Informal Pertussis Meeting  
Wednesday, 26 September 2012

Present: Helen Rees, Chair, SAGE, Thomas Clark, CDC; Peter McIntyre, National Centre for Immunization Research, Australia; Scott Halperin and Beth Halperin, Dalhousie University, Canada; Gayatri Amirthalingam, Health Protection Agency, UK; Kirsten Vannie, US (Minutes) 
WHO staff: Philippe Duclos, Peter Strebrel, Ana Maria Henao-Restrepo, Tracey Goodman.

Philippe described the purpose of the meeting: to discuss the current situation experienced in some countries, current views on pertussis transmission, and necessary steps for WHO. He noted the observation that immunity from acellular pertussis vaccines (aP) in some countries may wane faster than with whole cell pertussis vaccines (wP). In 2009, the SAGE Pertussis Working Group carefully reviewed the evidence to date but still had a number of questions that were not fully answered at the end of the process (such as maternal immunization and cocooning for which no recommendation). Philippe was particularly interested to know timelines for new data being collected in Australia, Canada, the UK, and the US.

Given the importance of the recent pertussis outbreaks, Philippe and Helen discussed the possibility of raising key pertussis issues at the next SAGE meeting in November. This would not be a specific session but rather a component of Okwo’s general report. SAGE members have flagged pertussis as a topic of current interest. Up to now, WHO has not expressed a preference for aP over wP, but there was a general assumption that countries were moving in that direction. Some partners have been moving towards aP, and some developing countries are already using aP vaccines. The possibility that wP may have certain benefits over aP has already been given visibility and discussed within IVB given the implications on prequalification and polio vaccines, for if IPV is used, it is far harder to combine IPV and wP. The move to hexavalent IPV containing vaccines for global use is still likely many years away.

Tom provided an overview of the situation in the US. The issue of waning immunity has been on CDC’s radar for a few years. In 2010, there was an epidemic resulting in over 27,000 cases nationally with markedly different transmission patterns than in previous years. A case-control study was conducted looking at vaccine efficacy (VE) by time since vaccination. Overall VE in 4-10 year-olds after 5 doses compared with 0 doses was about 88%, which was similar to past estimates. The study did find evidence of waning immunity, with VE 98% a year after the last dose, <90% three years after the last dose, and 71% 5+ years after the last dose. A paper published in NEJM looked at risk of pertussis by time since vaccination among individuals who received five doses, with an increased odds of 1.42 for each year since vaccination. It was a case-control study design defining pertussis as PCR+ and using PCR- controls. A similar study was done using vaccine status from registries, and the risk of pertussis five years after the last dose was about 5-8 times higher than 0 years after the last dose.

In the spring of 2012, an outbreak in Washington State erupted, and rates are high in many US states. By last week, epidemiologic week 37, there were over 25,000 cases nationally. Along with 3,000 known cases in Minnesota that have not yet been captured in the database, this already is more than in all of 2010. Over 50,000 cases are expected by the end of 2012, more than in the last 50 years. In 2010 the pattern of disease in school age children was striking. Rates of disease drop in adolescence with the Tdap booster, but the risk goes up again later. Similar studies as were done in California are being done in Washington looking at Tdap effectiveness by time since vaccination. These data can be looked at soon. So far 14 infants have died from pertussis in the US in 2012. There is a quirk in the case definition that in the absence of laboratory confirmation, two weeks of coughing are necessary for the case to be classified as pertussis. Infants who die from pertussis prior to two weeks of coughing are not attributed to pertussis. CDC is also looking at the effectiveness of maternal vaccination since there is little data currently available. Enrollment in a maternal immunization study occurred over the summer, so results will not be available for about a year. There is an active ACIP working group that will be looking at the results all data. At the October ACIP meeting repeat vaccination with Tdap and vaccination of pregnant women will be discussed.

U.S. States are responsible for responding to their local situation. In some cases, providers are being reminded to give Tdap at 10 years of age, but down the road more 14 year-olds will be at risk. No change in the CDC vaccination schedule is anticipated at this time, although there will be consideration of revaccination.

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with Tdap. There has been discussion within the Infectious Diseases Society of America (IDSA) about a spring 2013 meeting to summarize pertussis epidemiology in the U.S., identify critical gaps, and discuss near- and long-term strategies. One strategy could be a standalone aP vaccine.

