

SUMMARY
Centers for Disease Control and Prevention (CDC)
Clinician Outreach and Communication Activity (COCA)
Clinician Briefing: WEST NILE VIRUS
June 29, 2004

Emily C. Zielinski-Gutierrez, DrPH
Behavioral Scientist
Bacterial Zoonoses Branch
DVBID, NCID, CDC

****Please note:** *Data and analysis discussed in these presentations were current when presented. Data collection and analysis are ongoing in many cases, therefore updates may be forthcoming elsewhere on this website, through publications such as [CDC's Morbidity and Mortality Weekly Report](#) or other venues. Presentations themselves will not be updated. Please bear this in mind when citing data from these presentations*

OVERVIEW – WEST NILE VIRUS

- First discovered in 1937 in the West Nile district of Uganda
- Mild feverish illness
- Severe illness, like meningitis or encephalitis, was rare
- Wide distribution in Asia, Eastern Europe, Africa
- Transmitted by mosquitoes
- Can infect people and other animals
- Similar to some other viruses, such as *a flavivirus*, in the Japanese Encephalitis Antigenic Complex
- Also similar to other families, such as yellow fever, and St. Louis encephalitis (SLE) virus

The most recent update on the West Nile virus (WNV) situation in the United States follows. This will be posted on the CDC Web site, which you can find at: www.cdc.gov/westnile

- Activity is starting to heat up, which is typical for mid-June. This year we have seen continued westward movement. That is confirmed by the fact that the two top reporting states (in terms of cases actually reported officially to CDC) are Arizona and California. See www.cdc.gov/westnile for updated figures.
-

Some interesting things, certainly when you think about the southern parts of California and Arizona, is WNV activity is focused in the Phoenix area, not what you think of as a prime mosquito habitat. We're seeing a very different ecology than we were familiar with in the East (and from the Rocky Mountain region where we had the most intensive activity last year). While that makes it fascinating from the point of view of investigators and ecologists, it's also really quite a concern from the clinical perspective, because you have people in a huge variety of ecologies who may be at risk. There are [approximately] 37 or 38 different mosquito species that can be infected with the virus.

- Last year by the end of the year, we saw among the 9,800 cases that were reported:
 - About 25 percent of those were neuroinvasive disease
 - The balance was West Nile fever.
- As of June 29th, we have 35 of the cases are neuroinvasive and the 19 are fevers.

There is some intensive activity occurring. And not necessarily everyone with fever symptoms is getting diagnosed. It will remain to be seen how the season shapes up, but we certainly expect another year of intensive activity.

Additional online resources are also on the CDC Web site, www.cdc.gov/westnile :

- A clinical guidance page,
- A laboratory guidance page, and
- A link: **Physician's Information and Education Resource Guidance Statement on West Nile Virus Disease.** <http://pier.acponline.org/physicians/public/d951/d951.html>

This link does have a series of guides, everything from prevention to diagnosis. And it takes people through patient follow up.

BACKGROUND

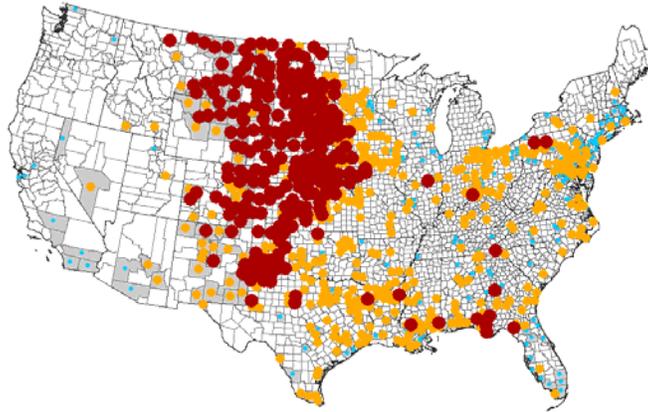
- Before 1996, WNV did exist. People only became aware of it in 1999 when it got to New York. However, it was discovered in 1937 in the West Nile district of Uganda, hence the name. Before 1996, it was primarily a mild feverish illness. The more severe illness such as meningitis or encephalitis was really quite rare. The virus does have a wide distribution in Asia, parts of Eastern Europe, and in Africa.
- The virus is considered an arthropod-borne virus (an arbovirus, for short), and it's transmitted by mosquitoes, the only arthropod known to transmit WNV. It can infect both people and a number of other animals, and it is a flavivirus, it's in the Japanese Encephalitis Antigenic complex. It's in a similar family to yellow fever, SLE virus, and dengue virus, for example, which can occasionally cause some issues with diagnostics.
- The basic transmission cycle of WNV is primarily through birds and mosquitoes. There are over 100 species of different birds that function as amplifying hosts, and that's the important thing that a lot of the general public is not always aware of. While humans and horses, for example, as well as a large number of other mammals can become infected, we're very unlikely to have a role as an amplifying host. The viremias are too low to be infective to new mosquitoes.
- We know that birds (certainly the corvids) exhibit a higher mortality. Those function as a very good part of the surveillance system in some areas. For example, one of the things we're currently seeing in Arizona is that they simply do not have significant corvid populations, so identifying which bird species are going to be good sentinels in terms of finding dead bird mortality is a whole other question. Humans are functioning as sentinels in that particular ecology.
- Again, the primary cycle is between the mosquitoes, mostly *Culex*, although there are 50 different species, including some *Aedes* that can act as vectors (at least in theory). But what we primarily are concerned about are *Culex pipiens*, *Culex quinquefasciatus* and *Culex tarsalis*, depending on the region.

