Panel discussion of Controversies in GBS Prevention

Panel; Prof Cathy Warwick (Chair), Dr Alison Bedford Russell, Prof Neena Modi, Dr Gopal Rao, Prof Philip Steer, Dr Andrew Thomson.

Cathy Warwick: So, shall we start with really this issue of the overuse of antibiotics, and Alison perhaps you'd like to start because you kind of gave quite a good exposition of that this morning?

Alison Bedford Russell: In fact, thanks very much Cathy. Just as general principle, we are in a global crisis with antibiotic resistance and I think we need to be very, very mindful that, any time we give an antibiotic, it has to be for a jolly good reason, in the appropriate dose and for as short a time as possible, that is appropriate. So, from a resistance point of view if we didn't have antibiotics, there would be no antibiotic resistance and, although part of the problem with antibiotics is that they are in the food chain and we can't do anything about that, there are practices that we can do everything about and it is everybody's problem... it's the midwives' problem, it's the junior doctors' problem, it's the microbiologists' problem, it's the pharmacists' problem, it's my problem, it's not just someone else's problem. And it's also the user's problem so everybody who is going to be given an antibiotic needs to be cognisant of the fact that they will change their floral pattern if they have an antibiotic. And our other organ - you know we have liver, kidneys, all that sort of thing - we have more bacteria sitting in our colon than we have human cells in the rest of the body. And for most of us we live in a little sort of symbiotic relationship with our faecal flora and our faecal flora keeps us immunologically healthy. And we know that people who have poor immune health often have abnormal bacteria. We know obesity is associated with abnormal bacteria. If you put obese mice's faeces into thin mice, they get obese and vice versa. We know that irritable bowel syndrome is mended by faecal transplant from someone who doesn't have irritable bowel syndrome so we are desperately, desperately dependent on our faecal flora for immune health and that is another reason we have got to be very, very very careful about using antibiotics unnecessarily. However, antibiotics are and can be life saving and they are life saving in infection- in established infection and they can be life saving for babies when the mother is at risk of transmitting group B Strep. So, for me it's all about judicious use. I think for the child... I just want to reiterate the sort of the clean child hypothesis as it's sometimes called, although it's more complex than that, dictates that immune health in children is heavily driven by maternal faecal flora. If we abnormalise maternal faecal flora, we will abnormalise the development of the naive immune system and we have to be very, very cognisant of that because there's increasing data to support that. So, the principles must be that we have jolly good reason for using antibiotics that are targeted at the right individuals and, for me, I think giving mothers antibiotics because

they *might* have something that we should give antibiotics is simply not good enough in this era. We have other tools, we hear about PCR for example, as well as culture based methods. I think we've got to get a lot more cleverer than this. So I'll shut up at that.

Cathy Warwick: Thank you Alison. So just before I bring in Dr Rao, can I ask the obstetricians on the panel, in that case if there's, you know, a positive move towards introducing more antibiotics for GBS, should we be changing some other guidelines. I mean what about routine antibiotic prophylaxis for caesarean sections? I mean is this a case of trying to make the guidelines work more together?

Gopal Rao: Caesarean section infection rates ... frequently they are superficial infections and not deep infections, superficial infections and they present frequently some days after the operation so we are not really differentiating between intra-operative acquisition of the infection and the post-operative acquisition and the midwives follow up the mothers for up to 10 days after the procedure. Now, for all this caesarean section prophylaxis, which is pretty much every hospital now complies with it - and you are taken to task if you don't, I'm not seeing a corresponding fall in the caesarean section infection rates because the prophylaxis acts only for the intra-operative infection rates. Subsequent to that a recent study which was done by Public Health England that some of your colleagues from Public Health England may be able to come in better on that but this was a study that was done by Jenny Wilson and others which showed that the consistent rate of infection was 10%. Now 10% is an awful lot of infection but most of it is superficial; most of them is post discharge infection.

Cathy Warwick: Thank you-

Gopal Rao: So I take your point if you were leading up to saying whether it was useful or not I would be a little sceptical about whether it's useful or not.

