Anencephaly Advisory Committee Meeting (webinar)
Minutes
June, 16 2014

Advisory Committee Members present:
Kathy Lofy, MD, Chair
Susie Ball, MS LCGC
Sara Barron, RN
Jessica Black, PhD
Nora Coronado, PhD, MPH, MSW
Philip Halvorsen, MD
Peter Langlois, PhD
Gina Legaz, MPH
Richard Olney, MD
Amy Person, MD
Kathleen Rogers
Melissa Schiff, MD, MPH
Christopher Spitters, MD, MPH
Vickie Ybarra, RN, MPH

WA Dept of Health Staff present:
Lillian Bensley, PhD
Mike Means, RS, LHG
Riley Peters, PhD
Mike Priddy
Mandy Stahre, PhD, MPH
Cathy Wasserman, PhD
Kristin Wendorf, Epidemic Intelligence Service Officer, CDC

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, community, academics, and Centers for Disease Control and Prevention.

I. Welcome and Introductions
Kathy Lofy began the meeting a few minutes past 8:00 am with introductions. She discussed the creation of the advisory committee, noted this was a public meeting and minutes would be sent to interested parties. She acknowledged the media interest in the anencephaly investigation and discussed recent transitions in staffing at the Department of Health. She noted Mandy Stahre completed her CDC fellowship and accepted a new position within the department and would not be leading the investigation moving forward. Juliet Van Eenwyk retired. Cathy Wasserman was hired as the new state epidemiologist and will take over the role of leading the investigation. She has been involved in the investigation since the beginning.

II. Expectations and Goals
Kathy Lofy discussed the primary goals of the advisory committee were to identify actions to take to prevent or reduce the likelihood of neural tube defects in the area, identify ways to improve reporting of neural tube defects to better ascertain rates of occurrence, and to determine if additional investigations should be conducted to assess potential exposures. The role of the advisory committee was to listen to input and provide feedback to inform and advise the public health system and response moving forward. She noted that she would like the advisory committee to help prioritize activities based on scientific evidence and using resources wisely. She asked if anyone or any group was missing in representation on the advisory committee. Migrant clinicians were identified as not being represented. Cathy Wasserman will follow up to identify clinicians to approach to join the advisory committee.

Kathy explained that today's agenda would be to share data gathered during the investigation and follow-up, answer questions regarding the investigation, and begin discussion around stated goals. It was noted a second conference call will be held in July to complete discussion around goals and develop an action plan to be completed over the next 6 to 12 months.

III. Presentation

Cathy Wasserman presented material on the background of the cluster investigation, follow-up to date, hypotheses considered, and concerns raised by the community. The presentation is attached.

IV. Questions from advisory committee members:

- Q: Could you explain the statistical analysis using different case ascertainment methods?
  A: We examined different ascertainment methods used by other states and systems. We calculated the rates we would have observed had we used those methods.

- Q: Do you find out about all pregnancy terminations?
  A: If pregnancy terminations were performed in hospitals, then we have the information on those cases. Additionally, if a woman was referred to a perinatologist, or went to the local hospital, we would have identified those cases. We potentially missed terminations occurring very early in pregnancy not performed at a hospital.

- Q: Are you checking for long-term effects of women who lived in the area, for women who live near Hanford or near exposures their whole lives verses just prior to pregnancy?
  A: We have not looked into this to date, but will add it to the concerns to be considered.

- Q: Do we have enough info about the rates of anencephaly to know they are different from the rest of the state?
  A: No, we have passive ascertainment of birth defects in Washington, and there is a time lag for the data. We conducted active ascertainment only in the 3-county area. As shown in the slides, we know active ascertainment identifies far more cases than passive ascertainment.

- Q: Do we really know if this cluster is new or has been going on for a while? Should we refer to the situation as a "cluster"?
  A: No, we do not know if this cluster is new or ongoing. We conducted active ascertainment back to 2009. Lack of electronic hospital and other medical records have prevented going back further.