MOVEMENT

The movement of the virus across the country has been something that's very much been followed by virologists and ecologists, as well as clinicians, throughout the first four years:

- In 1999, the activity was just around the greater New York City area,
- Some spread in 2000, but very few human cases,
- In 2001 [there were] still under 100 human cases, although there were a greater number of counties across the East, along the eastern seaboard and a little bit into the Midwest, reporting some level of ecological activity.
- In 2002, we had just over 4,000 human cases reported, most of which were neuroinvasive illness and activity throughout the Midwest and into the South, and started to spread toward the Rockies.
- We saw that westward expansion continue in 2003, with the states in sort of the Great Plains, Colorado, the Dakotas, Nebraska, as well as a number of other areas, and still some intensive activity back in the East, as Pennsylvania had more than 200 human cases.

- We just keep seeing the wave of the most intense activity shift westward.



Many of these were rural counties, which might not necessarily be what people would expect, given the history of some other vector borne diseases. But [WNV can be found] where you have *Culex tarsalis*, which a very competent and efficient vector— and linked to irrigation. [This] is what we see in many of the rural areas. You can see a tier from the Canadian border not quite yet to the Mexican border, but even in counties that have a very sparse population [have] a quite high incidence rate (e.g., Wyoming and Nebraska). That has changed the character of the disease from its initial recognition in New York City, the outbreaks in the Greater Chicago area, and in New Orleans in 2002, to a much more rural, and in some ways to a semi-rural epidemic last year.

TRANSMISSION

Transmission, the most important route of infection, is the bite of an infectious mosquito. Certainly in 2002 there was a great deal of attention to some of the novel modes of transmission that were recognized, notably blood transfusion, as well as organ transplantation, intrauterine infection, and percutaneous exposure. That step is primarily occupational and also a fairly small number of cases. Then there's also probable transmission through breast milk that has been reported.

BLOOD SUPPLY and WNV

- The screening of the blood supply is certainly a salient concern for people. As of July of 2003, all blood donated in the United States is now being screened for WNV, using nucleic acid amplification testing rather than antibody screening. This testing is still being conducted under an investigational new drug protocol. The fact that the blood transfusion risk was recognized and then IND testing was in use in less than a year was a feat, considering the large number of agencies [FDA, CDC, the blood industry] that were involved. Some questions are still remaining—CDC and others are looking at minipools vs. individual testing when areas experience more intensive transmission.
- Some of the blood donation collection agencies have decided they will switch from testing minipools of donations to checking individual donations. Obviously there's a huge increase here in terms of cost and time, but the greater sensitivity would yield results in the presence of very, very low viremias. If you look on the CDC Web site, under Q&As about blood donation and blood transfusion transmission: <http://www.cdc.gov/ncidod/dvbid/westnile/qa/transfusion.htm>, there's a link directly to the MMWR: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5313a1.htm> [for further information].
- There were some breakthrough infections detected last year. Viremias might have been suspected to be too low to actually be infectious, but that's what prompted a lot of the concern about whether or not individual [blood] donation testing would be needed.

