

**Anencephaly Advisory Committee Meeting (webinar)  
Minutes  
November 19, 2015**

**Advisory Committee Members present:**

Kathy Lofy, MD, Chair  
Susie Ball, MS  
Sara Barron, RN  
Gina Legaz, MPH  
Peter Langlois, PhD  
Amy Person, MD  
Christopher Spitters, MD  
Sarah Tinker, PhD  
Vickie Ybarra, PhD, MPH, BSN

**WA Dept of Health Staff present:**

Mike Means  
Zachary Holmquist, MPH  
Cathy Wasserman, PhD

Interested parties were sent information about the meeting and asked if they wanted to participate. There were several interested parties on the call, including representatives from the media.

**I. Welcome and Introductions**

Kathy Lofy began the meeting at 8:00 am with a quick introduction. Minutes from the June and August meeting were approved.

Cathy Wasserman gave a presentation updating advisory committee members on the status of surveillance, investigation and prevention efforts. (attached) The presentation included new numbers of cases confirmed since April 28, 2015, and the following highlights:

**Surveillance Update:**

- 2 new cases: 1 spina bifida cases and 1 anencephaly. Total number of neural tube defect cases in the 3 county area is 64 confirmed NTD since 2010, including 41 cases of anencephaly.
- Continue to see that there is no strong pattern in the timing or seasonality when cases occurred.
- Updated statewide data using vital statistics and linked files only. Have first nine months of 2015 which included 19 anencephaly and 37 NTD cases. Note that these cases are from vital statistics files only and have not been confirmed. They may include false positive cases, and do not include pregnancies that were lost or terminated prior to 20 weeks gestation.

**Investigation Update:** (Note this includes information from clarifying email sent after the call)

- Continue to follow up with 7 case mothers confirmed since April. We learned of 3 mothers in April and began follow up with two at that time. Letters were sent to both physicians and then to the mothers and we have called these mothers several times, but not yet 10 times. At 10 times, we will discontinue calling. The third mother was still pregnant and we were waiting until 6 weeks after delivery to contact her as was our protocol at the time. We began follow up with her in early November. We confirmed two cases by early August, and began follow up with them in October. One of these women

declined to participate, and the other is still under follow up. We identified an additional two cases at the end of October and began follow up at that time.

- Information sent to CDC.
- We are planning basic analysis of the data gathered by interview due to small numbers. If there is a signal that something may be going on, we can go more in-depth.

#### Addressing Community Concerns: Nitrates

- Concerns expressed by public during August call.
- Reached out to Dr. Jean Brender who has studied nitrates and congenital malformations for 20 years. She provided a book chapter that she recently completed that examines nitrates, nitrites, and n-nitroso compounds.
- Mechanism by which nitrates might be hypothesized to cause neural tube defects would be by endogenous formation of n-nitroso compounds. N-nitroso compounds have been shown to be teratogenic in animal studies.
- Drinking water only contributes a small portion of dietary nitrates if concentration is below the 10mg/L concentration.
- Nitrates in the diet are commonly found in vegetables, along with vitamin C.
- Nitrates by themselves do not create these n-nitroso compounds. They must be in the presence of nitrite or amines/amides to form the potentially teratogenic compound.
- Many common drugs are nitrosatable.
- n-nitroso exposures come from a variety of internal and external sources. We would not expect a simple association between anencephaly or all NTDS and drinking water nitrates below the maximum contaminant level of 10 mg/L alone.
- Nitrate in drinking water does not appear to be a clear risk factor for NTDs by itself. To be cautious, we did look at potential drinking water nitrate exposure for the 64 NTD-affected pregnancies.
- Of 64, we have drinking water information on 61 cases. 49 or 80% were on public water systems.
- Using the sensitive window (3 months before pregnancy, through the end of the first month after conception), we measured the nitrate concentration during that period. If there was no measure available during that period, we selected the closest testing date and used the highest nitrate concentration sampled.
- Looking at women on public water supplies. For the 32 mothers of anencephalic infants, the minimum level measured was 0.05 mg/L. The maximum was 9.26 and the average was 1.89. Only 1 residence had a measurement above 5 mg/L.
- The maximum nitrate level and the average nitrate level do go up a little bit when we included information we extrapolated for private water systems, but values are still below the 10mg/L MCL.
- We can say that mothers of children with NTDs in the three county area do not have troubling concentrations of nitrates in their water supplies.