Cathy Warwick: OK well I ... thank you very much for that. I mustn't draw us down a different issue which is caesarean sections but I suppose my point is really do the guidelines need to tie up more because we've heard today all about, you know, this issue of harm and could we minimise the harm of routinely screening for GBS by changing what we do in other areas. Andrew what do you think? Should the RCOG be looking more broadly across its guidelines?

Andrew Thomson: I suspect the practice of obstetricians and midwives is heavily influenced by the triennial confidential enquiries reports. I was explaining to Jane earlier about one of our guidelines - number 37A thrombosis prophylaxis is an incredibly complicated and very difficult guideline with lots and lots and lots of pages of risk factor assessment and yet that particular guideline was credited with reducing the number of maternal deaths in the UK from thrombo embolic disease. So, the confidential enquiries certainly influence our practice. The last 2 or 3 enquiries have highlighted sepsis as being a main cause of maternal

death and that's why I think whilst it is our concern, it's everyone's concern about our long term flora and fauna in our bowels, when we are actually working in a labour ward or we see someone with a suspected urinary tract infection in an outpatient department, I suspect that's why they are given antibiotics because it's in the front of our mind that sepsis can be life threatening in pregnancy.

Cathy Warwick: Thank you Andrew.

Phil Steer: Something that GBSS has promoted ever since it was formed is actually trying to stop the unnecessary administration of antibiotics. I would agree with everyone. I think when a woman is admitted with a bit of dysuria, with no temperature and no other symptoms and had been started on antibiotics, I used to have a little bet with the SHO that the culture would come back negative and I used to win 9 times out of 10. So, there are areas that we could all draw back and we've spent a lot of time stopping obstetricians giving repeated courses of antibiotics during pregnancy; even some well-known obstetricians have phoned me up and said "I've had somebody who lost a baby and I'm going to give her antibiotics every fortnight for..." and all this sort of stuff. The issue then arises as to what is the alternative. We're not talking here about using prolonged courses of broad spectrum antibiotics. We need to remember that in terms of upsetting the flora, we are using an antibiotic which is the longest one we've ever had, more than 60 years of penicillin. It's very narrow spectrum, we know a lot about it, most organisms that would have become resistant are already become resistant. It's given for a short period of time. Now, as we've heard, there may be some short term effects on the microbiome although in the longer term, up to a year, there don't seem to be any. But that doesn't mean to say that giving 20% of women penicillin is something that we're pleased about. If it was possible to determine which strains of GBS were more pathogenic, so we've already heard that that is something we should explore, so that we could restrict giving the antibiotics to those women who carry those pathogenic strains a bit like human papilloma virus is and CIN for example we know which ones cause the trouble, that would be great. If we can have a vaccine which works, that would be great. The issue for us at the moment is that, at the present time, the risk factor approach seems to be resulting in lots of women getting antibiotics which in fact are not necessary because the woman is not a group B strep carrier, and a lot of women who are carriers whose babies end up getting early onset are not getting it and actually those two are relatively balanced; the numbers are quite similar so it seems to us to be a bit more sensible to be giving it targeted in women that we know are carriers while we are waiting for the vaccines to be developed. So, if we have something which is better - great we can stop giving penicillin. Our immediate concern is, as of now, there are women in labour whose babies are going to end up with early onset group B Strep and what are we doing for them? And it seems to us that in the short term giving something like penicillin briefly in labour to reduce the risk by - and we've heard this question is it 70% or 90%? It might be worth mentioning here - that the meta analysis included all the studies of the effectiveness of antibiotics including large numbers of studies which were criticised at the time when they were written up as using the wrong swabs, poor culture medium, leaving them in the fridge

for 3 days before they were sent for culture and so on. If you look at the studies which have been done which followed best practice, we're talking much more in the region of 90% effectiveness not 70%. So I think at the moment what we should be doing is actually keeping our eye on all these issues so IAP for GBS but also looking at the issue of erythromycin for ruptured membranes. I mean there's a good case to be made for this is past its sell-by date and we should perhaps stop doing that. I am seriously concerned about the very large numbers of women being given broad spectrum antibiotics for caesarian section and the glib statement "no harmful effects have been shown on the baby" doesn't- absence of evidence is not evidence of absence. So I think actually it is a duty of all of us to bear this antibiotic resistance thing in mind and go for what seems best at the time, without ignoring the fact that there may be something better we can do in the future.