Philippe requested clarification of which aP vaccines have been used in the US, as there is some discussion over whether the 5-component aP gives better protection than aP vaccines with fewer components. Tom noted CDC has looked at this and so far there does not appear to be any differences. The first products licensed in the US were aP boosters following a wP primary series. Until Tripedia was phased out in 2002, a mix of wP and aP vaccines were used. Infanrix was licensed in 1998 and Pentacel in 2006 or 2007. Two-component aP vaccines were phased out relatively quickly. Vaccine shortages and concerns over thimerosal affected the market share of given products, which explain risk differences by brand more than anything related to a single product. Now the market is split about 50-50 between the Sanofi and GSK products. The booster product market is also split. A few MCOs have looked at questions around Tdap effectiveness by priming, but so far there do not appear to be differences. Scott noted that infants who received Pentacel are now only 5-6 years old, making them at a key age to study. Some two-component aP vaccines had very good efficacy, such as Sanofi’s (different products were used in Europe and the U.S.).

Tom further explained that in Washington, although there are serious cases, there have not been any deaths so far in 2012. The proportion of hospitalized children and infants with pertussis is a little lower than usual (30% vs. 50%), which may have to do with age. Whoop is always present in cases. There are not a lot of hospitalizations outside the infant age group, which is consistent with past years. Data suggesting that vaccination results in milder disease is outdated, so it is still open question. California appears to have a lower incidence of pertussis now, perhaps because of the recent boosters. It will be interesting to follow over time. He looked at data last week that suggests there is a lower incidence in 1-6 year-olds than there was in 2010. He was unsure what the implications were for the vaccine product. Peter asked whether U.S. HMOs were able to look at vaccination in pregnancy. Tom had not heard, but despite the increase from 0 to 7,000 doses in pregnancy in 2010, it is still a small fraction of the California birth cohort. Although it is possible to look at it, he has not yet seen any results.

Scott described the pertussis situation ongoing in Canada, which was using a 5-component vaccine until very recently. Ontario’s epidemic looks similar to what is going on in the U.S. Saskatchewan was the first province to experience an epidemic, concurrent with California. Rates were as high as 150/100,000, with six deaths in one year, all in First Nations communities. There were pockets of underimmunized susceptibles, which allowed disease spread to immunized populations. The next major outbreak occurred this year in Vancouver and New Brunswick. Vancouver is experiencing a similar transmission pattern as in the U.S., with an increase in infants. The rest of the province may not be experiencing such an outbreak, but with 50% of the population in Vancouver, it must be addressed. The epidemiologic profile may be changing, with cases now primarily in school aged children ages 9-10 years.

Peter noted similar results in Australia among 8-12 year-olds. There is much greater use of sensitive diagnostic tests now, so it is somewhat unclear what proportion of these cases have severe pertussis versus a mild coughing illness, and to what extent they are transmitting pertussis to unimmunized or underimmunized infants.

This year, New Brunswick (population 550,000) had 800 cases over the past year and only 3 cases in Nova Scotia which is adjacent. The main age group affected is school-age children. Rates in under-1s are also elevated, but this population does not have the highest rates of disease, unlike in the U.S. Between 15-20 infants under 1 were hospitalized out of 800 cases, so waning immunity seems to be the issue. Scott felt there was a strong need to do a review of the duration of immunity comparing wP and aP.

Scott continued, noting Canada changed from wP to aP for all doses at the same time, between 1997-1998. All were the same Sanofi pentavalent product. Sanofi had 100% of the pediatric market until recently, when British Columbia switched to Infanrix Hexa. Tdap programs were initially all with the Sanofi product until the GSK product was licensed, and now it varies by province and changes within a province across years.

Tom recalled a review heard at a meeting last week that summarizing aP trials. Two studies looked at duration, one in 6-11 year-olds with the suggestion of waning immunity with aP. It is difficult to compare with wP because of the variability across wP vaccines. Data from older studies may be available, although it would still be difficult to compare due to evolving case definitions. Scott noted the duration for some wP vaccines was short. The idea behind the 10-year interval for a booster was because some data suggested that at 10
years there was zero protection left. There was a period where high immunization rates along with natural boosting reduced circulation in school-age kids, so it is unclear whether wP was ever better than aP. It was felt that there should not be a return to wP, but rather an improvement in the aP product. Peter added that some wP vaccines were clearly poor (e.g. the one used in the clinical trial in Sweden), while others good (e.g. German-made wP product). Estimation of duration of protection likely appears greater when the entire population is vaccinated. There was agreement that although some products may have had a shorter duration of protection, the products did well to reduce mortality in higher-income and lower-income countries, although surveillance is hard in the latter.

