

Anencephaly Advisory Committee Meeting (webinar)
Minutes
May 24, 2016

Advisory Committee Members present:

Kathy Lofy, MD, Chair
Susie Ball, MS
Sara Barron, RN
Lisa Galbraith, MD
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
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 8:06 am with a quick introduction.

Minutes from the February 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 January 19, 2016 and the following highlights:

Surveillance Update:

- One new anencephaly case. Total number of neural tube defect cases in the three-county area is 68 confirmed NTD since 2010, including 43 cases of anencephaly.
- Total number of births in area in 2015 increased by three with a more complete file. This had no impact on the rate.
- Identified through interview that one of the cases we reported for 2015 did not reside in Washington at the time of conception. The case definition requires that the mother be a resident of the three-county area at the time of conception, so we will be removing this case and updating our numbers. (Note: numbers have not yet been updated in the attached presentation.)
- Continue to see that there is no strong pattern in the timing or seasonality when cases occurred.
- To explore whether there were differences within the overall three-county area, we took a look at three population subgroup areas to see if anything stood out when they were analyzed separately. The three areas included cases in the Tri-Cities area, in the wider Yakima City area, and cases in the lower Yakima Valley. We looked at:
 - o Anencephaly to Spina Bifida (SB) ratio
 - o Cases by month and year
 - o Seasonality
 - o Water source

- Numbers are very small and we would expect a lot of variability due to chance alone. We did see that the Anencephaly to Spina Bifida ratio varied by area. About 1:1 in Yakima City area, about 2:1 in Tri-Cities and about 4:1 in Lower Yakima Valley.
- Cases across the time period in all three areas
- No seasonality
- Some variability in public vs private water source, but all three areas had at least 69% of case mothers on public water source.
- Cases across Washington ascertained passively, and identified through birth, fetal death and hospitalization records. These cases have not been confirmed, which is a major distinction from the cases in the three-county area. There are also almost certainly some false positives, but we do not know how many. We grouped the counties together into Accountable Community of Health (ACH) regions that focus on some of the healthcare transformation work that is ongoing in the state, because the numbers of cases in individual counties are often very low. There's variability in rates, ranging from a low of 1.7 per 10,000 in King County to a high of 4.5 per 1,000 in Greater Columbia. We looked to see if we could discern differences between two time periods, but the numbers remain too small and we could not determine a difference between the two periods.
- Mapped the rates across Washington by ACH region (Slide 8). Rates appear higher in Eastern Washington and in the Pierce and Olympic ACH regions. We do not know if differences are true differences or may be due to demographic differences, or to regional differences in terminations after a diagnosis of an NTD.
- We wanted to look at the prevalence of NTDs across the US (Slide 9). We looked at the variability in rates reported to the National Birth Defect Prevention Network (NBDPN) from 2007-2011, and the impact that case definition has on prevalence. Prevalence rates ranged widely. The blue dots indicate states that looked at live births, terminations, and stillbirths, and they range from a low of 0.4 per 10,000 live births to a high of 4.4 per 10,000. They include states that have active ascertainment of cases like California and Texas, states like Maryland that have passive ascertainment and Rhode Island that is passive with periodic quality reviews for accuracy and completeness. Some only include terminations after 20 weeks – some include terminations, but only those that occur at hospitals. The orange dots are from states that include live births and stillbirths only. They range from a low of 0.3 per 10,000 live births to a high of 4.9 per 10,000. The green dots are from states that include only live births in their ascertainment of anencephaly and range from a low of 0.3 to a high of 1.5.
- We looked at information that we have from the three-county area to compare it to state-based rates (Slide 10). We are including live births, fetal deaths, and terminations of all gestational ages in our case definition. Terminations make up about 46% of our anencephaly cases. For 2010-2015 the number of anencephaly cases was 41, and the rate was 8.2 per 10,000. If we only included the terminations after 20 weeks gestation, there would be 22 cases and the rate for live born and fetal death cases only would be 4.4 per 10,000. If we included only cases that were live born, there would be nine cases and the rate would be 1.8 per 10,000.
- On slide 11, we superimposed the data from our investigation in the three-county area onto the slide of state rates reported to NBDPN. Our total rate of anencephaly for 2010-2015 is 8.2 per 10,000, which is off the chart, but we are including terminations of any gestational age length. We do not know how many other states are doing the same. When we restrict to live births, fetal deaths/terminations greater than 20 weeks, our rate is on the high end of what is reported by the National Birth Defects Prevention Study (NBDPS). When we restrict our rates to live cases only, our rate is only slightly higher than rates across the country. This provides a comparison to the rest of the country, and what we are experiencing.
- In summary: cases have occurred across all years with no defined peaks in time, both overall, and in sub-population areas. There is no seasonality overall, or in sub