Neena Modi: I mean, I'm here as a neonatologist and let me say first of all I think it seems that we should agree with the conclusion that the current guidance is inconsistent and that doesn't serve families well at all. The second point is that there is a great danger of the imposition of a consistent guideline when the evidence base is insecure because of course you may well impose guidance that is in fact the wrong thing to do. So I think the imposition of a consensus based guideline, in other words a guideline that is not based on good evidence, is a really serious patient safety issue. And I'm going to give you a graphic example of that from neonatal medicine which is that for years we used 100% oxygen routinely for resuscitation; that was considered best practice and there was a great deal of dissent when people said actually, hang on, this is a powerful oxidant and it might actually be doing babies harm. Roll on several decades, we no longer routinely use oxygen for routine resuscitation. So, I think as clinician scientists, if we are really concerned about the best outcomes for our patients, we do actually have to recognise that imposing consensus based guidelines may well be extremely dangerous indeed. But where does that leave us then today? Well, it leaves us with, as I say, one firm conclusion that I hope we can all agree with: the current guidance is inconsistent. It also, I think, leaves us with the position that there's a great danger in actually imposing something that may well be harmful and therefore, for me, it seems that the self-evident conclusion that we have to draw, we have to reach is that we really must stop trying to draw up guidelines on the basis of inadequate evidence but instead put all of this passion, energy, effort and well-meant determination to improve things for our patients towards actually addressing the science, doing the studies and getting a sensible outcome. And if we have collaborated to do this 5, 10, 15 years ago; we would now have the answer. So I would like to say that, on behalf of the Royal College of Paediatrics and Child Health, I'm very, very happy to work with my colleagues in the Royal College of Midwives, the Royal College of Obstetricians and Gynaecologists to actually advocate and lobby in order to secure the funding to do the sorts of trials that we need to do.

Cathy Warwick: Thank you Neena

Alan Cameron: I think you told us that the study proposal that went in and was rejected was around £11 million so this is a time of austerity, I think we would struggle to get- I very laudably accept Neena's kind offer but I think getting funds and resources to do that study now would be quite a struggle.

Cathy Warwick: Right, further comments. Dr Rao you mentioned earlier that you'd noticed that the baby's flora returned to normal. Do you want to ....?

Gopal Rao: I must hasten to add that it was not my study, it was a study that was published in the British Journal of Obstetrics and Gynaecology; this was a study that was done in Canada actually. This is a group which has been long interested in looking at the microbiota of the mothers and the babies, in fact just as a matter of interest for the obstetricians, the microbial flora of the mother's vagina actually changes during pregnancy as does also the faecal flora. So I think without any antibiotics itself, you do find a change in the microbiota. The truth be told this microbiota is proving to be a tool that a lot of people are using and I don't know what to make out of it in terms of the veracity of the results, the implications of the results, whether one population of bugs go up, another population comes down, and how much is a natural phenomenon, how much is drug induced. It's often quite difficult. That's one. The second thing which I just want to ... as somebody who has been involved with the MRSA screening and I say this with conviction, the MRSA screening, risk based screening was something that was advocated for many years by our hospital and professional society and all those august bodies and every time what would we find? That 1. that those who needed to be screened would not be screened; you tried screening and finding out the risk factors in the A&E department which is heaving. 2. who is to ask those risk factors - is it the nurse, the doctors, the person who actually does the swab? 3. is that many people deny a third of the – or what the figures that are published which is something like in 2015 20% did not have the risk factors. So it's again the same thing what I've found by introducing a systematic screening - leave the antibiotic argument aside for the moment - costwise, effortwise, operationally it is far easier to have a system in place that you know like they did in the years gone by ask everybody to paint everybody's tongue with gentian violet. The same thing we need to do today, patient woman is pregnant, she is offered the screening; at 35-37 weeks, once again offered and, if she's agreeable, do the screening and be done with it. This business of trying to identify the various plethora of risk factors, trying to- the person who established the risk factors and the midwife who did it went off on maternity leave - all sorts of things can happen. So I really do believe that a systematic way by which anybody can get into the computer and sees this lady is GBS positive at the time of delivery and gets the antibiotic is far more easier operationally. A recent review that was done which was commissioned by the Dept of Health for MRSA concluded yes, there are some people more at risk of having MRSA than others but then they said there is an operational difficulty in identifying these people at risk and we come back to square 1. That today anybody who comes to A&E if they're going to get admitted, they get screened. Period. It costs a few bob but we waste a lot more money on useless stuff.