- The algorithms are still being completed and worked out, and will be put in place in areas of intensive transmission. So presumptively viremic donors, the people who come in to donate blood, and have absolutely no recognition of the fact that they could be infected, because they are entirely asymptomatic. They are very important for surveillance in a number of regions, and an important tool that is a by-product of the blood supply screening.
- The MMWR and CDC's WNV website will provide updates as more information is found out about the way the blood supply screening is functioning. At this point, people feel confident in saying that the risk through transfusion is extremely low. It is not completely eliminated, however, and certainly with the move to individual donation testing the risk will become even lower.

VECTORS BY GEOGRAPHY, BEHAVIOR, AND FEEDING

- *Culex tarsalis* (western states)
 - *Culex pipiens* (midwest, and elsewhere)
 - *Culex quinquefasciatus* (south)
 - Different behaviors – some fly very long distances
 - Feeding habits, infection rates, breeding are all important
 - Nearly 50 species are capable of transmitting WNV; *at least in the laboratory*
 - The important vector really varies by geography. We will probably be looking at some important *Culex tarsalis* link to an outbreak in the West again this year.
- The important thing is mosquitoes have very different behaviors. The way that people can be at risk, and the type of activities that patients engage in, may make them think that living in the desert (and golfing) is not a big risk. Well, if it's an irrigated golf course, they may, in fact, be at risk.

WEST NILE VIRUS ~ HUMAN INFECTION

- Prior to 1996, WNV was primarily a mild illness with some fever, and outbreaks were rather infrequent. [In fact] WNV probably was not detected. Mostly young adults were affected and there was rare involvement of a neuroinvasive illness. Since 1996:
 - There have been more severe illnesses,
 - More of those people who became ill have died,
 - More older adults have been affected,
 - More frequent outbreaks have been noted, and
 - There has been an increase in reporting in meningitis and encephalitis.
- Serosurveys that have been done here in the United States (with fairly consistent results) show about 80 percent of people are asymptomatic and never realize that they had any type of infection at all. Roughly 20 percent develop West Nile Fever and then approximately one out of 150 have severe infection. Less than one percent do develop CNS disease (i.e., meningitis, encephalitis and now acute flaccid paralysis). Approximately 10 percent of the CNS cases are fatal.
- What this means is a great deal more virus activity is in the area than what may come to [the public's] attention. Certainly we do know that the 20 percent of fever cases, do not all get diagnosed.
- Most of the people who get sick from West Nile infection have West Nile fever. The time from exposure, typically the mosquito bite, is about three to fourteen days, but it can vary. The symptoms include fever, chills, headache, fatigue and these can be severe.
- While typically in the past, we have used words like "mild disease" to talk about West Nile fever, we've tried to get away from that. We've seen people who have reported persistent headache and

fatigue for weeks and even longer, among otherwise healthy people. A rash can also be a feature of a West Nile fever infection.

- Meningitis is similar to meningitis from other viruses; fever, headache, white blood cells are seen in the cerebral spinal fluid, and the headache may be quite severe. Most people do improve, although some report persistent headache and fatigue.
- Encephalitis can range from mild confusion to coma and death, and people who are over 50 or those who have other chronic medical problems, are usually the ones who will develop West Nile encephalitis. There are a number of other problems that people with West Nile encephalitis may suffer. They have problems with balance, dizziness, and again with an extreme headache. Those may include a tremor. A quick uncontrolled muscle jerking is often tells people that there's something extreme going on, and they need to seek medical attention.
- A newer phenomenon (since 1999), (not necessarily that it's newly occurring, but more that it's newly documented) is the West Nile associated acute flaccid paralysis. This has been identified more frequently over the last two years. It's really not known exactly how frequently this may be happening, and it does tend to affect relatively young people who are otherwise healthy. These are often what you see in news stories, because they tend to attract more attention.

The person may not present with a fever or headache before paralysis, and many cases are marked by persistent weakness. One of the clinical hallmarks is the onset may be early in the infection. The weakness may only be in one limb. A great deal of study is ongoing to follow these cases and try to clinically describe the whole spectrum. There's an absence of numbness, although sometimes pain is present. I think we'll be seeing more of what is sometimes described as a poliomyelitis-like illness in the next several months. It's something that has caused a lot of intrigue in clinicians who are working with, and following up, these cases—*especially in the area of prognosis*.

