

Dr. Peter Aaby: We are going to change gears now in terms of we are going to the low-income countries, and we are also going to talk more about children than adult problems, but it will still be about power structures.

I have based 40 years ago I started what is it called a health and demographics surveillance system, where we are registering sort of all the tracking system deliveries, child interventions and survival, and that's the basis for the data I am going to present you. I've also collaborated with a lot of other health and demographic surveying sites in Africa and Asia, so some of the data will be coming from there.

This is about vaccines, and I think it's important to recognize that no routine vaccine was tested for all the effect on mortality in randomized trials before being introduced. I guess most of you think that we know what all our vaccines are doing, we don't.

The program we are talking about at this time the vaccine program was introduced sort of in the late seventies after the successful eradication of smallpox. WHO made the first immunization program for the low income countries.

The program used initially was BCG for tuberculosis and oral polio vaccine at birth and then they got free doses of DTP - diphtheria, tetanus and pertussis and oral polio vaccine free dose in the first month alive. Then you got measles vaccine around nine months and then booster dose of DTP and OPV. That has been the basic of the program and now they're a lot more of vaccines being introduced and that's part of the problem we are going to talk about.

If you thought that public health was a rational science, you should look at this curve. This is what has happened in the 40 years I have been in Guinea-Bissau. Mortality dropped 85%. That's a staggering reduction in under five mortality. 85%. I don't think that ever happened in the human history.

But it's not like a learning curve. If it had been a learning curve, it would have gone down gradually like this. This is going down and up, down and up. It is essentially saying we don't know what we are doing. Sometimes we are doing something which is very good, but we have no clue of what we are actually doing here.

The first point here is when we introduced used Measles vaccine. So from one year to the next mortality dropped threefold you have it here and that was a very strange experience—it is out of your mind suddenly see that the data coming out. All the children we had vaccinated that didn't die. Whereas those who had been traveling and they'd also got the vaccine, they still continued to have high mortality.

I guess that experience defined my life and therefore I've been trying to look at what has happened in other places. What do we actually know about the introduction of measles vaccine

and there are already five studies in the literature you have them here. All of them show more than 50% reduction between the year before and the year after the introduction of vaccine. This is not selection bias, this is everyone in population. Some of them will not have been vaccinated but there were some campaign they introduce measles vaccine and mortality dropped with 50%. Measles is assumed to reduce mortality with something like 10 to 15% by WHO.

We have a contradiction here. Measles vaccine protects much more against much too much. How's that possible? I was very encouraged with this first experience and therefore I want to just go, can't we vaccinate earlier to save more children's life.

Saving had developed some interesting and new measles vaccine, which could be immunized in the present and maternal antibody. Saving is the guy with the oral polio vaccine. Then it showed that you could actually immunize in the present and maternal antibodies, so therefore you could potentially to give it earlier. We start randomized children at four to five months of age and we randomized to high titer a measles vaccine and we are giving them in up higher dose and then inactivated polio vaccine as a controlled vaccine. Then we switch over at nine month this is the recommended age for measles vaccine, and these guys got IPV after the measles vaccine and this one got the recommended measles vaccine.

Something very strange happened in both Bissau and Senegal. If you can see the curve, it might be a bit difficult but the blue lines are the boys and so there are no difference in mortality, in the control group whose got measles at nine month or that those who got the new measles vaccine around four month and the same, you see the same thing in Senegal.

If you look at the red ones, which are the girls that is two-fold higher female mortality if they got the new Measles vaccine, if they've got the measles vaccine early. When you saw the first part of this curve, I wrote to WHO and said, "Please check with other people who have used this vaccine. Is there anything going on here?" And yet I got a letter back saying, "Thank you for your interest, but we note that you have small numbers". Which meant that, if you look at the girls and no doubt there's a problem here, but you can't do a subgroup analysis unless you had planned it.

I'm a naive anthropologist, so I don't know nothing about statistics, but I can look at data and see this does not make sense. They didn't do anything but then eventually because it was a Dane who was the director of the vaccination program at that time, I managed to convince them that had to have an expert panel to discuss these data and we presented the data that we saw in Senegal.