populations. There is continued predominance of anencephaly over all other NTDs. Our rates from the three-county area appear on the high end of state rates across the country, but there is a lot of state-to-state variation and our rates do not appear to be substantially higher than other regions when we try to match similar case definitions.

Investigation Update:

- We have continued to follow up with women, attempting to interview new cases. Of the five cases identified last summer and fall, two were interviewed and included in the data on the 17 completed interviews we shared in February and later this morning. Twelve of the 17 mothers had anencephalic infants. In addition, one mother declined to be interviewed, one mother completed part of the interview and we were not able to schedule another appointment despite multiple attempts, and one woman agreed to interview, but we were never able to schedule an appointment despite numerous attempts. We identified three new cases in February – one case of anencephaly, and two cases of spina bifida. We interviewed mothers of one anencephaly case and one spina bifida case, and the other mother declined to be interviewed.
- We have already contacted the mother of the newly identified case this spring. She has agreed to be interviewed, and we are working on setting up a date for interview. We currently have two completed interviews and one partially completed interview. When we have five completed interviews of a given case type (anencephaly or spina bifida respectively), we will key enter the data and update the interview analysis. This precaution is taken to preserve confidentiality.
- Interview response (Slide 14) Overall, we've approached 38 women for interview, including the mothers of 24 anencephalic infants in three different phases. The first phase is the women who were initially approached who had infants with a confirmed NTD before 2015. They were all due to deliver in December 2012 or later. In phase 2 we included women with NTDs confirmed in 2015, and in phase 3 we have women with NTDs confirmed in 2016. We have only included the women in phase 1 and 2 in the analysis presented. The table on the left shows the response rate for phases 1 and 2 combined. You can see that we interviewed 50% of all case mothers we approached, and 55% of mothers of anencephalics.
- Folic Acid Supplementation Use (Slide 15) In the gray shaded area, you can see that all 17 women interviewed used prenatal vitamins at some point during their pregnancy, and 10 or 59% used them during the critical window from the month before, through the end of the first month of pregnancy. Eight or 75% of the mothers of anencephalic infants reported taking prenatal vitamins during the critical window. This information shows the interviewed women were more likely to take folic acid than our estimates from the case control study and PRAMS would indicate. We can't determine if the women interviewed are representative of all mothers of infants with NTDs or not. However, given that the interviewed women are less likely to be Hispanic/Latino than all cases, and are more educated than all birth mothers, they may be different from all NTD mothers.
- Dietary Folate (Slide 16) This slide shows dietary folate equivalents, which is the sum of the naturally occurring food folate and folic acid from fortified foods, taking into account differences in bioavailability. This nutritional information is from the year before the pregnancy. In the gray shaded area we have the mean, median, and range of dietary folate. The median dietary intake is about 360 micrograms, which shows that about half the women interviewed had dietary intakes very close to the recommended daily intake of folic acid. One of the two women with 200-299 mcg folate began vitamin use after the month before conception, One of the five women with 300-399 mcg folate began vitamin use after the month before conception, and two of the three women with greater than 400 mcg folate began vitamin use after the month before conception. The interviewed women do not appear to be folate deficient. It could be that we have a

biased group of women who have been interviewed, or it could be that these women have a higher need for folate than other women.