Cathy Warwick: How worried should we be that other NHS Trusts are going to introduce their own screening programme in the absence of a national decision to do this. I mean how dangerous would it be for little screening programmes to pop up all over the place. Neena, you're looking at me so I'll ask you to start on this one.

Neena Modi: Once again Cathy you read my mind because I think that this too is an extremely worrying precedent. One of the things that this country has been known for is its very, very egalitarian approach to healthcare. We really do not want to go back to the days of a postcode lottery. And once again not only do we not want a postcode lottery but we also want to do the right thing for all patients so I think you have read my mind correctly and I applaud the enthusiasm of the Northwick Park group but I do wish that you'd decided to implement a randomised control trial rather than simply introduce a new screening programme. If you have introduced a new screening programme, then what I would say- and you clearly have done that and you've done it with great enthusiasm and with great success. I'm not suggesting that we should turn the clock back but I do encourage you to continue to evaluate what has happened as you are clearly aiming to be because I hope you will be able to provide us with some interim answers so I really encourage you to continue your evaluations.

Cathy Warwick: I'm going to bring in Phil because you were having a little reaction there which means you're thinking something.

Phil Steer: Yes, Neena the way to avoid the postcode lottery, of course, is to offer every woman in the country the opportunity to know about GBS and decide for themselves, as individual families, whether they wish to undergo screening or not, given the benefits. A lot of people always look askance when you suggest giving the patient power to decide about their own healthcare. I've always been a lifelong believer that this is the right way forward, I think things are moving more and more in that direction. I think the Montgomery judgement was another move towards that. I think, in future, we will look back and be embarrassed about the amount of paternalism or maternalism that goes on in medicine and I think that increasingly there will be choices which will to be made by individual people about their healthcare, whether it is to have cancer care or assisted dying, all these other things I think patient autonomy will come to the fore and in that regard I would like to pose a question If I may, just one, to the rest of the panel and that is, while we have a situation where there is no national screening programme, we have already seen that more than half of units said that if women requested a test -which I'm told by the National Screening Committee is not screening because they are simply asking for their individual test - that 56% I think it was of units would agree with that. I am actually worried about the situation in the 44% where they would simply say no. What happens if that baby dies of early onset GBS disease and the woman has specifically had documented that she requested testing? And, indeed I can give you an example - and I won't mention the hospital but I had a communication with the Clinical Director in one Trust, where if the women took matters in their own hands, literally and sent off to one of the private units, had the swab, sent them

off and came back and said to their doctor, "I am known now to be a Group B Strep carrier", they were refused acknowledgement of that finding and no recommendation for intrapartum antibiotics would be made. It seems to me unbelievable but I promise you that has happened within the last 18 months in the UK and I have the emails to prove it. And I think that's an issue that perhaps we all ... so perhaps the question is: if a woman comes and asks you to be tested, what would you say?

Cathy Warwick: Panel - responses please? Alan?