The expert decided this is not plausible. There's no biological explanation, so it can't be true. Secondly, you said it had not been planned and I said you cannot plan to kill children. What does that mean as an argument? This is what it is in the public on the record in the weekly Premedical record that there was unplanned studies so you couldn't rely on them.

Luckily one of the members of the panel was American from Johns Hopkins. He went back to answer how you think, where he used the vaccine and he found the same thing and they the Sudan found out, Canadians in Sudan found similar observations, so just one year later WHO withdrew the vaccine.

There were no real explanations that just went back and interestingly they made no attempt to understand what has happened. If that kind of thing can happen with our vaccine it can obviously happen again. Well there's nothing-I think there are three very importantly elements here, one is that you can have a vaccine which is fully protective against the specific disease but associated with higher mortality. How's that possible? That's nowhere in the textbooks.

Secondly that it's sex differential. Everything we do is about children. No one who report children data separately for girls and boys.

Thirdly it's the size of these problems. The next analysis of the African studies showed that the mortality between four months and five years of age, so that's most of childhood mortality, was at 33% increase all of it being female increase in mortality. Just in Africa that would have meant half a million, at least half a million deaths, additionally female deaths pay year.

We are talking about big numbers If we play with the immune system. What about the other vaccines? This office raised the issue. What does the other vaccines do? I started, I went back to look at the data we had been collecting in the interior, where we visited the village to stay for six months. We registered, we weighed the children, and then we registered their vaccination stages based on the vaccination cards.

We are coming back every six months. That's why the line here is six months. If you take the children who had received no vaccine at the first visit, you see here, they had, over these six months they have 5% mortality. Very high mortality but that was not uncommon in Africa at that time.

If you take the children who have received BCG they have only half the mortality. All of those who have been trained to be even volunteers, they will know, this is because it's the best children getting vaccinated.

This is a selection bias. You shouldn't pay attention to this. However, if you get another vaccine, then mortality should have been up here. That should be even better if you get the next vaccine, but actually if you've got both BCG and DTP you ended up very close to the unvaccinated group in terms of mortality.

If you put this data into survival analysis what comes out is that BCG reduces mortality with 45% but DTP, diphtheria, tetanus, pertussis, which is the most commonly used vaccine in the

world, increases mortality by 84%. I had sent this data for years earlier to WHO and nothing happened at our first analysis. Then when BMJ accepted the paper they got a bit nervous.

We were called to a meeting in Geneva and I invited them, you're welcome to come to Bissau and check our data. They sent a mission of three people to Bissau. Then they started sponsoring several other sites in terms of finding out can we find the data somewhere else.

I clearly had the feeling that they were going to come after me. That's the feeling you get if you come up with something which is unpleasant to those who hold power. You know they will be coming after you, so I said I'd better go back and see what data do we actually have, can we use some of our data, is this a fault, a track or is there anything to this evidence?

I went back to when we had introduced DTP in '84 in the rural areas of Guinea Bissau. It was my team which was visiting the villages every six month. We were weighing the children in terms of identifying the malnourished children. The malnutrition was really the issue of our research agenda and that was what we had been paid to do, but and we did provide the vaccine as a service to the community. Not really as a research project, but the data was there. We had registered who had been vaccinated, who had been absent and who had been too sick to be vaccinated.

The un-vaccinated children here are children who were traveling or were sick and there were days where the fridge didn't work in the regions so we couldn't have any vaccines there. You shouldn't expect that those kinds of children should have been higher mortality, they had low on nutritional stages so they should be worse off.

However, what you see here is that over the next six month there were two times higher mortality with those who had received DTP, so the whooping cough vaccine or pertussis vaccine was associated with two-fold higher mortality. Please note that the tendency is that this seems to be slightly worse for girls.

By now, I had made three studies of the introduction of DTP in the early 80's. They all show a negative effect. These are methodologically the best studies as a natural experiment, we won't have time to go into the detail, but what you see here in the selection bias, it is the worst children who are not getting vaccinated.