- Q: Could you be missing seasonality because the migrant population would not necessarily give birth at the time of exposure? How did you deal with Hispanics who are not in residence year-round, and may give birth in other states or countries?
  A: We looked at seasonality by date of delivery (which can be extrapolated back to an exposure time period just before or in early pregnancy). We asked about seasonal migration, and learned this population has decreased migration over time in the three-county area. If people on the advisory committee or others believe this is incorrect, please provide that perspective or any additional information you have on the migrant population. We need more information in order to say more about births from this community.

- Q: How are you evaluating follow-up from the public information campaign moving forward in terms of ascertaining cases?
  A: I think you are asking two questions. We have not evaluated our public information to date. Public information campaigns have not included public service

announcements. More can be done with public information campaigns. We are continuing to track and ascertain cases through passive surveillance with active follow-up and feel that hospital staff are very sensitized to the issue and notifying the Department of Health.

- Q: Is it that mothers don't know about folic acid or is it access to folic acid supplementation that is the problem?
  A: We aren't sure, but we know women need to take folic acid before pregnancy, since the neural tube closes by day 28 after conception, often before a woman knows she is pregnant. About half of pregnancies in Washington are unintended.

- Q: Are there any nutritional surveys in Washington measuring folic acid in the diet?
  A: We are not aware of any survey data with this information.

- Q: Because the mean age of mothers is 26, I assume the majority had a previous pregnancy? Pregnant teens don't always know about folic acid.
  A: Most women appear to have been pregnant before. It would be interesting to note the mean age of women during their first pregnancy.

- Q: How many of the women are actually undocumented?
  A: We do not have that information.

- Q: Have you considered interviewing women to get more information about who they really are, because women don't always tell the truth in clinic appointments and medical records.
  A: Based on discussions with the advisory committee, we would consider interviewing women if we conclude this would add useful information.

- Q: When during gestation did you ascertain residence of the moms?
  A: We tried to get residence during the last menstrual period.

- Comment: You need more background information comparing rates in the 3-county region to national rates. Nationally, Hispanic women do experience higher rates of NTDs. This should be acknowledged.

Discussion: Questions by Department of Health (DOH) are in bold, discussion points and questions by advisory committee members are noted with an "AC" and those by DOH staff are listed by "DOH"

Is the current case definition adequate? What is potentially being missed with current methodology?

DOH: We were contacted by a pathologist who mentioned there are other diagnoses that could be mistaken for anencephaly although these are rare conditions, too.

Q(AC): Is the case definition excluding babies with multiple diagnoses or anomalies?

DOH: No. There are a few cases that had multiple anomalies. There is at least one case with a chromosomal anomaly.

AC: If there is a chromosome problem, then it will not be related to environmental exposure.

AC: Recommend doing initial analyses with all cases and follow up analyses with isolated cases only.
AC: National estimates include ALL cases. Chromosomal cases are rare.

Q(AC): Did you only include cases diagnosed by ultrasound or pathology? What about live births?

DOH: We also included live births diagnosed at delivery. All of the prenatally diagnosed cases were diagnosed by ultrasound and/or pathology.

Some cases were diagnosed very early in pregnancy and terminated. If you find a case diagnosed at 13 or 14 weeks and terminated, is this reliable?
AC: Ultrasound at end of first trimester should be accurate.

Q(AC): Is it possible some terminations occurred outside of the geographic area and were missed? There are places in the western part of the state performing abortions.

DOH: We heard from one provider in Spokane who mentioned seeing patients from the three-county area, but have not been able to investigate further. We also looked at all fetal death certificates for residence in the three-county area.

Are the ascertainment methods appropriate? Should we be doing anything different to ascertain cases at this time?
(AC): Some doctors are still unaware, need to publicize through:

- Health alerts to the providers through health jurisdictions
- Perinatal regional network
- Flashback alerts that list the total number of cases in the area
- Contact WACMHC = Washington Association of Community and Migrant Health Centers
- Benton/Franklin County OB newsletter for the medical society (Yakima has a similar one)
- Washington State Medical Society newsletter

Are national estimates that we use (2.1/10,000 live births) comparable?
AC: National estimates separate different ascertainment methods. Active ascertainment systems show higher rates than national estimates. A limitation of those systems is that early terminations are not captured.