#### Addressing Community Concerns: Pesticides

- Pesticides are challenging to study because of the large number of compounds in use, and most people are unaware of their exposure. Exposure can occur through multiple means, activities, and occupational exposures.

- A recent (2014) California study is the most rigorous study we have recently seen. The study calculated exposures within 500 meters of the case locations, and adjusted for a variety of covariates.
- It explored exposure to 461 chemicals, and 62 groups of chemicals. Overall, there were few associations found, and they may be due to chance based on the large number of analyses.
- We decided to explore the chemicals this study reported as associated with NTDS. We looked to see whether these chemicals are used in WA, and the potential for higher exposure in the three county area compared to the rest of the state and surrounding states.
- We looked at allowed pesticide use, reports of drift exposures, USGS maps of use across the country, whether compounds were identified in drinking water, and conducted discussions with Washington state agriculture experts.
- 6 pesticides: Abamectin, 2,4-D, methomyl, imidacloprid, permethrin, and bromoxynil octanoate. They all have different mechanisms of action.
- 5 of the 6 compounds are expected to have higher use in counties other than the three county area. Four of the compounds have significant use in the home environment, and are used throughout Washington for agricultural/non-agricultural uses. Methomyl and bromoxynil are agricultural use only.
- WSDA reports do not suggest that pesticide drift was an issue in the three county area.
- Methomyl is used more frequently in the three county area than outside of that area in the state, primarily in Benton. Methomyl is a carbamate, and has high acute toxicity. It is registered for use around dairies to control fly populations, and is the main ingredient in lannate used on potatoes, onions and wheat.
- CA and FL have much higher use of Methomyl than all other states combined, and if causal, we would expect to see increased rates of NTD in those states/areas.
- Our conclusion is that there is no clear association between pesticide exposure and NTDs.

#### Addressing Community Concerns: Genetics

- NTDs are associated with genetic factors, but those factors are not entirely clear.
- There are clinical concerns related to NTDs, and these should be discussed individually between a woman and her health care providers and genetics specialists.
- Our advisory committee is charged with investigating the cause of NTDs in the three county area. For our investigation it would be useful to separate out cases with a known etiology from those with unknown etiology. We hope to be able to do that with the fifteen cases that we've been able to interview.
- From a statistical standpoint, the number of women that we have been able to interview has been very small. This does not take away from the tragedy of this situation, but it does make firm conclusions about potential causes difficult.
- Some common polymorphisms in genes related to folate and homocysteine pathways have been associated with NTDs.
- One such variant is in the gene that codes for methylenetetrahydrofolate reductase (MTHFR). A common genetic variation is 677C to T. It results in reduced activity of MTHFR, especially at high temperatures. Individuals with 2 copies of the variant have low tissue concentration of folate and increased homocysteine levels. Can be overcome

with folate supplementation. This polymorphism is fairly frequent in the population at 5-14% of women – the majority do not have infants with NTDs, although there is a slightly increased risk of NTDs.

- It's more effective to recommend that women supplement with folate, rather than recommending genetic testing among all women of reproductive age.
- There is nothing to suggest that this polymorphism is more common in the three county area than elsewhere in the state. Even if it were, not all women with the polymorphism have infants with NTDs, so we would still want to identify a common exposure.

#### Prevention Efforts Update:

- Last meeting we talked about the non-profit Vitamin Angels providing free vitamins for distribution in the three county area.
- Vitamin distribution is ongoing in Yakima County. We are still waiting to see how many have been distributed at this point.
- Beginning mid-November, Benton-Franklin will begin distributing prenatal multivitamins from Vitamin Angels.
- Health Care Authority (HCA) and DOH have discussed coverage of prenatal vitamins for women of reproductive age on Medicaid prior to pregnancy. HCA will let the provider community know via written communication that daily multivitamin with folic acid supplementation is covered for women of childbearing age on Medicaid. That written communication is expected to be released shortly.
- DOH Folic Acid: B Aware materials are available for download and dissemination to clients online.
- Folic acid fortification of corn masa flour stability study has been completed and findings provided to the Food and Drug Administration. We are awaiting their decision.

