Neutral Citation Number: [2026] EWHC 560 (KB)

Case No: KB-2023-001891

IN THE HIGH COURT OF JUSTICE
KING'S BENCH DIVISION

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 13th March 2026

Before:

THE HONORABLE MR JUSTICE KIMBLIN

- -

Between:

LXLP **(By her mother and litigation friend, CYLP)**	**Claimant**
- and -	
ST GEORGE'S UNIVERISTY HOSPITALS NHS FOUNDATION TRUST	**Defendant**

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Susan Rodway KC and Melanie Sharp (instructed by **Shoosmiths LLP**) for the **Claimant**

Jeremy Hyam KC (instructed by **Bevan Brittan LLP**) for the **Defendant**

Hearing dates: 3rd to 9th December 2025
Draft circulated 16th February 2026

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Approved Judgment

This judgment was handed down remotely at 10.30am on Friday 13th March 2026 by circulation to the parties or their representatives by e-mail and by release to the National Archives.

MR JUSTICE KIMBLIN

MR JUSTICE KIMBLIN:

[1] Introduction

1. By a claim form issued on 4th April 2023, the Claimant child, acting by her mother and litigation friend, brought a claim for damages arising from the alleged negligence of the Defendant during April/May 2016, resulting in bilateral, four-limb cerebral palsy.

2. The Claimant was born on 10th May 2016 at St George's Hospital in Tooting. After an uneventful early pregnancy, the Claimant's mother ('mother') attended the hospital on 25th April 2016, when she was 27 weeks plus 5 days gestation. She reported leaking clear fluid. It is now agreed that there was pre-term, pre-labour rupture of membranes ('PPROM') and that chorioamnionitis developed during the 12 to 24 hours before the Claimant's presentation on 10th May. This resulted in an ascending maternal amniotic infection which triggered pre-term labour, funisitis, a foetal inflammatory response which in turn led to periventricular leukomalacia.

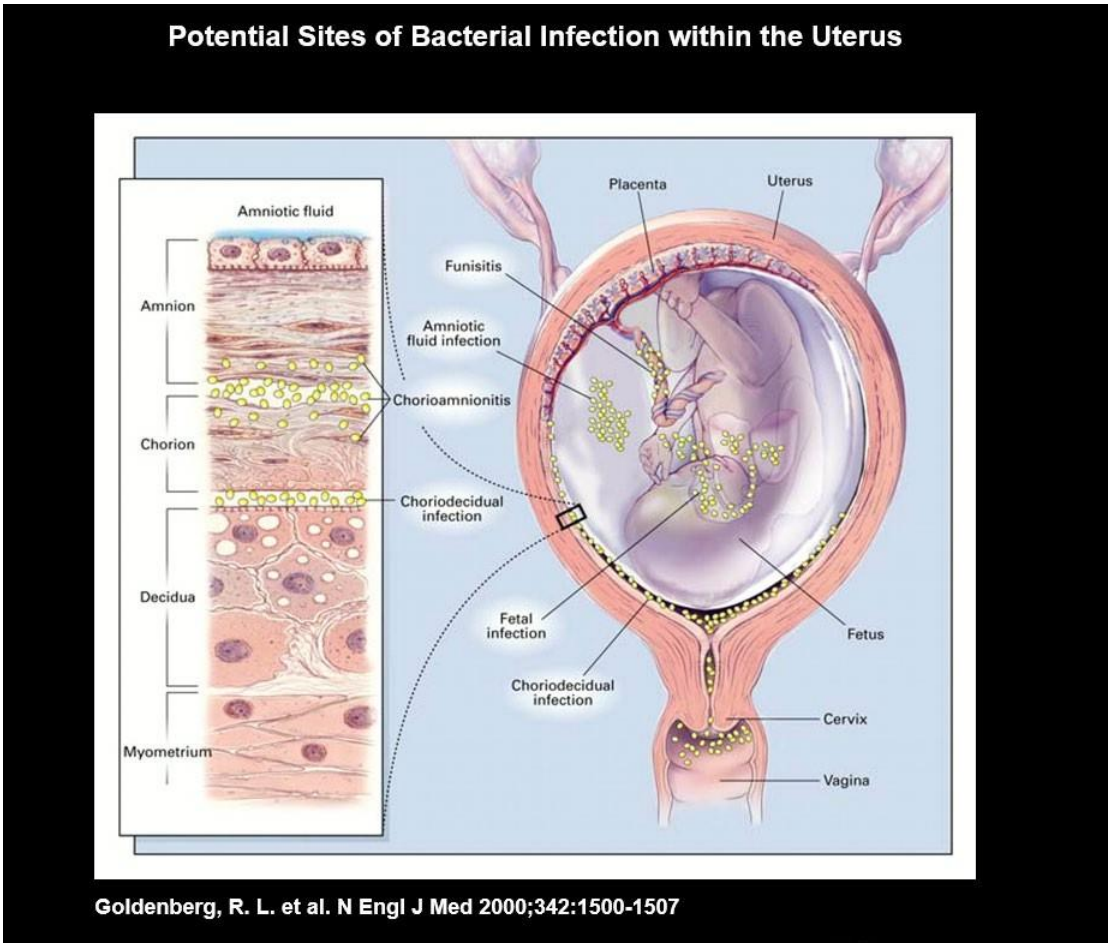
3. It is also agreed that there were opportunities to decide to offer and administer antibiotics between 26th April and 10th May and that there were negligent omissions in that regard. In large measure, this case is concerned with the evidence and issues of causation of the cerebral palsy. The evidence and submissions focussed on the roles and effectiveness of antibiotics, and combinations of antibiotics. Those roles included the suppression of particular bacteria and the microbiome in the genital tract, potential infection of the chorion, inflammation, and consequential impacts on the development of the baby's brain.