Q(AC): Does it make sense to find national areas that are similar (rate of Hispanic, rural); has that been done?

DOH: We attempted to compare race-specific rates for the Central Valley of California and rural Texas, but couldn't find race-specific rates for just the Central Valley (only for all counties included in California).

Any thoughts on why we are seeing a predominance of anencephaly cases instead of spina bifida? Are the root causes of anencephaly different from spina bifida? Are the risk factors the same?
AC: We don't really know for sure the answer to that question. There are some instances of different risk factors in the literature, but they are difficult to explain.

AC: Does that ratio poke holes in the folate supplementation theory? Would we expect proportional increases in both types (in relation to folic acid)?

AC: Some suggest that nationally there was a greater decrease in spina bifida compared with anencephaly after folic acid supplementation. Evidence from China did not show differences between the two conditions. It varies geographically. Not sure how it would relate here.

What should be the next steps in the investigation? Should we do another epidemiologic study?
AC: To the extent it's feasible, we should consider interviewing recent cases to get a better idea of who these women are socio-demographically, their responses to known risk factors and possibly compare them to controls. It would be great to know, but don't know about feasibility.

AC: For people who live in Central Washington there is a desire to know as much as we can, but are further studies warranted and what type of studies? It would be good to compare three-county rate to the state and compare to other similar parts of the country first.

AC: Consider active surveillance in nearby counties or statewide.

AC: Have you considered looking for biomarkers for mold? Do you know about test or the cost?

DOH: We might begin with testing in tortillas before looking for biomarkers in humans. There was an outbreak of equine encephalitis in Texas prior to the Brownsville cluster.

AC: There was an outbreak of equine illness preceding the Brownsville cluster in 1991, and both were caused by fumonisin. There was a group thinking about doing that, but not funded. You may want to work with them.

Q(AC): (from email during mtg). Why was a red flag raised on this cluster? One thought was CAFOs (Commercial Agricultural Feeding Operations) in the lower Yakima Valley, nitrates and pesticides. I agree with comparing rates with other farming or migrant farming areas in the US. You have excluded nitrates, pesticides and nuclear plants as important contributors. It seems to me the medical community should focus on promoting folic acid, and see what happens.

What should next steps for community outreach/prevention?
AC: Community education tends to be ineffective, missed opportunity not to include promotion of folic acid in corn masa flour (currently under FDA review). Recommend to lend voice from the area to support the fortification efforts.

AC: Sending emails to various medical societies, 50% of pregnancies are unintended, neural tube closes quite early in pregnancy, people have often not been exposed to adequate folic acid. Start folic acid prior to pregnancy.

AC: Educate promotoras in the field about supplementation of folic acid.

AC: Work with March of Dimes RFP of folic acid education/supplementation.

Additional Discussion points brought up by advisory committee members who were not able to participate by phone.

- AC: I agree with additional active surveillance for the rest of the state. How else will we know if this is not a statewide issue or if other specific regions are experiencing the same issues? Comparing regional rates to the US rate is helpful but rates vary regionally and so US rates represent heterogeneity. In addition, it appears that rates remain elevated through 2014 and we do not have an answer to why this is continuing to occur. More investigation with case control interviews may lead to some answers. Also – if the exposure that explains the "cluster" is something local, seems like cases and controls would be too similar to detect this and using controls from outside the three counties might be elucidating. Lastly, from the experience in Brownville, seems like getting increase in folate use for all women in WA is a good public health intervention.

- AC: I wanted to comment that I believe the confirmed cases should continue to be followed subsequently to see if any recurrence. I have had 2 patients with subsequent pregnancies and no problems. I believe there needs to be a better reporting system. I think continued case-control studies should be continued and other similar regions should do the same to compare data.

Wrap-up:
We will take feedback and draft a plan of action to be sent prior to the next meeting on July 28th. We will aim to complete our action plan at the next meeting, and move forward in the investigation. Additional questions or comments from the public will be shared at the July meeting.