#### Advisory Committee Comments

Advisory Committee (AC): Thank you for taking our concerns to heart and looking into it with such great depth.

AC: I want to echo Sarah's comments. My question is about the over the counter products that are associated with n-Nitroso compounds. In the fifteen women who have been interviewed, have you seen a lot of use of those over the counter medications or prescription medications that include nitrosatable compounds?

DOH: I haven't looked at that yet, but the CDC and experts will help us look into it. Slone group in Boston has recently looked at nitrosatable drugs and NTDs, but I haven't had an opportunity to look at that paper in relation to our current investigation yet. We are not sure how much time it will take to look into. The surveys are very extensive on their coverage of drug history, including the timeframe, the duration of that use, and other factors. It's a very extensive process. I don't know at this point how in depth we can look at that. We're hoping to characterize the proportion of women who have any exposure to these types of drugs, but we can't promise anything at this point. Sarah, do you have anything to add?

CDC: No, we should look at the women who have been exposed and go from there.

#### Public Comments:

Seattle Times reporter: Question about the seven cases that we've detected since spring that haven't been interviewed yet. Why haven't they been interviewed yet?

DOH: We are following up with five mothers. Two of them we have made numerous attempts to reach and haven't been able to reach. The additional three we have begun tracking in the last six weeks. We start by contacting the provider and asking them to contact the patients to let them know about the study, ask them if they would be willing to be contacted. If they refuse, we don't follow up with them further. If they are interested, we get in touch with them, get their consent, and schedule their interview. The interviews are very extensive and take a lot of time. It is sometimes difficult to find a time that will work for the mom.

Seattle Times: It sounds like you've just started the process. I would like to know why there is not more urgency in reaching out to them?

DOH: We are reaching out to them. We have had a change in staff. I don't think the time it's taking us to reach out is all that unusual in this sort of investigation.

Seattle Times: When we're talking about looking at the interviews that have already been conducted, are you saying that it is too difficult to look at those questions to see if they've taken those nitrosatable drugs.

DOH: We can certainly look into it, but we are going to start with if they have taken those drugs yes/no before doing additional analysis.

Seattle Times: Since we have a small sample size, and there doesn't seem to be a lot of urgency, I'm wondering why we can't look at these fifteen in more detail.

DOH: What we're doing now is entering all of these questions into a database. The questionnaire asks about many different health problems, drugs taken for the problem, times of use and for how long in order to assess exposure. It can take some time to determine the exposure level. We are hoping to compare levels we see to levels among other NTD cases and to controls. I would say we are moving with urgency on these issues.

Seattle Times: There are fifteen cases that have been interviewed. This has been going on for such a long time. To say that the data has not been entered and the state is moving with urgency would surprise people.

DOH: Thank you for your comments. Are there other comments or concerns?

Public: You're determining if a case of anencephaly was inside or outside of city limits. Did you map plot the cases within the city limits?

DOH: We looked case by case to see what water source they were on.

Public: Someone can have a Yakima address but not be on Yakima city water. Did you map plot to see if they were within city limits?

DOH: We're very well aware that even if you're within city limits it doesn't mean that you're on city water. We used the actual addresses to determine the source of water that they were on to determine the nitrate concentration.

Public: My next question is about the mapping that was used to test the nitrate concentration. I am hoping that you would tell me more about how you determined that?

DOH: I would like to clarify that it doesn't matter if you're in the city limits or not, there are multiple types of water systems even within city limits. We looked at each individual site to best see how they were served by water systems.

Public: Are you seeing clusters around certain zip codes or areas (i.e. lower valley vs. upper valley)?

DOH: What we observed was that we generally had more cases in the more populated areas. The zip codes have a variety of different size populations.

Public: There is a European Union standard for testing for nitrates in vegetables. I hope that you will maybe open that up for consideration because that would be another place that nitrate load could be coming in.

DOH: The studies to date have not found an association between dietary nitrates and neural tube defects.

DOH: Are there any further questions?

DOH: Our next advisory meeting is scheduled for 02/11/2016. We will post today's presentation to the website today, and get the notes out to the advisory committee ASAP.

End of Meeting: 8:54AM