4. The Claimant's primary case was pleaded in the amended Particulars of Claim, dated 3rd November 2025, to be based on the 'but for' test for causation, with a subsidiary case based on material contribution, in that the Defendant's negligence made a more than minimal contribution to the neurological injury.

5. The Defendant's case is that chorioamnionitis of the same severity and duration would always have been suffered, with the same inflammatory response, the contributory factors to which are not well understood. It is misconceived and wrong to elide the issue of material contribution to risk of injury, with material contribution to injury.

6. Many users of this judgment will have either medical or medico-legal training and experience, but some will not. So that this judgment is accessible, a plain language description of the medical issues is worthwhile. There is a Glossary annexed to this judgment. Much of the credit for the Glossary goes to Dr Sharp of Counsel, to whom I am grateful for both its thoroughness and its clarity.

7. Dr Janet Rennie provided expert evidence on neonatal medicine. Uniquely amongst the experts, she included some illustration within her evidence, including this diagram which explains the terminology and anatomy.



8. Within the womb, or uterus, the baby develops within a fluid. The fluid is retained and maintained sterile by membranes until, typically, the 'waters break' at the onset of labour. The membranes include the chorion which is one of the two innermost membranes.

9. Infection of the innermost membranes may be assessed after delivery of the baby by analysis of the placenta in a laboratory. Alternatively, it can be detected clinically by symptoms such as a mother's elevated temperature.

10. The baby is connected to his or her mother via the placenta and its connecting umbilical cord. If the umbilical cord is inflamed this is given the term funisitis. In turn, this may prompt periventricular leukomalacia, abbreviated to 'PVL'.

11. Images of a baby's brain can be obtained after delivery by use of ultrasound. The grey-scale images show the shape and extent of brain development and also 'white matter'. The white matter surrounds areas of fluid which are deep within the brain. There is a helpful image of these areas (lateral ventricles) within the Glossary. The ultrasound images can show injury. In this case the pattern of injury is agreed to be a known form of reduction in the white matter which appears as cysts, or holes, and which is PVL.

12. It is the PVL which gives rise to the Claimant's disorder of movement and posture which is given the term cerebral palsy. As Miss Rodway KC submitted in opening the case, these injuries have very severe consequences for the Claimant and her evidently committed and caring family.

13. She has asymmetric four-limb cerebral palsy, so all limbs are involved; the right upper limb is more affected than the left. She has neurodevelopmental speech and movement problems throughout. Her main mobility is wheelchair or other wheeled access, but she will remain in a wheelchair and unlikely to be able to walk independently. She will need 24-hour support for independent living later in life. She will need accommodation or adaptations as well as the usual medical and other therapies.

[2] The Claimant's Brain Injury

14. On 17th May, a bilateral periventricular flare was reported in addition to the previously seen bilateral haemorrhage. By 25th May there was reported to be bilateral frontotemporal PVL.

15. As I have indicated, PVL is a lesion characterized by bilateral, but not necessarily symmetrical, coagulation necrosis within the white matter located adjacent to the lateral ventricles. Due to the topographical arrangement of the descending motor fibres, PVL often leads to a spastic diplegia with legs much more affected than arms. It may also be associated with visual impairment and/or learning disability.

16. There is agreement that PVL results from the vulnerability to a number of different insults of a population of developing supportive cells within the nervous system, the pre-oligodendrocytes, which are the most numerous glial cells in the nervous system in the 26-34 week gestational window. It is this that is thought to explain the temporal specificity of the lesion, although PVL is sometimes noted in more mature foetuses.