DIAGNOSIS OF WEST NILE VIRUS

- Diagnosis of West Nile virus infection is based on:
 - A high index of clinical suspicion, essentially if virus activity, mosquito, dead bird, veterinarian activity, as well as human activity has been reported in a specific area, *and*
 - Obtaining specific laboratory tests
- In many areas of the U.S., you need to consider other arboviral diseases, such as SLE, and other unexplained causes of encephalitis or meningitis
- In older adults, WNV should be considered as an explanation for encephalitis or meningitis, especially in the summer and early fall. The local presence of enzootic [bird, mosquito, vet] activity should raise suspicion. And travel history can be important. A great number of people, who came to the Rockies for a vacation last year, left Colorado with the West Nile infection. There is importation of cases, even just within the U.S.
- Testing can be obtained, typically through your local or state health department, and now increasingly through private laboratories. The public health laboratories typically perform an IgM antibody capture enzyme-linked immunosorbent assay [MAC-ELISA]. With the test, the virus specific IgM can be detected in nearly all CFS and serum specimens from a West Nile-infected patient, at the time of their clinical presentation
- The serum IgM antibody can persist for more than one year in some cases, so physicians will need to determine whether the antibody is a result of a current or a previous WNV infection. You can get a positive result that's not related to the current clinical presentation. In areas of new activity, it is

obviously less likely. If you are looking in an area that had activity last year, it does make it a bit more difficult to identify WNV.

- The most conclusive test to identify a person with a CNS infection is WNV-specific IgM in CSF, using the MAC-ELISA. This strongly suggests an acute CNS infection. If no CSF specimen is available and you're using serum, paired acute and convalescent-phase samples should be acquired. The acute can be gathered at the initial presentation, and convalescent seven to fourteen days later. This obviously presents some challenges in getting convalescent samples. However, if there's no convalescent sample, the acute specimen can be tested with MAC-ELISA.
- If the sample is IgM negative, West Nile infection is unlikely; but if it's positive and clinically compatible it may be a recent WNV infection. Be alert for the possibility of *other* flavivirus infections, particularly SLE. It is possible to use plaque reduction neutralization testing (PRNT) to confirm if you're in an area that has SLE. [The patient may have had] a recent vaccination for yellow fever or related flavivirus infection, such as dengue. If you have someone with a travel history in Latin America or Asia, it would be important to collect that information.

There's a good deal of detail about diagnosing, both on that PIER website and on a fact sheet for clinicians on the CDC clinician resources page on the WNV URL.

REPORTING WNV

Reporting varies by state and we refer you to your state WNV coordinators. Check your state health department websites, to see exactly how they want to handle reporting. Neuroinvasive disease is nationally notifiable and I don't know what decision was made a couple of weeks ago, in terms of whether or not fever would be reportable. States at this point still differ in their reporting [requirements].

WNV ILLNESS OUTCOMES

In terms of illness outcomes, there's not a lot of information currently available. The fatality rates overall have been roughly 10 percent of those with severe disease. Reported fatal outcomes are primarily among the elderly or those who are immuno-suppressed. I think the median age of fatalities last year was in the 70s. We still don't have a lot of risk factors to explain why some people do get ill, and others remain nonsymptomatic, other than age.

WNV PATIENT QUESTIONS

“When am I going to feel better?”

Most people eventually do get better, based on limited observations we have to date—but it can end up taking a number of months. The outcome for the poliomyelitis illness in particular (which has been studied more in-depth than some of the others) can have varied outcomes. Some people have had dramatic recoveries and others have had continued weakness. Again, we don't necessarily know what factors predispose some people to improve more than others.

“If I get infected, am I still at risk for WNV?”

Essentially, people do develop long-lasting, if not lifelong immunity, after infection. Most certainly they could still be subject to SLE if that's in the area. This doesn't mean that you get a free pass on mosquito bites for the rest of your life, unfortunately.

“What is the status of a human vaccine?”

There are several agencies and companies working on a vaccine for humans, and some testing planned for later this year, but it's probably still several years until there's a workable human WNV vaccine on the market.

TREATMENT

In terms of treatment, there are a number of proposals that are out there.

