Anencephaly Advisory Committee Meeting (webinar)
Minutes
February 11, 2016

Advisory Committee Members present:
Kathy Lofy, MD, Chair
Susie Ball, MS
Sara Barron, RN
Peter Langlois, PhD
Gina Legaz, MPH
Christina Nyirati, PhD, FNP-BC
Amy Person, MD
Christopher Spitters, MD
Sarah Tinker, PhD
Vickie Ybarra, PhD,MPH,BSN

WA Dept of Health Staff present:
Zachary Holmquist, MPH
Katie Meehan
Paj Nandi, MPH
Cathy Wasserman, PhD, MPH

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. Kathy Lofy also introduced new Advisory Committee member, Christina Nyirati, Nursing Director from Heritage University.

Minutes from the November 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 October 10, 2015, and the following highlights:

Zika virus – Department of Health (DOH) has received questions asking if the Zika virus could be associated with the anencephaly cluster in Central Washington. Microcephaly is not considered a Neural Tube Defect (NTD), and has been associated with some infections during pregnancy. Anencephaly has not been associated with any infections that we know of.

Surveillance Update:
- 3 new cases: 2 spina bifida cases and 1 anencephaly. Total number of neural tube defect cases in the three-county area is 67 confirmed NTD since 2010, including 42 cases of anencephaly.
- Rate for 2015 based on preliminary birth file is 12 per 10,000 for all NTDs, 6.0 per 10,000 for anencephaly.
- Continue to see that there is no strong pattern in the timing or seasonality when cases occurred.
- No differences in the rates of NTDs by race/ethnicity in the three-county data. Both groups have been experiencing elevated rates. Over two-thirds of cases overall are

anencephalic. This is different from scientific literature. In addition, the proportion of cases that are anencephalic differs by race/ethnicity in the three-county area:
    - 25/35 or 71% of Hispanic cases are anencephalic whereas 13/28 or 46% of NH White cases are anencephalic
    - Both percents are higher than National Birth Defects Prevention Study.
- Updated statewide data using vital statistics and linked files only. They may include false positive cases, and do not include pregnancies that were lost or terminated prior to 20 weeks gestation. Anencephaly is more than two times higher in the three-county area than the rest of Washington. As noted previously, this may be a true difference or artifact due to differences in termination after diagnosis.

Investigation Update:

- Special thanks to Sarah Tinker and CDC for providing analytical capacity, despite demands on their office due to Zika virus investigations.
- These numbers do not include the three recently ascertained cases confirmed after October 10, 2015.
- Have interviewed 17 mothers of NTDs including 12 mothers of infants with anencephaly. This includes 53% of the mothers we approached for interview, but only 27-29% of all cases.
- Age of mothers – Women interviewed are the same ages as all mothers of NTDs, but on average, they are older than mothers of births in the three-county area.
- Race/ethnicity – The percentage of interviewed women who are Hispanic (41% of mothers of NTDs and 50% of mothers of infants with anencephaly) is lower than the percentage of all case mothers who are Hispanic, but not statistically different from the proportion of Hispanic mothers among all births.
- Education - About 29% of interviewed mothers of infants with NTDs had less than a high school education and 65% had more than a high school education. This educational level is higher than for all births in this area. About 44% of births had more than a high school education.
- Parity - Almost all the women we interviewed had a prior pregnancy and all of the mothers of anencephalic infants who were interviewed had a prior pregnancy. These 12 women had 37 prior pregnancies.
- Pre-pregnancy Obesity - We explored the body mass index of interviewed women. 33% of all women interviewed were obese as measured by a body mass index greater than or equal to 30. 20% of the mothers of anencephalic infants were obese. About 37% of all mothers in the three-county area were obese prior to pregnancy.
- Medications - Medications were reported one month before and one month after the pregnancy.
    - Only acetaminophen and ibuprofen were reported to be used by more than one mother. In the NBDPS, acetaminophen was associated with a decreased risk of anencephaly and encephalocele when used as a fever treatment.
    - Depakene is associated with NTDs in the literature and the NBDPS, and in a recent analysis looking at its association with spina bifida.
- Folic Acid Supplementation - All 17 women who have been interviewed used prenatal vitamins at some point during pregnancy, including 10 (59%) who used them during the critical window from three months before pregnancy to one month after pregnancy. 8 (75%) of the mothers of anencephalic infants reported taking vitamins during the critical window. This information shows that the women who were interviewed were more likely to have taken folic acid than our estimates from the medical records case-

control study and PRAMS data indicated. Importantly, we can't determine if the women interviewed are representative of all mothers of infants with NTDs or not.