[3] Clinical History

17. Mother's witness statement, in combination with the medical records show the following which are uncontentious and which I find as facts.

18. On 25th April 2016 she observed a leak of clear fluid from her vagina and she went the Hospital where she was admitted and a Registrar did a visual test with a speculum, took swabs and blood tests were done.

19. Both the Registrar and a Dr Pillay thought it likely that the membranes had ruptured. Dr Pillay thought it likely that Mother would go into labour.

20. On 26th April, Mother was seen on the ward rounds and PPROM was discussed, including the risk of chorioamnionitis. The mode of delivery was discussed. The plan was to monitor temperature, pulse, respiration and the colour of the liquor. An ultrasound scan showed normal amniotic fluid volume.

21. On 27th April, Mother was seen again on the ward round by a different consultant. She was said to be keen to go home; she lived 5 minutes away. A C -reactive protein test, a marker of inflammation, had not yet been done. It was noted that the results were not yet available for the high vaginal swab. The low vaginal swab taken on 27th April 2016 isolated GBS on 28th April 2016 and on 30th April 2016 GBS resistance to Erythromycin and sensitivity to penicillin was identified. No antibiotics were administered.

22. On 28th April the C-reactive protein result was normal. Mr Ugwumadu saw Mother. He was the named consultant for the pregnancy. He was in no doubt that membranes had not broken and that Mother could be discharged.

23. On 29th April in the morning, Mother found that she was still leaking fluid from her vagina and so called the hospital. She was updated on the test results and informed that the high vaginal swab taken on 25th April subsequently grew GBS which were resistant to Erythromycin and sensitive to penicillin. Mother telephoned Mr Ugwumadu's secretary, who spoke to Mr Ugwumadu and advised that the results did not change anything.

24. Mother returned to the Hospital on 4th, 7th and 9th May when she was told that there were no signs of infection. On 4th May, Dr Sivanandan, the clinical fellow, noted that Mother was positive for GBS and 'Amnisure positive'. This was a test to detect amniotic fluid. This indicated loss of amniotic fluid. Her impression was of PPROM, i.e. ruptured membranes.

25. At midday on 10th May, Mother was admitted, having been contracting since 0900 and with reduced foetal movements, with the impression of early labour. C-reactive protein remained normal. At 1350 Mother's temperature was 38.3 degrees, i.e. was elevated. She was given paracetamol, gentamicin, amoxicillin and penicillin between 1402 and 1440. The Claimant was born at 1805 at "29 + 3 weeks" (this is the standard notation, which means 29 weeks, plus three days).

26. The infection which caused the chorioamnionitis only developed in the 12 to 24 hours prior to delivery of the Claimant.

27. The placental membranes were yellow and there was acute inflammation in the walls of both the umbilical artery and umbilical vein and the membranes showed acute chorioamnionitis. The diagnosis was of recent ascending amniotic infection which was a secondary complication and not the cause of the membrane rupture. The placenta swab grew no organisms.

[4] Breach of duty - penicillin

28. The Amended Defence admits that a 10-day course of Erythromycin at a dose of 250mgs, four times a day, should have been commenced on the morning of the 26th April, or the evening of 28th April, or on 29th April and/or on 4th May 2016. It is denied that it was a breach of the reasonable standard of care to give oral penicillin for the purpose of eradication of GBS.

29. The Claimant's case is that given the knowledge of GBS resistance to Erythromycin, a 5-day course of penicillin should also have been commenced on 28th April in the evening or 29th April in the morning, to end on 3rd May 2016. Alternatively, such a course should have started after review on 4th May, to end on 9th May. The same alternative case is made in respect of the opportunity on 5th May.

30. This case raises the question of weighing risks and benefits of offering, or administering, antibiotics in various circumstances during a pregnancy and delivery. The evidence of the two clinical medical microbiologists is key to understanding risks, benefits and potential circumstances. That expert evidence is also central to

determination of the causation issues. I therefore prefer to consider the evidence as a whole and to return to this issue of breach of duty after setting out the facts as I find them.

[5] Law

Breach of Duty

31. A medical professional is not guilty of negligence if he or she has acted in accordance with a practice accepted as proper by a responsible body of medical men or women skilled in that particular art. Putting it the other way round, the medical professional is not negligent if acting in accordance with such a practice, merely because there is a body of opinion who would take a contrary view: *Bolam v Friern Hospital Management Committee* [1957] 1WLR 582 McNair J. Differences of opinion will exist and there is seldom one answer to the medical question or decision. Preference of one body of opinion over another is no basis for a conclusion of negligence: *Maynard v West Midlands RHA* [1984] 1WLR 634 per Lord Scarman.