- There's one clinical trial that meets the complete standards for CDC (for referral) being conducted by NIH. There's a link to get information on that trial off of the clinical practice WNV URL [<http://www.cdc.gov/ncidod/dvbid/westnile/clinicalTrials.htm>]. There are a number of other studies being conducted that don't meet the criteria of being IRB reviewed. Some of the criteria that's in place include:
 - Randomized,
 - Double-blinded,
 - Placebo-controlled, and
 - IRB approved
- It would be important when patients come to you with trial information they have heard about to investigate the protocol being used.
- Because treatment is symptomatic, *prevention is really critical*. The prevention measures people can take is to engage in the use of personal prevention; things like using insect repellents (those containing DEET are really the most effective). While this is important for everybody, it's particularly important for those at higher risk of neuroinvasive disease:
 - People with a chronic condition, and
 - People over 50
- Certainly you can encourage anybody who doesn't want to lose a few weeks of their summer and potentially have neuroinvasive disease, to use.
 - Personal protection
 - Be aware of mosquito bites from dusk to dawn when the biting times are the most intensive, and
 - Use insect repellents with DEET, integrating that as a regular behavior during summer months

QUESTION AND ANSWER SESSION

Dr. Dan Baden:

Looking at the blood supply, you said the testing changed from the nucleic acid amplification from antibody testing. Will that allow us to detect the people earlier, before they've developed antibodies?

Dr. Emily Zielinski-Gutierrez:

Sure. Let me clarify a little bit. Typically when an individual goes to their physician we're using antibody testing, because if you sort of plotted out the viremia and the antibody response the viremia is very short-lived. So by the time somebody feels enough symptoms to go in, they typically would not have a detectable virus.

We're looking at exactly the reverse situation with a blood donor who's going in, because they always ask you if you feel any symptoms on that particular day that could indicate some kind of infection. Thus, you're already deferred by that point. What you really want to identify is the person who may be going to develop symptoms in two days. They would still be viremic, or they're never going to develop symptoms and they're in that viremic phase of their infection.

That's exactly the point. The nucleic acid amplification test permits us to identify the people who are earlier in their infection and who are infectious and have simply not developed enough of any [symptoms] or enough of an antibody response yet. That's because people do develop such low viremias. It's good on one hand, because it means that they're not infectious to new mosquito bites. But on the other hand, it means that there's a real challenge to identify them *and keep them out of the blood supply*. That's where the difficulty came in last year. I think we were looking at six cases (maybe) of people who had undetectable (through the current testing protocol) viremias.

Once they went back and looked at the individual samples, they were just very low logs of viremia. Still it was enough, amazingly, to be infectious. That's the real challenge right now, where to draw that line. How sensitive can you make a system where it's still sustainable?

Dr. Dan Baden:

I've got a second question, if I may. I'm looking at the IgM and the testing for IgM in the cerebral spinal fluid. I'm thinking that IgM doesn't cross the blood brain barrier, and I'm trying to see if that's part of the reason why you're checking for IgM. Can you talk about IgM versus IgG, or anything along that line?

Dr. Emily Zielinski-Gutierrez:

I probably would want to refer you to somebody in our laboratory who can answer some of the specific questions, because they work with so many samples. But I believe that if you do see IgM in CSF, that will pretty much tell you the likelihood is that you do have somebody with an acute CNS infection. What we can do is make sure the information is clear on the CDC website, because that has been a question that has come up time and again, especially with people trying to identify whether or not to submit to giving a CSF sample -- perhaps a lab person can give us a good range of what they've been seeing, as far as CNS specimens.

Dr. Dan Baden:

I'm curious about the flaccid paralysis, poliomyelitis-type or like illness. For example, how do you differentiate that from general CNS, the meningitis, and the encephalitis? Are they a subset of that? Will they have similar symptoms?

Dr. Emily Zielinski-Gutierrez:

Let me stipulate that the investigation of these is primarily happening within the last two years. There has been a lot of clinical follow-up in 2003 to try to understand that range of symptoms. But as I understand it, one of the issues that has come up is people who have acute flaccid paralysis are typically younger than those who have meningitis or encephalitis. They may not have other symptoms. The severe headache is very much a hallmark of the meningitis and the encephalitis cases and [these patients] may not have those symptoms. They may not even have a fever in the acute flaccid paralysis illness. It does have a different clinical onset. And they may not have any of the mental confusion that occurs with the encephalitis patients and can have a whole range of just some asymmetrical weakness to the people who have ended up with respiratory.