Alan Cameron: Yeah it does happen and it happens not infrequently at clinics and Andrew mentioned how uncomfortable you feel, especially when you Chair the Guidelines Committee and I oversee it. You cannot turn that request down but I'm disappointed with what Phil says - if somebody actually goes and pays for it and then it's ignored, that's appalling; it's unethical.

Cathy Warwick: Alison?

Alison Bedford Russell: I totally agree with Neena's aspiration, it's always good to have proper randomised control studies but as part of the group that spent many a day poring through protocols and meeting up and meeting up and meeting up and talking and conference calls and then there was a big collaboration which was led by Peter Brocklehurst who, some of you will know, heads up the NPEU and is an obstetrician by training; we were declined and it was desperately disappointing. So, in the absence of that, we know, we heard this morning, there are pockets where Group B Strep is encountered more commonly than others; Northwick Park was one of them. In fact, my own unit contributed quite heavily to the current BPSU study and we're still considering - this is at Birmingham Women's - whether we need to adopt a screening programme because of the rate is above 1 per thousand and we also know - thank you very much to the earlier speaker who talked about the study that we published in the Lancet from St George's some years ago - that culture proven Group b Strep sepsis is only the tip of the iceberg; it's probably double that incidence for actual disease and this is where we know that it's very difficult to grow any positive culture in a baby but if they have a CRP which goes from 1 to sort of 90 and they're sick and they have Group B strep in their ear swab, it's most likely that that's the cause. So those were those sorts of babies. But if I were living in Scotland, where the incidence is very low, I might not feel quite so inclined to support a screening programme. So it really does depend - I think we have to be cognisant of the fact that there are some areas where the rate is particularly high and so for those women there is even higher risk than others and I'm not so sure it's such a bad think to offer those screening empirically but surveillance in the absence of a screening programme, surveillance is absolutely critical in order to evaluate, just as Gopal's team's been doing.

Cathy Warwick: Thank you Alison. Now, I'm going to have to draw the panel to a close but I just want you all very quickly - if you were walking to Ladbroke's this afternoon and you could place a bet on where we are going to be in let's say 3 years time, will we have a national screening programme or not? 5 years - OK, Andrew wants me to give 5 years so in 5 years, right. Starting with you Andrew.

Andrew Thomson: Yes there will be a screening programme within the next 5 years

Cathy Warwick: Neena?

Neena Modi: I'm going to say that if we put our collective efforts to it, we might have a trial done within 5 years.

Cathy Warwick: Catherine?

Catherine O'Sullivan: Difficult to say. Possibly yes and hopefully we'll be further along with the vaccine trials.

Cathy Warwick: That's right. Phil?

Phil Steer: My answer when I'm asked that question is always you wouldn't want a gambler for your obstetrician.

Alan Cameron: OK well, I'll gamble and I'll agree with Andrew, I think we will have a screening programme in 5 years. I think these so called "creeping developments", I don't find them a threat at all, what Northwick Park have done as long as we get that data. Because I think that will be supportive - although it's not randomised trial data, I think it's still very useful data to inform the process.

Cathy Warwick: Alison?

Alison Bedford Russell: I don't know the answer to that. I hope very much we do. When I started working with Group B Strep Support and had the privilege of being asked to be on the panel as the paediatric adviser, I was absolutely terrified about the potential increasing use of antibiotics and I was known as "she who was against antibiotic usage". I now know from the data that actually if we have more solid information about whether a woman is carrying a potential pathogen or not, then actually it reduces the burden of antibiotic use. So I hope so, I hope we have a screening programme well within 5 years and then I'll retire very happily but it's watch this space.

Cathy Warwick: Rao?

Gopal Rao: I'd like to just take up on what Professor Modi and I discussed while having a cup of coffee earlier this morning - why can't we, and this is a proposal to the RCPCH and RCOG

and possibly RCPath, who probably don't count for very much in this argument, is basically why can't we try it out, universal screening, for a short period of time and see how it goes?

Cathy Warwick: So, there's a proposal! Thank you Dr Rao.