QUESTIONS AND ANSWERS FROM PSBI COP WEBINAR 11-29-18

RESPONSES BY DR. RAJIV BAHL (WHO)

PSBI Implementation Research

QUESTION: PLEASE CLARIFY THE WAY YOU CALCULATE THE NUMBER OF LIVES SAVED?

We are assuming that there are six million cases of PSBI every year, based on previous data. If we were able to treat 75% of the six million cases, you're treating 4.5 million cases. Then you apply the difference. If it were at 7% of case mortality, 7% of 4.5 million children would die. If it were 2% case mortality, then only 2% of the 4.5 million would die, or that we would save 5% of the 4.5 million. And that is 225,000 [potential lives saved per year]. So essentially what we think we are doing is reducing case mortality. We are reducing case mortality because we are treating more children. If we are treating more children, we have lower case mortality, and therefore this is consistent with what was included in the calculations at about 85% or 90% efficacy of antibiotic treatment.

QUESTION: IT'S EXCELLENT TO SHARPEN CRITERIA AND FOCUS ON THE MORE SEVERE. PLEASE TELL US RESOURCE REQUIREMENTS (HUMAN, FINANCIAL, ETC.) TO IMPLEMENT PER CAPITA?

We are currently working on two things. One is a paper has already been written and is now being submitted on the costs of PSBI programs. The paper is based on AFRINEST data, which means that it is higher cost because it was essentially done in the research system and the costs were probably higher. And even with that, I don't remember exactly what the costs are, but they are much lower than what is considered to be highly cost effective. I don't want to give you a wrong number, but I am happy to send this around. The paper is submitted for publication.

We are also doing costing on the implementation research studies to get a more realistic programmatic estimate of costs. As far as human costs are involved, essentially all these projects or research studies did not envisage using new human resources. They are using the same human resources—the nurses who are treating children and newborns in health centers, or the doctors in some settings in Asia who are at the primary level, etc. There are no new resources, but there is of course the question of how they perform. The community health workers, for example. If there are only 10% of home visits, but in this case with the implementation research this increased to 60-70%, that would of course require effort and add some costs. If the community workers were paid, for example, based on their performance, it would increase the costs. There would be financial costs and some human costs in terms of supervision and treatment provision, but no separate human resources were used in most settings. The exception

being in Nigeria and DRC where the study team was trying to replace non-existent workers. In that case it was not that they were adding workers, the workers were not there.

QUESTION/COMMENT: THERE WERE 3.2% DEATHS AMONG THE CLINICAL SEVERE INFECTION (CSI) GROUP. HOW MANY OF THESE CSI CASES WERE TREATED IN HOSPITALS AND HOW MANY IN OUTPATIENT SETTINGS OR PRIVATE HEALTH CARE FACILITIES? ALSO, IT IS VERY INTERESTING TO SEE THE NUMBER OF PSBI CASES SEEN BY HEALTH FACILITIES. IT WILL BE VERY INTERESTING TO ALSO SHOW THE TOTAL EXPECTED PSBI CASES TO APPRECIATE THE PROPORTION OF PSBI CASES WHOSE CAREGIVER HAVE SOUGHT CARE FROM HEALTH FACILITIES.

FIRST PART: WHAT PROPORTION OF CLINICAL SEVERE INFECTIONS WERE TREATED IN HOSPITALS VS. OUTPATIENT FACILITIES.

The proportion was 10-20% in hospitals. Some sites were as low as 10% in hospitals and 90% in outpatient facilities. Others has about 20-25% in hospitals, so 75-80% in outpatient facilities. Almost every site had 80% treatment of clinical severe infections, which is consistent with the previous data that only 20-25% of the cases go to hospitals. One thing we have been observing repeatedly, but don't know the exact explanation of, is that those children who end up in hospitals consistently have higher mortality rates than those in the outpatient settings. This can be due to three different reasons: one possibility is that we are treating early, and once you go to the hospital it takes time, and by the time the family reaches the hospital the child might be more severely ill; another possibility is that children go to hospitals, get better and then get worse because they get infections and then die; but the third equally likely possibility is that the parents make a decision to go to the hospital based on the signs they see that their child is more sick, and the more sick children end up in the hospital. All those are feasible. We are not able to make a conclusive comment on this, the only comment I have is the proportion who die in the hospitals is excessively high. For instance, about 30% of those with critical illness will die in the hospital. That should not happen if good treatment is available. We know that it is possible to reduce the mortality to less than 5% based on our experience from higher levels of care in richer countries. Not only is it important to send children to hospitals but also to improve the quality of care in hospitals.

SECOND PART: IT WOULD BE INTERESTING TO ALSO SHOW THE TOTAL EXPECTED PSBI CASES TO APPRECIATE THE PROPORTION OF PSBI CASES WHOSE CAREGIVER HAVE SOUGHT CARE FROM HEALTH FACILITIES.