Tom mentioned a JAMA research letter\(^2\) that suggested children who were primed with wP had a lower rate of disease than those primed with aP. This was also true for mixed primary courses, suggesting even one dose of wP elicits different protection over time. Peter also noted studies in which those who received wP were much less likely to be identified as pertussis cases than those who received aP. To be able to repeat these with larger numbers and data linkages would be helpful. Scott added that he hoped that this issue will be looked at using data from New Brunswick.

Gayatri described some key changes in the UK. In 1990, the DTP schedule was set at 2, 3, and 4 months. In 2001, a preschool aP booster was offered to children 3.5 -5 years of age. Whole cell pertussis was used until 2004 in the primary infant schedule, when vaccines were switched to aP. Pertussis transmission was not a large problem until 2011. Changes in disease surveillance over time makes some of the more recent results hard to interpret. Widespread serological testing since 2005/6 has improved case ascertainment in older age groups, so rates across years are not always comparable. Looking at infant disease though lab-confirmed cases and hospital data, Despite 3-4 yearly cyclical peaks in activity until 2011 the incidence of pertussis in infants had been on a downward decline. In 2011, there were seven deaths. Most of the disease increase in 2011 was being seen in individuals over 15 years of age without an increase in infant rates until 2012. Now there is a large increase in pertussis rates in infants up to three months of age. Up until September 2012 there had been 10 infant deaths, which is the highest number of deaths for more than a decade. All of the deaths occurred in unimmunized young infants. The other group with an increase in pertussis is the 10-14 year age group. Most should have been eligible for the preschool booster after priming with wP (but this group does include cohorts who may have either had 3aP or 5aP for their priming and preschool booster dose due to temporary changes in vaccine supply) and a case-control study looking at different products is currently underway.

A national outbreak was declared in April 2012. As a result, a number of potential issues and strategies have been discussed, including introduction of an adolescent booster, maternal immunization, and timing of the first dose of infant vaccination. Most children get their primary DTP series on time. As more deaths occurred as a result of the epidemic, there was an urgent meeting in August to discuss various strategies and what should be done. A public announcement will be made in a few days (currently confidential) announcing a temporary maternal vaccination program. The recommendation will be for all pregnant women to get vaccinated during weeks 28-38. The program will last for as long as the outbreak continues, but it will not be routine. She added that although the evidence for the effectiveness of this strategy is limited, given the current outbreak, this was seen as the only measure to reduce infant morbidity and deaths. The program will be evaluated once data is available in about 6 months. The results will include impact on disease burden in infants, vaccine effectiveness and any potential impact of maternal antibodies on the infant response. To look at infant disease and vaccine effectiveness, a case-control study will be done. The impact on infants will be assessed through serum samples collected before and after the primary series, as it will be important to show evidence that maternal immunization does not impact later responses in infants using an accelerated schedule. She acknowledged the challenge in clearly marking the end of the outbreak, and indicators that could be used are under discussion. Because of the high burden in the 10-14 year age group, one indicator could relate to incidence in this group and trends over time.

Scott noted with interest that the wP cohort that also received the preschool booster is now getting disease and the lack of disease in the 1-5 year age group, which is a difference compared to the US. Gayatri clarified those born after 1996 were eligible for a preschool booster shot. Peter added that there is not a lot of general provider awareness of pertussis in older age groups, so there could be disease not currently being captured. Prior to the preschool booster in the UK, no one knew the burden was so high in school-age children.

Given the number of cases in infants and very young children, Philippe questioned whether this could be attributed to more circulation of disease so more exposure or to reduced protection from passive antibody transfer by mothers immunized with aP. Tom noted that the coverage of Tdap in adolescents is about 70% so there is not a lot of boosting. Another study underway is a case-control study in California looking at infant Newborn Screening (NBS) blood spots to look at pertussis antibody protection in newborns. A serosurvey is planned within NHANES, but children under five are excluded from that study. Gayatri also felt the answer was more in disease circulation rather than poor passive antibody transfer, but it is an issue being looked into. UK infant positivity rates (based on PCR testing) are approaching 70%, which was seen as extremely high, even for an epidemic (in Canada, for example, it is more like 20%) but PCR testing is only offered to hospitalized infants with suspected pertussis and not in the community.