Essentially some of the fatal cases with flaccid paralysis have been respiratory failure, because they have had paralysis in a number of regions. Those have been, obviously, clinically fascinating cases, but it's a great concern, because you do have these younger, often vibrant people. A lot of times their infection has been linked to the fact that they were outside and engaged in sports, or coaching football or baseball, and exposed to a number of mosquito bites. The younger age and the absence of both fever and headache have marked the [some] flaccid paralysis cases. In retrospect, people are now looking back and seeing, even in some of the earlier cases in 2001, that there was some lingering weakness reported in certain limbs.

Dr. Dan Baden

That is interesting; tragic, but interesting.

Dr. Emily Zielinski-Gutierrez:

Yes. The number of cases in which that happens is something like 15 percent of all cases with CNS involvement. They may have some aspects of acute flaccid paralysis. There is an increasing effort to identify those [cases] and to get a better catalog. Currently, they're reported as neuroinvasive illness [note: AFP cases can be reported separately from other neuroinvasive disease], so it's not always possible in the surveillance data to separate [the information] out. It takes a lot of intensive investigation involving local health authorities and local physicians to followup and get complete histories.

If there are people who have an interest in that, and there are cases in your practice, or in those of people in your groups, case history reports [will be of great interest]. [This is especially true] on the flaccid paralysis cases, meningitis, and encephalitis cases, and is even [documented] on a cohort of fever patients. There's a lot of room in the medical literature for those in order to start forming a body of evidence and documenting what's happening with these cases.

Dr. Dan Baden:

That's good to know, too. My understanding is that these are [cases] in otherwise healthy people, right? Not people with underlying neurological problems?

Dr. Emily Zielinski-Gutierrez:

A number of the flaccid paralysis cases are, as are the encephalitis and meningitis cases. There's some evidence to say that people who had (again we're looking at a relative handful of cases) [transplantation surgery]. These patients in particular developed severe illness. That was because there was a very alert physician at a transplant program who noticed a number of her cases had WNV. Those were followed up extensively. Those people did develop a severe illness. There's some validity that people with other chronic conditions are at particular risk.

A good number of the cases that you see, even in your kind of typically healthy seventy year old who's spending a bit of time outside, is doing something [such as playing in the garden or participating in sports] to put them at risk. These tend to be the people who are infected. But is that because of their risk exposure? There's a need to separate out if it's their biological risk factors that are predisposing people, or is it the fact that they're otherwise healthy and able to engage in outdoor activities that put them at risk?

Dr. Dan Baden:

Following up on what you were saying, Emily, is there any indication that the level of disease that people will acquire is related to the level of viral load? If they get 15 mosquito bites from infected mosquitoes, will they have a worse disease than one infected bite?

Dr. Emily Zielinski-Gutierrez:

There's really not any data on that for a couple of reasons. The number of infected mosquitoes in an area is generally not so high that you would expect one person to get several infected bites. Then the other issue is that typically we rarely get people in the viremic phase of their illness. By the time they're symptomatic, it isn't possible to assess the viremia that has developed.

Dr. Dan Baden:

My last question is related to the vaccine and the potential vaccine trials that you mentioned that may come up this year or in a year or so. Is there any way that people can find out about participating in those trials?

Dr. Emily Zielinski-Gutierrez:

Acambis has the product that would be most likely to come to trial soon, and certainly once they have a trial that's been fully approved, we'll be posting information on the CDC website about that, depending on how they're seeking participants. In the meantime [you can check] on the Acambis website (<http://www.acambis.com>) to see what the status is of their trials.

COCA ANNOUNCEMENTS

- **Our next call is scheduled for July 20th, at 2 p.m. Eastern Daylight Time. We're currently planning to talk about nerve agents. Dr. Ziad Kazzi will be presenting the overview and Q&A session.**
- **We hope to have our COCA Web site up by July 20th, where you'll be able to have COCA overheads and summaries available to our members—and many other items that can potentially be of service to COCA members.**
- **If you have questions that you think of after this presentation, you can submit those to coca@cdc.gov and you can also call the office. Those numbers are included in the COCA weekly updates.**

###