NOTE: SLIDES WERE TURNED ON AT THIS POINT, SCREEN PREVIOUSLY HAD NOT BEEN SHARED

- Risk Factors: We looked at risk factors for case mothers, including race/ethnicity, birthplace, body mass index, prepregnancy diabetes, and family history of NTDs.
    - 12 (71%) mothers of NTDs and 9 (67%) mothers of infants with anencephaly had at least one risk factor.
    - 7 (41%) mothers of NTDs and 4 (41%) of mothers of anencephalics had at least one risk factor that was not Hispanic ethnicity.
    - Risk factors are not the same as causality, but these results shown that the etiology is complex and multi-factorial.
- We are planning to continue analysis and presentation of additional data at our May meeting. Our analyses will be contingent on continued partnership with CDC. This work could be impacted by CDC efforts to address Zika virus transmission and surveillance of pregnancy outcomes related to Zika virus.

Prevention Efforts Update:

- Updated our folic acid outreach efforts, identified gaps and begun to address additional needs
- Strategies at three levels – statewide, community and health care; Outreach incorporated in many programs at DOH – WIC, Healthy Eating and Active Living, and Access, Systems and Coordination which addresses perinatal and women's health. Also working with many partners: Yakima Public Health, Benton-Franklin Health District, March of Dimes, Commission on Hispanic Affairs
- Reviewed previous efforts and touched on current efforts
- Statewide current efforts:
    - Developing Spanish webpages that include folic acid information
    - Partnering with Health Care Authority to get information out about Apple Health coverage of prenatal vitamins
- Community current efforts:
    - Distribution of free vitamins provided by Vitamin Angels at clinics and through public health programs.
- Health care current efforts:
    - Outreach to Medicaid providers about Apple Health prenatal vitamin coverage
- Folic acid fortification of corn masa flour stability study – US FDA has extended its review of the petition asking it to allow voluntary fortification of corn masa with folic acid.
    - In April, US FDA must either act on the petition or request additional information
    - DOH and HCA jointly sent a letter to FDA requesting approval of fortification absent scientific concerns about safety
    - Congresswoman Jaime Herrera-Beutler circulated a congressional letter to the FDA with the same message. Bipartisan support, including bipartisan support of WA delegation.

What's next:

- Complete analysis of interview study data
- Continue surveillance in three-county area

- Continue folic acid outreach
- Continue working with Health Care Authority on communication regarding prenatal vitamin coverage
- Continue working with local health and other partners
- Continue work to ensure stable state and local public health funding.
- Also shard that Secretary Wiesman approved spending $25,000 on prevention efforts.

Advisory Committee Questions and Comments

Advisory Committee (AC): Have you looked at the distance of case mothers to agricultural fields? I would like to see this information in your slides. I met a nurse who has seen numerous NTD affected babies, but didn't report it.

Department of Health (DOH): We haven't looked at proximity to fields for interviewed women, but we have for all cases. We're planning to look at cases reported in vital statistics and hospitalization data by Accountable Communities of Health (ACH) regions. We can't look at it in counties because there aren't enough numbers to look at. We will look at that in regions across the state and present that at the next meeting.

AC: I like the idea of looking at many rural areas because it would increase the numbers of cases that could be investigated, and if that were possible it may be possible to look at some interactional effects using logistic regression models. For example, if obesity and exposure to certain agricultural toxins exist, maybe there's an interactional effect that we couldn't otherwise see. Usually things aren't caused by one factor, and would it be possible to look at this in relation to the large agricultural areas.

DOH: I think our numbers are going to preclude that type of analysis. That could be conducted with the NBDPS because they have 2000 plus NTDs to look at. We have 17 cases total, including 12 anencephalic infants. We are going to see what we can look at in concert with the NBDPS, but it gets complex quickly because the controls we have for comparison are from that study. The controls represent the populations included in that study - not our population. We really need to think through what our next steps in the investigation are going to be. I think it will be difficult to tease apart any one constellation of factors that we see here.

AC: I was going to say I see how difficult this could be given the small number of cases. I think that the investigation has done a good job so far given the data limitations.

DOH: I was wondering if anyone knows whether the NBDPS has looked specifically at large rural areas?