Peter described the situation in Australia. The pertussis epidemic was localized in 2008 but moved to every part of the country by the end of 2011. It has been associated with high PCR+ rates in 3-4 year-old children. Previously, a case-control study was done with the national register, and the vaccine was found to be highly effective against hospitalization even following one but especially after two doses, but with lesser effectiveness for two doses against non-hospitalized cases. When cases following the third dose were examined, effectiveness was the same against hospitalized and non-hospitalized cases. Because PCR is so sensitive, more cases in unimmunized infants are being found that never present to the hospital. As a result of the epidemic from mid-2008, a number of state governments made the decision to make Tdap vaccine available free of charge to parents and variable categories of other adults in contact with young infants. New South Wales introduced the most general policy, i.e. everyone in contact with an infant could get a free pertussis booster dose. That policy was implemented in 2009, and most other states followed as their epidemic peaks emerged.

In New South Wales, data collection for a case-control study has just been completed looking at 220 PCR+ cases under 4 months of age and 600 birth date-matched controls from the birth registry between 2009 and 2011. It was found that the proportion of parents vaccinated under the program reached nearly 80% by the time the case infant or matched controls had reached 4 months of age. Around one third of mothers had received Tdap pre-pregnancy; vaccination during pregnancy has not been recommended but is under active consideration. As some women who received vaccination post-pregnancy went on to become pregnant again, a larger number were classified as having a pre-pregnancy dose in year 2. Because most vaccinations are given through primary care rather than in the maternity hospital, most mothers and fathers were immunized more than a month after the infants birth. When eligible vaccine exposure was limited to receiving a dose more than one month before disease onset in the case against this same index date in controls, the unadjusted odds of pertussis in infancy was about 0.40 when both parents were vaccinated, but less than half of controls met this strict definition, in keeping with immunization relatively late after birth in most cases. Ana-Maria noted the multitude of interventions underway and asked how the impact of each individual component would be assessed. Peter replied that because it was an observational study, a number of key variables would need to be controlled for in the analysis and this made model development complex.

In states of Queensland and Victoria are planning similar case control studies, and have had a much higher proportion of vaccines delivered in maternity hospitals. This will result in higher proportions of mothers being vaccinated early in their settings and as they are including cases with onset up to 12 months of age, there will be larger case numbers. Both states have since decided to stop the program providing free cocoon doses, and New South Wales continues to supply just mothers up to 3 months after birth. Western Australia had a somewhat later epidemic and is still fully funding cocoon doses with prospective collection of data about the maternal immunization status of infants with PCR+ pertussis. Similar to the experience reported from California, the State of South Australia, which did not offer cocoon doses, has had a big decline in cases in 2012 following the highest documented pertussis incidence of any Australian state in 2010-11.

A neonatal trial has just been completed in 4 centres, with 440 infants randomized to receive monovalent aP GSK vaccine within 4 days of birth, followed to 8 months. All participants received Infanrix Hexa at six weeks, then 4 months and 6 months. Around 100 of the 440 mothers had received Tdap vaccine pre-pregnancy. Immunogenicity data from this study are expected in the first half of 2013.

There was discussion about strain differences and disease severity. In Australia it has been difficult to study due to most strains now in circulation having the PTXa variant and the reduction in pertussis. However some retrospective data on relative disease severity with different strains may be able to be obtained. The CDC is also hoping to study this. Confidentially, evaluations in Washington State suggest a lot of isolates have
pertactin deletions, and CDC will look at the clinical presentation of these isolates at some of their surveillance sites.

Ana-Maria noted that most of the studies discussed are case-control studies. Also, many interventions are being introduced with limited data to support their effectiveness. She asked whether data will be generated that will be able to inform future policy. Tom believed so, noting that the problem of pertussis will not go away and data are much needed to optimize vaccination policies. Peter added that a better vaccine will not be available in the near term, so in the absence of a better vaccine, it might be necessary to prioritize strategies that are most effective against mortality, acknowledging that it will be impossible to stop mild disease transmission. Tom noted that while a better vaccine is important, the broader vaccine development community has not yet prioritized a new vaccine. Other strategies, such as optimizing the booster schedule, may make sense. At this moment, Tdap is licensed in the U.S. only for a single dose. Scott highlighted that the objective has always been to protect against death, and to stop transmission requires many primary doses and boosters. The 10-year interval for a booster is probably too long, and five years may be more appropriate. Cost-effectiveness of intensive vaccination strategies, especially cocooning, also has to be taken into consideration; in some countries cost has decreased, while in others it has increased.