32. The court has to be satisfied that the exponents of the body of opinion relied upon can demonstrate that such opinion has a logical basis. If, in a rare case, it can be demonstrated that the professional opinion is not capable of withstanding logical analysis, the judge is entitled to hold that the body of opinion is not reasonable or responsible: *Bolitho v City and Hackney Health Authority* [1998] AC 232 per Lord Browne-Wilkinson. None of this means that the court delegates its task to experts.

33. Miss Rodway submits, and I accept, that the *Bolam* test must be read subject to the clarification of the House of Lords in *Bolitho*, to the effect that the body of practitioners' opinion relied upon as supporting his/her practice must have a sound and logical basis; see p. 241 – 242 [my emphasis added]:

> *"…the court is not bound to hold that a defendant doctor escapes liability for negligent treatment or diagnosis just because he leads evidence from a number of medical experts who are genuinely of opinion that the defendant's treatment or diagnosis accorded with sound medical practice. In the Bolam case itself, McNair J. [1957] 1 W.L.R. 583, 587 stated that the defendant had to have acted in accordance with the practice accepted as proper by a ' responsible body of medical men.' Later, at p. 588, he referred to 'a standard of practice recognised as proper by a competent reasonable body of opinion.' Again, in the passage which I have cited from Maynard's case [1984] 1 W.L.R. 634, 639, Lord Scarman refers to a 'respectable' body of professional opinion. The use of these adjectives responsible, reasonable and respectable - all show that the court has to be satisfied that the exponents of the body of opinion relied upon can demonstrate that such opinion has a logical basis. In particular in cases involving, as they so often do, the weighing of risks against benefits, the judge before accepting a body of opinion as being responsible, reasonable or respectable, will need to be satisfied that, in forming their views, the experts have directed their minds to the question of comparative risks and benefits and have reached a defensible conclusion on the matter."*

34. I have directed myself accordingly.

Causation

35. Miss Rodway accepted that the orthodox test for causation is the "but for" test: *Barnett v Chelsea & Kensington Hospital* [1969] 1 QB 428; *Zgonec-Rozej v Pereira* [2025] EWCA Civ 171. But she submitted that it is not possible to decide the Claimant's case by the orthodox test. Science cannot demonstrate the precise causative contribution for every pathogen. The Claimant suffered injury which is indivisible. The test is whether the breach of duty in failing to prescribe antibiotics made a more than negligible contribution to the injury.

36. Mr Hyam KC submits that the orthodox "but for" test is to be applied in this case. Both leading counsel made detailed submissions on the approach to a material contribution test, if it applies.

37. I have been particularly assisted by the review of this area of tort law by Stuart-Smith LJ in *Holmes v Poeton Holdings Ltd* [2023] EWCA Civ 1377; [2024] KB 521 at [29-71]. That review was prompted by "*complex and difficult questions of law in an area that has been bedevilled by apparent inconsistency and imprecision at the highest level on multiple occasions"* and in respect of which the Court of Appeal was assisted by the analysis of Professors Stapleton, Steel and Green. From this analysis, I note in particular:

    i) A characteristic of divisible disease is that severity is influenced by the total amount of the agent that has caused the disease. But, once contracted, an indivisible disease is not influenced by the total amount of the agent which caused it [31].

    ii) A central point of distinction between a case in which a single agent causes injury (eg asbestos in *Fairchild v Glenhaven Funeral Services Ltd* [2002] UKHL 22; [2003] 1 AC 32) and a case with multiple potential agents is that in the latter case, the burden is on the claimant throughout to prove that the defendant's tort caused the injury. That is on the basis of the "but for" test, on the balance of probability [38].

    iii) The principle in *Bonnington Castings Ltd v Wardlaw* [1956] AC 613 about making a material contribution to a disease was expressed in terms that are appropriate to indivisible diseases rather than to divisible ones [46, 53,54].

    iv) The material contribution principle applies to cases of indivisible injury and in such cases the claimant does not have to show that the injury would not have happened but for the tortious exposure for which the defendant is responsible: *Bailey v Ministry of Defence* [2009] 1 WLR 1052 [63].