- Drinking Water (Slide 17) Similar to what we reported for all cases, most of the interviewed mothers had public residential water supplies. Most of the women reported drinking one glass of cold and one glass of hot water per day. They also reported drinking water consumed away from the home, and most of the women reported having just one glass of water away from home per day. This does not seem to be a major source of exposure for them.
- Occupational Exposures (Slide 18) The interview asks if mothers worked at least one month from conception through the end of pregnancy. If so, mothers are asked about the name of the company, job title, what their company did/made, what they did/made and how they did it, if any chemicals or substances were used, the start and stop dates of their work, the days per week they worked, and the hours per day that they worked. Eleven (65%) of the interviewed mothers of infants with any NTD worked during the critical time period for neural tube formation, including nine (75%) of mothers of anencephalic infants. For comparison, occupational data from birth and fetal death certificates for 2010-2015 indicate about 18% missing data. Among those records with data, 82% of women report an occupation on the certificate, 16% report being a homemaker and 2% report being unemployed.
- Industrial hygienists reviewed the jobs and using a job exposure matrix determined the probability of exposure based on the job tasks and responses to questions on the interview. Among the interviewed mothers of all NTDs, one woman had a medium probability of solvent exposure during the critical window, two women had a low probability of polycyclic aromatic hydrocarbon (PAH) exposure, and five women had exposure to pesticides, including three through farm jobs and direct exposures and two from non-farm jobs. Unfortunately, we don't have good data on the prevalence of the exposures among all birth parents to use as comparison. We can report that among women who reported an occupation on the birth/fetal death certificate, about 2.5% reported being a farm laborer or wage worker. An additional 1.5% reported being a fruit/nut/vegetable grader or packer. Three mothers had jobs with high physical demands – all were mothers of anencephalic infants. Among mothers of anencephalic infants, no women had solvent exposures, one woman had a low probability of PAH exposure, and four women had exposures to pesticides, including three through farm jobs and direct exposure, and one from a non-farm job.
- Pesticide Exposures (Slide 19) One mother was assessed to be occupationally exposed to insecticides. Mothers of two infants with any NTD, including one mother of an anencephalic infant, were assessed to be occupationally exposed to fungicides. Mothers of five infants with any NTD, including four mothers of anencephalics, were assessed to be occupationally exposed to herbicides. Overall, three mothers of anencephalic infants were assessed to be occupationally exposed through farm work.
- With respect to pesticides and their use around the home, six mothers of infants with any NTD, including four mothers of anencephalic infants, reported pesticides used around the home from three months before pregnancy through the end of the first trimester. Only two of these women applied the pesticides themselves. One woman applied ant traps and weed killer. The other women reported using head lice products that could only be obtained with a doctor's prescription.
- In summary: interviewed women were slightly older than all birth mothers, were less likely to be Hispanic/Latino than all cases, were more likely to report prenatal and folic acid vitamin use than birth mothers, and did not appear to be folate deficient. Many interviewed women experienced risk factors for NTDs, and about one third of interviewed mothers were assessed to have occupational exposures to pesticides, predominantly herbicides, not all through farm work.
- Since our last meeting, we have also followed up with mothers who were interviewed. We contacted them again and verified that they have our information and are receiving investigation results if they are interested. We also asked mothers if they would like to

be informed of research if they are eligible, and have provided that information when requested.

- Proximity to Agriculture - The concern with proximity to agriculture is pesticide exposure. Our prior analyses used a database that identified lands for tax purposes. As we dug a little deeper, we found it includes lands that are in production and those that are fallow, and possible even range lands. These would have no potential for pesticide exposure. As a result, we are currently exploring different ways to look at this issue, and potentially we can look at specific crops and look at distance from the case homes. We will be assessing the level of effort required to analyze these maps, as well as how informative such analyses might be.

Prevention Efforts Update:

- Updated our folic acid outreach efforts, identified gaps and begun to address additional needs
- FDA approved fortification of corn masa flour in the middle of last month, and nationally it is estimated that this fortification will prevent 40 neural tube defects among infants born to Hispanic/Latino mothers each year.
- Ongoing efforts to improve folic acid use among women of reproductive age in Washington include a variety of efforts. Statewide, we have made our DOH webpage on the anencephaly investigation available in Spanish. We also released a press release in English and Spanish with information about prenatal vitamins available through Apple Health just after the folic acid fortification announcement. In the community, we've been engaged with students from Central Washington University. They are working with us to interview mothers about their folic acid and birth defect information needs. We have also developed folic acid digital messaging for Facebook and Google Ads. With respect to providers, we have been developing a training module for community health workers that focuses on health and nutrition during pregnancy.

What's next:

- Continue surveillance in three-county area
- Continue to interview new case mothers
- Continue folic acid outreach with local and other partners
- Continue to learn about needs for information and how best to communicate
- Complete Community Health Worker training module and make it available

Advisory Committee Questions and Comments

Advisory Committee (AC): Can we go to the map of the ACH Regions? Is Okanogan part of North Central?