Ana-Maria described a project undertaken at WHO to optimize the immunization schedule. The goal is to examine alternative schedules, see if they work, and if so, in what contexts. Through a competitive process they have selected the School of Public Health in Paris to do a systematic review of DTP schedules for aP and wP. A similar process has already been done for Hib, rotavirus, and pneumococcal conjugate vaccines. The disease epidemiology and evidence of vaccine impact though different strategies is examined. A protocol for the study has been developed, and a small group of experts will be convened to provide input, look at the protocol, and ask questions. Ad hoc external consultations will occur one month prior to the SAGE meeting to ensure the interpretation of the data is correct and complete. Scott asked how far back data would be reviewed. He noted that part of the issue with systematic reviews is that older studies are typically of lower quality and thus omitted from the final review. Ana-Maria responded that no studies will be removed, but the quality is taken into account with discussion of susceptibility to bias.

Tracey stated that the current vaccine recommendations call for a booster dose between 1-6 years of age. However, few countries have adopted this recommendation, implementation seems to be poor, and there is little monitoring. Ana noted about 40% of countries have one booster officially in the record. Tracey also suggested that there could be synergies for vaccine delivery with other vaccines given during adolescence (like HPV). Experience with maternal immunization is limited, but there is some infrastructure in place for Td and influenza. Scott highlighted poor mortality surveillance in most countries. Perception of a problem with a disease is not enough, and gathering data on the epidemiology and burden of disease is a primary need. Putting in place surveillance to monitor and assess the impact of maternal immunization should also be a priority. Tom noted that many countries in Latin America adopt ACIP recommendations, and an evaluation is planned in Argentina to see how well the program is being implemented.

Philippe summarized the major points of the call. In developing countries there is little surveillance, but there are activities in Latin America and other middle-income countries. There are very little data on pertussis vaccine coverage beyond DTP1 through DTP3. Although many strategies are being implemented to address the current outbreaks, the only recent published data comparing acellular and whole cell vaccines in the field are the Klein paper and JAMA letter (referenced). Pertussis vaccines have had an effect on severe disease, and there is to date no evidence to support reduced effectiveness with new strains of pertussis or smaller numbers of antigenic components in the vaccines. New data on 1-2 dose priming and the effect on severe disease should be shared and flagged for consideration.

The WHO position paper was published in 2010, so it is still fairly recent. There is no urgency to change it now because serious cases are being better managed than before. Despite the increase in cases and infant mortality, numbers are still relatively small and far better than many years ago. WHO’s focus remains on prevention of mortality and severe cases. There does seem to be a clear signal that there are limitations to aP, but the problem remains poorly defined. Many more analyses are needed, and while there should be no haste to switch to aP from wP, policy should not be reversed to prefer wP either at this point. Solid data are lacking on the effectiveness of maternal immunization and cocooning. However, in the next 6-12 months more data will be available. He suggested flagging the issue to SAGE, highlighting the limitations of the current data, and priming a process to look at the issues more in depth in the future. The best time for this closer examination could be in November 2013 or April 2014, with the reactivation of the pertussis working group. It is also important that Ana have all of the upcoming data for the systematic review, and it would be a great
omission to complete the review without the new data. Philippe encouraged continuous discussion of published and unpublished data, including timelines for results.

Scott added that in the past a lot of work has been done modeling duration of protection, and many different estimates were generated. Efficacy studies made clear exposure to the natural disease did not confer lifelong protection. He suggested that further work with modeling could be done. Tom suggested perhaps protection derived from natural exposure is more important, and Peter estimated duration of protection from natural infection lasts about 20 years, wP 7-10 years, and aP about five years. Philippe noted this is much lower than the 10-12 years duration of protection discussed in the pertussis working group.

Tracey suggested that with all of the attention to these current outbreaks, WHO will need to draft some kind of written response. Philippe agreed and asked whether there were any additional critical steps needed by WHO. Everyone agreed that encouragement and facilitation for improved vaccines would be helpful.