over age 65 (96%) as shown in Figure 8. Morbidity and mortality rates in males and females of all ages were almost identical (data not shown).

**Virus Isolation and Phylogenetic Analysis**

During the outbreak no attempts were made to isolate virus or diagnose cases by molecular assays (RT-PCR). After the outbreak, specimens stored at −70°C were used for virus isolation. Virus isolation from serum was successful from four living WNV IgM-negative patients. Patient 1 (WN_0043) was a 51-year-old female from the central region. Patient 2 (WN_0233) was a 20-year-old male from the north-central region. Patient 3 (WN_0247) was a 5-year-old male with encephalitis residing in the center. Patient 4 (WN_0304) was a 55-year-old female from the north. Only the 5-year-old patient developed meningoencephalitis, while the others did not develop a CNS disease. All four virus isolates were confirmed as WNV by IFA. The WNV isolates derived from patients 3 and 4 had grown faster on Vero cells than those isolated from patients 1 and 2 (4 days versus 7 days, respectively). Isolates from patients 3 and 4 were positive by RT-PCR directly from serum; positive RT-PCR results from all 4 isolates could be achieved after culture amplification. The analysis of the four isolates is presented in Figure 9.
FIGURE 7. WNF cases in different age groups, during the outbreak, Aug.–Oct. 2000. Assayed by CAP-IgM ELISA.

FIGURE 8. Mortality rate during the WNF outbreak in humans. Morbidity by age.
RT-PCR, sequencing and phylogenetic analysis of a region encompassing 1662 nucleotides of the PrM, M, and partial 5′ E genes revealed two lineages. One lineage comprised two identical isolates from central Israel and was most closely related (99.7% homology) to flamingo, mosquito, and horse isolates from New York, 1999, or Israeli gull, 1999. The other lineage, comprising two isolates from the north and north-central regions of Israel was most closely related (98% homology) to an avian isolate from northern Israel, 2000, a mosquito isolate from Romania, 1997, and to a Russian isolate from the 1999 outbreak in Volgograd. The presence of two lineages is compatible with an endemic situation or with repeated introductions.

**DISCUSSION**

WNF is not a reportable disease in Israel, but several outbreaks and clinical cases were documented between 1951 and 1982. The last outbreak in Israel was in 1980 and the last three encephalitis cases were reported in 1981. The large outbreaks in Romania in 1996 and in southern Russia in 1999, and the reappearance of WNV in...
migratory and domestic birds in Israel, presaged the reemergence of the disease in humans, potentially on a large scale, in Israel. To investigate the extent of human infections by assessing the population immunity and tracing human cases, we have re-established diagnostic abilities in the CVL. New and improved ELISA methods for detection of IgG and IgM antibodies were developed during 1998–1999 and virus isolation, neutralization, immunofluorescence and RT-PCR assays were established. Concomitantly, serum specimens were collected from volunteers in communities considered to be at high risk of infection (goose farmers and veterinarians and residents of communities located along bird migration routes). Control sera from the general population were collected in 1998 from the CVL serum bank. We found that the seroprevalence in the general population in 1998 (22% in adults) was lower than the seroprevalence reported during the 1980s, which reached 42%. However, our sample size was small (60 adult control sera) and cannot support any final conclusion. Studies with much larger samples are under way, with special attention to new immigrants and their place of birth.

By following the flyways of sick birds, we detected recent human infections in two population groups: (a) goose farmers and veterinarians residing in the central region of Israel who came in close contact with sick geese, and (b) members of rural communities in the southernmost region of Israel (Eilot district). In both groups we found high IgG prevalence and high IgG titers, and a high rate of IgM positivity in the Eilot district population. All these are markers of recent WNV infection. Reports from many of the volunteers from these two groups describing a recent WNF-like illness and the three encephalitis cases in the Eilot district were compatible with the laboratory data. The data collected by our investigations prior to the outbreak confirmed that WNV was active in recent years and human infections were very common around goose farms in 1998 and 1999 and in Eilot in 1999.

The two fatal human cases, which occurred in Tel Aviv in the late summer of 1999, were a clear indication that the virus spread was not limited to rural areas. Repeated alerts issued by the Ministry of Health to all health-care providers in Israel prompted infectious disease specialists to include WNF in the differential diagnosis of high fever and encephalitis cases. This resulted in a large number of laboratory-confirmed cases which were identified during the late summer and fall of 2000, forming an outbreak-like epidemiological curve. An unusual feature of this outbreak was the spread of the disease in almost all highly populated areas of Israel, including primarily the central and northern regions. This is in contrast to previous outbreaks which were more localized and were reported in one region only each time. Viruses isolated from four patients’ sera were sequenced and showed two clusters. Of particular interest is that these two lineages corresponded to the lineages found in birds in Israel, presenting a similar geographic distribution: a strain most similar to the Romanian-1997 strain was found in patients residing in the north, and a strain most similar to the New York-1999 strain was found in patients residing in the central region. Although the number of human isolates is too small to draw any conclusions regarding the routes by which the virus spreads or any association of virus strain with the severity of the clinical symptoms, the finding of two lineages suggests either that the virus has been endemic for many years (supported by the high prevalence of antibodies in sera from 1998) or that migrating birds have introduced several virus strains concomitantly in recent years.
Alternatively, one can hypothesize, based on the early signs of disease in geese in 1997, that after the 1996 outbreak in Romania, a new strain with a modified genome was introduced into Israel’s local birds via migratory birds. By finding geese as new, highly susceptible hosts the WN virus was amplified and might have changed further and passed on to other birds, mosquitoes and, with the overflow, to humans. Changes in the viral genome could have happened in recent years via a dynamic process in Africa, Europe, the Middle-East or Israel. Isolation and phylogenetic analysis of viruses from many birds, mosquitoes, and humans, and comparisons to isolates from other countries, may provide more clues to the virus zoonotic cycles and routes of spread.

The conditions that allowed the development of such a widespread morbidity are complicated and include in addition to the virus also environmental and host-related factors which require further investigation. The increased morbidity could be attributed to the following promoting factors (as recently suggested by Lustig et al.): (a) climatic factors—consecutive warmer-than-usual summers for the last three years in Israel (Israel Meteorological Service, personal communication) might have forced the bird population to congregate at diminishing water sources, increasing the bird to bird transmission via mosquitoes carrying more virus particles than usual, and finally leading to transmission to humans. Similar climatic descriptions were observed in Romania, Russia and the northeastern United States. (b) Demographic changes—in the early 1990s approximately one million people from Russia moved to Israel as did immigrants from other countries and foreign workers who most likely had not been previously exposed to WN virus. These immigration waves apparently increased the size of the population susceptible to WNV infection.

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