Department of Health (DOH): Yes, the diagonal lines on the map are irrelevant for our purposes; Okanogan is part of North Central.

AC: How long do we continue to monitor new cases?

DOH: I would turn it back to the advisory committee for what your recommendations are.

AC: The numbers made it look like maybe the rate is going down, and maybe we should follow this year or maybe next year to see if this was a fluke. It looks like it's going down, but it might be nice to see if it continues or not.

DOH: I appreciate that, and I'm cautiously optimistic. With small numbers rates can obviously bounce around, but at least to date it seems like a step in the right direction.

AC: I would like to agree with previous commenters that continuing to do surveillance would be very helpful. Especially with the FDA's recent approval of fortification, we could continue to surveil for 6-12 months.

AC: I also agree with continuing to monitor for another year if you have the resources to do that.

AC: It looks like there are more cases in rural areas than urban areas, is there some way that you can get this published so that you can look at other rural factors? Also, do you include herbicides as part of your pesticides?

DOH: Yes, we included herbicides.

AC: Have any studies been done that show that herbicides by name can have an impact on NTDs?

DOH: We looked at a study out of California that looked at NTD rates and pesticide use. There are a few studies that have looked at specific compounds, but it's difficult to do because most places don't have records of the specific herbicides or pesticides that have been applied to crops.

AC: In my brain, a pesticide is not an herbicide. They're not the same, so it's interesting that they study them together.

DOH: In response to your question about rural areas, can Sara or Peter comment about the NBDPS and whether you've seen any analyses that look at rural versus urban areas? If I remember, you don't have even addresses.

CDC: We do have addresses that are geocoded and we've looked at this sort of analysis, Peter can speak to it better, but I'm not sure if we've done a pure rural vs urban analysis.

AC: I agree, but the individual centers gather data on geocoded addresses so they can combine them across states and nationally. That takes much more IRB work, so consequently we've done little work on those sorts of exposures. Aside from NBDPS we've done work in Texas, and other states have as well, that look at the variation and occurrence of NTDs by urban versus rural categories.

DOH: If you send them to us we can send them out with the minutes (Attached)

DOH: Do you have an overall conclusion?

AC: It varies with the birth defect. With heart defects it varies by urban/rural, but we think that might be a study bias. I'd be happy to make these available so people can judge for themselves.

DOH : Have studies looking at anencephaly in particular been undertaken in Texas?

AC : They don't show as much variation if I remember correctly, but I'll share those as well.

DOH: Any feedback on the next steps?

AC: I agree with monitoring for another year.

AC: I have another question about analysis of interview data. If I understand correctly, you've analyzed the data for case mothers very completely, but you haven't looked at control data. Is that correct?

DOH: We haven't, but your input would be helpful. The controls in the NBDPN study are different from the controls of the birth population in the three-county area, so we're not really sure what to make of any differences that we might see. We don't have enough numbers to control for the factors that we think might be confounders that might make them different than the controls from the NBDPN compared to our three-county controls

AC: Sure, and I should make clear that I'm not insisting on this, it just might be an interesting approach if you have the personnel to do it. You could try to control for race/ethnicity factors, but that does require numbers which we may not have. We could restrict the controls to those from states with populations that are somewhat more similar to the Washington state cases, so perhaps just using the NBDPS controls from California and Texas for example that may have a higher proportion of Hispanic/Latinos. That's just one strategy, but those are the only ones coming to mind right now.

DOH: Perhaps we'll have another conversation about what we can do and include you and Gary Shaw from California in coming up with a strategy.

AC: I'd be happy to do that.

DOH: I have another question about the agriculture analysis, I think that was another area from Cathy's slides where we want any feedback that people might have. Do people feel we need more analyses there, or do people think that control data would be more helpful?

AC: From what was presented, it seems like the agricultural data that would be needed may be available. Is that accurate?

DOH: Yes, potentially what we have available are crop maps. We don't think we'd be able to look at proximity to any crop, but we could potentially investigate specific hypotheses, and what I'm thinking of doing is looking at people who have occupational exposures and looking at those specific crops, or if we think the apple crops are involved we can look there or with corn, but we really need to look at what is available, and the level of effort that is required to look at those maps in a way that is reliable. It's not clear to me what the level of effort for the analysis is right now.