In spite of that what comes out here is you had 2.3 times higher mortality if you are DTP vaccinated, and that is the most commonly used vaccine in the world. Note again that this is clearly worse for girls than for boys. It's not good for boys but it's, look, the girls do worse. By now we have I think 16 studies on what happens on if what happens-no selection bias here- This is boys and girls getting vaccination and in West Africa, the coverage for boys and girls is essentially the same. They are all compliant.

You are comparing what happens to the mortality of boys and girls who receive the vaccine. It's 50% higher mortality for the girls than for the boys who have received DTP vaccine. That is an unnatural observation because prior to the introduction of vaccines there were no, there were no excess female mortality, was slightly lower female mortality, and it's always unnatural in the sense once you give them measles vaccine, girls have lower mortality than the boys.

This is clearly an unnatural event. Please note that this seems to be negative boosting. DTP one is 20% higher mortality, but then when you come to DTP three it's 70% higher mortality for the girls for the boys. You should know that DTP three is the vaccine they use to monitor the vaccination program in low income countries. It means that all vaccine performers out in the low income countries, they will emphasize and getting DTP three out. They won't pay too much attention to measles and BCG coverage, but they will pay attention to DTP three because that's what's determined whether they get rewards and promotion.

That vaccine is actually killing children. It's not just a differential effect. It's killing children. It's not because it saves boys. The vaccine is killing children and that's the vaccine that we are using for monitoring the performance. We need to have a vaccine which is, have beneficial effect for covering the vaccination program.

This observation on the sex differential effect of DTP suddenly gave a totally different interpretation of what we had already showed through the high titer vaccine. When we introduced the high titer vaccine what had happened was that we gave measles vaccine already at four to five months of age. That was so early at that time that most of them, and nearly all of them got DTP after the Measles vaccine.

Then we said let's go and see what happens if you've got DTP after measles, if you did not get DTP after measles and here is all the data from Africa and you can see these are what's shown here is the number of female and male deaths. If you have a no DTP after high titer measles vaccine, you have essentially no difference in the mortality, but if you've got DTP or IPV after measles vaccine, there are two-fold higher mortality for the girls.

In a sense that solves the problem with the high titer vaccine. It was a question of the sequence of vaccination and it's the last vaccine which has a strongest immunological influence. It was associated with very strongly higher mortality.

This was published in 2003 and in 2004 WHO actually got their act together in terms of having analyze the data that they had commissioned and therefore what's called the Global Advisory Committee on Vaccine Safety. That's the main party in the world to decide about vaccine safety issues and they came with a statement. Analysis of WHO sponsored Studies is now complete. The studies did not show any negative effect of DTP vaccination and no difference was found between males and females. The committee concluded that the evidence is sufficient to reject the hypothesis of an increased nonspecific mortality following vaccination, and the effect seen in Guinea-Bissau was properly explained by a confounding factor in the dataset.

They could have said that I was an idiot but they didn't say it directly. They just said that there is a confounding factor in your dataset. They didn't help me by saying which confounding factor, how could that actually happen if it's the worst children who are not vaccinated, how can it be a confounding factor? It doesn't make sense.

There were several other dataset already at that time, but they only came with their statement that their own studies had shown no negative effect. Then to back up their point they got an esteemed group of very well-known professors from the London School to come with, to form a task force on routine infant vaccination on child survival. This taskforce was only about the DTP issue.

The conclusion of this task force, that their report is not published. The data they actually analyzed is not there but the conclusion is on the Internet. It's like the task force were unanimous that the totality of the evidence provided in the paper review does not suggest a deleterious effect of DTP vaccine. On the contrary, they provided substantial evidence against such an effect.

Furthermore, with the exception of the studies from Guinea-Bissau, there was little differential effect between boys and girls. That's saying yet another time that I'm an idiot and I have to report back to my foundation that I was being declared idiot, however we had actually predicted this when they had the discussion on the vaccines in 2001, we said that the WHO sponsors studies would produce survival bias.

Survival bias is that and you give information is better for those who survive. That happens very easily in this situation. Give you a simple example. You visit two children and then you come back six months later, one child survive he was vaccinated three months ago, and you will count that child as vaccinated from three months ago, but there is another child would have died. You actually don't know anything the parents threw the card away. What happens? It declares the client as un-vaccinated because we have no information, but no information is not un-vaccinated. If you put that into survival, it means that this time it's risk free because if the child had died, it would have been classified as un-vaccinated.