AC: Within the NBDPS it's a little challenging to look at this because when each state sends its data to the CDC, its identifiers are erased. This includes where the mother lives for both cases and controls, making it difficult to identify where they are from. It can be done, but it requires IRB approval of each center in NBDPS. The short answer to your question is: I'm not aware of anything so far in the NBPDS asking if there is a difference in rural versus urban areas.

DOH: Are there any questions about the surveillance effort, the results, or the future investigation efforts that we've outlined? I think the challenging part of this investigation is that there are probably some cases in this group that could be prevented by folic acid, but it's hard

to sort out when we have a birth defect that's caused by multiple factors. It's difficult to sort out which might be associated with which factors.

AC: I was wondering as I was looking at the data, if we'll ever be able to tease out the folic acid question? There is a correct answer to that question, and I wonder if consciously/subconsciously the mother wants the interviewer to think well of her biasing her response around that item.

AC: I agree with that, there could be a biased response based on desire to get provider approval. There have been some theoretical models based on incidental case reports of women using valproic acid, and other things affecting neurulation. There have been studies of the impact of taking higher doses of folic acid to overcome the impacts on neurulation, but maybe more work is needed.

DOH: I think that's a good point.

AC: I know that there are some women who start taking prenatal vitamins at higher doses. I know that some high risk prenatal clinics for women who are taking valproic acid are taking four times the normal dose of folic acid.

DOH: Are there any recommendations for things that we should be doing differently? Any suggestions?

AC: I wonder if you've reached out to the University of Washington or Washington State University for doctoral students who could help you with the investigation?

DOH : We have been contacted by people who are interested in helping out. I'm interested from the committee what additional work you would recommend we do at this point?

AC : I think it would be good to break the analysis out by county or region, not King County because of the large population. Take soil samples, animal samples to look at pesticide levels.

DOH: I understand your questions, and there is frustration in how far we can take this investigation looking at agricultural exposure and pesticides. We don't have a narrow list of chemicals to investigate that research has identified as good candidates to explore. Without more specific hypotheses, we don't have the capacity to be able to address these kinds of questions. I know that's frustrating. We have looked at agricultural data from the area, yes there is a lot of pesticide use, but we need to have a specific hypothesis to be able to explore further. The NBDPS and other large centers are set up to conduct well designed studies to look at these exposures - we support this work, and support asking women if they want to participate in this research. Every case of NTD is a tragic case. From an investigation and statistical standpoint, it's very challenging to conduct that type of exploratory research study when we have such small numbers.

DOH: Do people agree with Cathy, or have different opinions?

AC: It's a cost-benefit question. We could really exhaust the entire resources of Cathy's offices and ancillary supporting investigators and resources, but I'm not sure that we will be able to come up with an answer, a smoking gun. It makes the cost-benefit of extensive exploratory research without a hypothesis astronomically expensive, notwithstanding the tragedy of the individual cases. From the public health perspective, I'm much more supportive of the outreach efforts that are going on in the area. I'm a little bit skeptical about the community-wide value of diverting existing scarce resources further into exploratory work. It sounds harsh, but that's my perspective. I would support the future plan that Cathy has laid out, to support

surveillance, but I'm a little reticent to collect soil samples and do other analogous exploratory work on an uncertain hypothesis.

DOH: Thank you, would anyone else like to comment?

AC: I think it isn't even just a cost analysis; the numbers we are talking about are so small that what we would be able to identify even without a known hypothesis would be so small that we couldn't make any firm conclusions regardless.

DOH: We sent the outreach efforts to the advisory committee members via email yesterday, and we are looking for feedback on that plan. We have some additional plans, and we have some questions about how you think that money could be spent. We would like to hear from those of you in the community as well as the advisory committee. It looks like there are some questions in the chat.

DOH: [In response to question about fumonisin research] We are looking at corn consumption among women, and considering the hypotheses about fumonisin and NTDs. The data about high fumonisins on corn focused on corn from the center of the country. We asked why we would see more NTDs here if the fumonisins were on corn in the Midwest. One expert we spoke with hypothesized that there were conditions in our area that may lead to more mold formation, but it seemed that that hypothesis lacks supporting evidence – we would be seeing increased rates of NTDs across the country instead of just in the three-county area.

DOH: We're out of time, but will look through the questions we've received, and try to email you back with answers. Thank you for joining us.

Meeting End: 9:15 AM