DOH: I'm thinking about hypotheses from the literature, and I can't think of any that propose any specific crop.

AC: Looking at your map, it looks like those more rural counties are experiencing a higher rate. Is there a thought of doing the sort of surveillance that you're doing in our counties in other regions with increased rates? In the big states and big reviews, we could go by county or these types of ACH districts; perhaps we could look nationwide and see if there is a higher rate in other rural areas. In the big picture, not specific crops, just in the big picture, then perhaps we could start to focus down on what crops might be involved. I would like to see more national analysis.

DOH: We can review the literature, Peter is going to send some of that, and what we can do is see what is already being done nationally around rural and urban areas.

DOH: We're a few minutes past 9:00 AM, are there more questions? We are always willing to receive comments/feedback after the webinar as well.

DOH: We received some questions in the chat that we will include in the minutes. We need to discuss when we are meeting next as well.

DOH: We had a meeting scheduled for August 11th, but you're not available.

DOH: When should we meet next?

AC: I think quarterly is still a good plan.

AC: I agree

AC: I agree with that as well.

DOH: It sounds like there is some consensus with that, so we will look at scheduling our next meeting and will let you know about that in the next week or so.

DOH: Thank you for all the feedback, and if you have any additional questions you can reach me at the contact information provided at the end of the presentation. You can contact me or Ramona with any questions that you might have.

Meeting End: 9:10 AM

Online Questions: (These questions were not taken during the call as we ran out of time)

JoNel Alecia (Seattle Times): Can I ask a quick question Cathy?

Public: I understand that some of the community water systems need to mix water sources to keep the nitrates within an acceptable range. Do we really want to trust the numbers that the managers of these systems give us? Recently a physician told me that arsenic can contribute to NTDs. Since the Yakima Valley has an arsenic load because of previous agricultural practices, should we be getting arsenic levels on all new cases that occur? Also, should we be checking the water for nitrates on all new cases?

DOH: The data we have used to assess nitrates in drinking water is from our Office of Drinking Water whose mission is to protect the health of the people of Washington by assuring safe and reliable drinking water. To do this, they ensure that water systems comply with state and federal drinking water regulations, including testing and reporting. At times, community water systems blend water from different sources to ensure safe drinking water at the tap. Blending water to address nitrate concerns requires an approved blending plan and extensive monitoring to ensure ongoing consistency with the blending plan: daily field sample collection, monthly sample(s) analyzed at a certified lab to verify field information, and quarterly raw water samples from each source. We looked extensively at nitrate levels of public water supplies serving cases and did not see any evidence of elevated levels. Furthermore, nitrates in drinking water alone, do not appear to be a risk factor for neural tube defects.

With respect to your questions about arsenic, neural tube defects (NTDs) have been observed along with skeletal anomalies in mice exposed orally to high doses of arsenic during pregnancy (Hill et al., 2008; Baxley et al. 1981), but NTDs have not been associated with elevated oral exposures to arsenic in several studies of human populations (Mazumdar et al . 2015; Jin et al. 2008; vonEhrenstein et al. 2005). Arsenic doses in the animal studies were much higher than exposures in human observational studies. It is possible that even in populations with elevated arsenic in their drinking water, human exposures are too low to cause NTDs. At this point the data do not support an association between environmental arsenic exposure and NTDs but it is important to recognize that the data are not sufficient to rule out a contribution

either. Arsenic levels are routinely monitored in public water systems to ensure they do not exceed the maximum contaminant level of 10 parts per billion.

We continue to recommend that people who get their drinking water from private wells make sure the wells are tested at least annually for nitrates and bacteria. We also recommend that private well owners check their water at least twice for arsenic – once in the summer and once in the winter to check for seasonal influences.

Public: Sorry I don't have audio as I am in overseas. I asked about any linkage with corn consumption last time. It was quickly answered as NO since the corn consumed in the area is likely from national suppliers. I totally agree. However, my question was about consumption of local or home grown corn in the area. I am wondering if they were asked about consumption of locally/home grown corn?

DOH: The interview does not ask about locally grown corn. The researcher who has done the most work on the fumonisin hypothesis indicated that the corn would be from the Midwest and Texas where high temperatures in the summers of 2011 and 2012 led to extreme drought and potential fumonisin infection. We asked why this would only result in an increase in our area, but did not get a very satisfactory response.

References

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