If you put that data into survival analysis, you essentially get not garbage, you get nonsense out of it. That was what WHO studies had done. It took several of us 30 years to convince the people from the London School. Yes there was a problem with survival bias and they eventually wrote an editorial, a global advisory task force accepted this and then the Global Advisory Committee on Vaccine Safety came to us with an issue. They said we will watch out for potential deleterious effects. WHO then in 2014 made their own review. We had produced enough data to say there are nonspecific effects of the vaccines, and then they made a review which included 10 of the 16 studies with age on DTP and vaccination.

They came out with an estimate that DTP was associated with 38% higher mortality. That would be difficult to see, but what they said is the findings were inconsistent with a majority of the studies indicating a detrimental effect of DTP and two studies indicating a beneficial effect. These studies aren't here.

However those two studies have major survival bias, so they in spite of the previous discussion they had included the studies with survival bias. If you exclude the studies with survival bias, which comes out is for the studies we have now is that there are two-fold higher mortality if you have received DTP vaccine.

The findings were not inconsistent, the methodology had been inconsistent. One interesting aspect here is you've triggered all the studies in this review you will see a very clear pattern. These the studies where you evaluated both DTP and some of the live vaccines tuberculosis and measles vaccine. You see all of the DTP effects are about one and all of the effect of measles and BCG is about well below in terms of in fact on survival.

We are talking about BCG and measles being associated with 45% lower mortality and DTP clearly being associated with higher mortality. Most of you have not been trained in this the immunology is coming now. It's been developing for the last five to 10 years that we forgot about the innate immune system. That's the first line of defense, it's not about T cells and B cells. It's about innate immune system, and the innate system is changed when you get these vaccines, so you can induce enhance performance by the live vaccine, but you can also induce tolerance with an activated vaccine and that's what happening. If you give DTP after measles vaccine, you get the same picture, two-fold higher mortality. Again, it's the girls.

I'm saying this because WHO had planned to introduce booster dose that we have in the Western world problem with a booster dose. Therefore, they wanted to introduce a booster dose also in the low income countries that will have negative effect. This is not just about DTP, I'm just showing you so there was one of the last slide that GSK have developed a malaria vaccine and that's going to be introduced now. We eventually got the data by sex from the malaria vaccine.

What you can see here is that didn't really matter for the boys, but for the girls there were two-fold higher mortality if you have received them. In spite of the protection against malaria, there were two-fold higher mortality for the girls who had received the new malaria vaccine. We are currently testing this. WHO is testing this vaccine in Africa in three countries with 720,000 children.

If there's anything to their own data, we are going to kill somewhere between 2,000 and 5,000 girls unnecessarily. What I have been trying to give you here is a very brief in 20 minutes to give you 40 years of work, but there's good news and there's bad news, and the good news is every time we introduce a live vaccine, measles, BCG, measles again and what has happened towards

in the last 20 years is not appreciated. The information is nowhere. We don't know why did mortality drop 70% in the last 20 years.

Mortality dropped because we made campaign after campaigns after campaigns with BCG, inevitable with measles vaccine and OPV and we have documented this for both of these vaccines. When you have these campaigns then your mortality level is dropped, so you have to de-learn everything you learned at the university. It's not about specific diseases is how you train the immune system and these live vaccines, apparently train the vaccines beneficially but the negative part is when we introduce DTP or DTP booster, that was what I showed you earlier when you introduce DTP booster mortality goes up. When we introduce Hepatitis B, was this also an inactivated vaccines, the same thing happened. By now we have shown negative effect for girls for six inactivated vaccines. I would argue that we should have to do something about a DTP and that's in the sense I think is the question to this new center.

What to do, how can we actually approach this kind of situation? WHO has said that they would recommend nonspecific and thorough research on nonspecific effects, but they also said they cannot study DTP, so the committee which was sit down to work on these issues has declared that they cannot study DTP. That's a challenge.