Sure, we can do that. We have given coverage and can share the two numbers.

QUESTION: PLEASE ALLUDE TO THE CAUSE OF LOW TREATMENT COVERAGE IN BANGLADESH.

One has to understand the health system and at what level this intervention was implemented. What we have learned is there was a huge question mark on who should provide this treatment when WHO issued these guidelines. For example, in Ethiopia initially it started with health extension workers at health posts, which is the lowest level facility, but not at the outpatient hospital level where a lot of children end up in the hospital but don't want to be admitted. So, if we want high coverage, one of the lessons we learned is that Ethiopian early guideline of only doing it at the health post level has stumped the flow. A similar guideline was issued by the government of India which said that only ANMs (Auxiliary Nurse Midwife) would do outpatient treatment if there was no referral. But ANM's don't come into contact with these children just like health extension workers. The parents don't usually bring these

children to the health workers, and therefore ANMs only treated 9% of children who received treatment.

That's one side of the story. On the other hand, Bangladesh said they didn't have a community level worker, and didn't feel the community clinic was sufficiently prepared to treat these children. They would only treat the children at the union council level, which is a higher level. That means these facilities were far away from home, and that is reflected in the low coverage. It is also reflected in not getting to see these children on day 4, because it is very difficult, particularly if the baby is doing well, for the family to bring the baby back if they live far away from the facility. So that was one side. The other side is the efficacy of community health worker programs. Where there was a solid community health worker program that was doing postnatal care visits and served as a link between communities and facilities, coverage was much higher. In Bangladesh, there were hardly any postnatal care community visits. From my perspective, those two appear to be reasonable explanations for the causes of low treatment coverage.

QUESTION: PENICILLIN RESISTANCE HAS BEEN REPORTED IN NEWBORNS IN PAKISTAN AND CULTURES SHOW THAT THE ORGANISMS ARE SENSITIVE TO AMINOGLYCOSIDES. IS THERE A NEED TO RECONSIDER THE RECOMMENDED DRUG REGIMEN?

I have two responses to this question: the first is, in 2009 or 2010 when we were planning the first set of studies (i.e. SATT and AFRINEST) one of the biggest concerns we had was antimicrobial resistance and that there would be penicillin resistance, or gentamicin resistance, and whether using this simple protocol would be helpful. Interestingly, the findings from Bangladesh, Pakistan, and the three African countries—I haven't seen a more consistent database. The outcomes were so consistent between groups, the failure rates, mortality, etc., were so similar to each other. That was one piece of good news. That even if there is invitro resistance, we know from previous research that it does not translate to in vivo resistance.

Achieving very low mortality rates and low rates of treatment failure in these large implementation research initiatives also reflects the fact that clinical efficacy is good. Now, using only gentamicin is one thing that you have to consider very strongly, is that for gram negatives the combination of two antibiotics has often been recommended in severe cases just to make sure that we cover the resistance in both ways. So, the risk of using monotherapy is actually a generation of resistance against aminoglycosides. That is something I would be very concerned of, if we end up having monotherapy and resistance against aminoglycosides increasing. Personally, I see very little logic in monotherapy with gentamicin.

QUESTION: SOME COUNTRIES ARE AFRAID THAT THE RECOMMENDATION OF THE SIMPLIFIED ANTIBIOTIC REGIMEN WILL LEAD TO FASTER DEVELOPMENT OF ANTIBIOTIC RESISTANCE?

This antimicrobial resistance is as much politics as it is science. I often look at it from two perspectives: first examine where is the antibiotic being used in terms of the total number of antibiotics being produced and consumed. If I am right, the majority is in animals, and not in sick animals. It is for dairy, cattle, chickens, and the rest. The second is the environment in which it is being used and how it is contributing to the environmental impact of unused antibiotics. The third is use in humans. Now, when it comes to humans there is the question of the ethics of using antibiotics judiciously vs. non-judiciously. If I see the doses of antibiotics used for upper respiratory infections in any of these countries, compared to newborns who have signs of sepsis, it will far outweigh them. It's not the question of use of antibiotics, it's the question of when is antibiotic use justified? Things that have high mortality, and the

risk of death associated at a high level, it is justified to use antibiotics, vs. where the outcomes are two more days of cough and cold. That should be our model. If we are talking about untreated PSBI, the risk of death is 15%. When you use antibiotics for adults, by rate of condition, you might be talking about risk of death that is .5- 1%, and you still think it is highly justified. When we talk about sepsis, we are talking about very high risk of death situation without treatment, and the benefit is that you can reduce the risk of death from 15% to around 1%. So, the cost effectiveness in terms of lives saved would justify the slight increase in use of antibiotics. The bigger problem with newborn sepsis treatment today is use of third, fourth, fifth generation antibiotics. These are very rare antibiotics. I think that is causing more trouble than a standardized treatment of all suspected cases with limited antibiotics.