38. *Bailey* was followed by the Privy Council in *Williams v Bermuda Hospitals Board* [2016] AC 888. Waller LJ summarised the position in *Bailey* at [46]:

    i) If the evidence demonstrates on a balance of probabilities that the injury would have occurred as a result of the non-tortious cause or causes in any event, the claimant will have failed to establish that the tortious cause contributed;

ii) If the evidence demonstrates that "but for" the contribution of the tortious cause the injury would probably not have occurred, the claimant will (obviously) have discharged the burden;

iii) If medical science:

a) cannot establish the probability that "but for" an act of negligence the injury would not have happened,

b) but can establish that the contribution of the negligent cause was more than negligible,

c) the "but for" test is modified and the claimant will succeed.

39. Turning from the principles to the evidential considerations, *Williams* holds at [40]:

> "A claim will fail if the most that can be said is that the claimant's injury is likely to have been caused by one or more of a number of disparate factors, one of which was attributable to a wrongful act or omission of the defendant: *Wilsher v Essex Area Health Authority* [1988] AC 1074. In such a case the claimant will not have shown as a matter of probability that the factor attributable to the defendant caused the injury or was one of two or more factors which operated cumulatively to cause it."

40. As to the role of risk as evidence of causation, the Privy Council observed at [48]:

> "If it is a known fact that a particular type of act (or omission) is likely to have a particular effect, proof that the defendant was responsible for such an act (or omission) and that the claimant had what is the usual effect will be powerful evidence from which to infer causation, without necessarily requiring a detailed scientific explanation for the link. But inferring causation from proof of heightened risk is never an exercise to apply mechanistically."

41. On the topic of risk, Mr Hyam relied upon *Gregg v Scott* [2005] 2 AC 176 in which the House of Lords addressed the topic of loss of a chance in the context of medical negligence and *Zgonec-Rozej v Periera* [2025] EWCA Civ 171 at [78]. In the majority, Lord Hoffmann (in *Greg v* Scott) referred to the cases which I have cited above. He then held, at [79]:

> What these cases show is that, as Helen Reece points out in an illuminating article "Losses of Chances in the Law" *(1996) 59 MLR 188* , the law regards the world as in principle bound by laws of causality. Everything has a determinate cause, even if we do not know what it is. The blood-starved hip joint in *Hotson's* case, the blindness in *Wilsher's* case, the mesothelioma in *Fairchild's* case; each had its cause and it was for the plaintiff to prove that it was an act or omission for which the defendant was responsible. The narrow terms of the

> exception made to this principle in *Fairchild's* case only serves to emphasise the strength of the rule. The fact that proof is rendered difficult or impossible because no examination was made at the time, as in *Hotson's* case, or because medical science cannot provide the answer, as in *Wilsher's* case, makes no difference. There is no inherent uncertainty about what caused something to happen in the past or about whether something which happened in the past will cause something to happen in the future. Everything is determined by causality. What we lack is knowledge and the law deals with lack of knowledge by the concept of the burden of proof.

42. Lord Hope, dissenting, said at [106, p.203D-F]:

> "the trial judge held that the appellant had not proved that he had suffered an injury as a result of the delay. This was not because the consequences of the delay were too remote or were not reasonably foreseeable. It was because the appellant had not proved that it was more probable than not that, had there been no delay, he would not have suffered those consequences: para 44. He said that, although he might have suffered them at different times, the appellant would on balance of probabilities have gone through the same sequence of setbacks and treatments, and that his outlook was not shown to be different from what it would have been had there been no negligence: para 48. It is axiomatic that the wrongdoer is not liable for any loss, injury and damage that would have happened anyway. It was not shown that, on a balance of probabilities, the outcome would have been any different if the doctor had not been negligent. So he declined to award him any damages for what had been proved, namely that the negligence caused a reduction in his prospects of a successful recovery. As these were the only damages claimed, the result of his decision is that the appellant has suffered a wrong but has been left without a remedy"

43. As Mr Hyam submits, the wrongdoer is not liable for damage which would have happened anyway.

[6] Causation Issues

44. The Claimant's case is that by reason of the Defendant's (admitted) failure to prescribe and administer prophylactic antibiotics following a diagnosis of PPROM, Mother developed chorioamnionitis some 12-14 hours prior to delivery at 1805 on 10th May which she otherwise would not have done, and which chorioamnionitis caused the Claimant to succumb to a foetal inflammatory response which caused her severe brain damage (PVL), which has given rise to a biplegic cerebral palsy. That case is advanced on the basis of Erythromycin alone and also Erythromycin in combination with penicillin. If either of those courses had been taken, labour would have been prolonged so as to avoid chorioamnionitis or reduce its severity in a material way, particularly as to the foetal inflammatory response.

45. Mr Hyam submitted that the causation issues were:

    i) On the balance of probabilities, would oral Erythromycin, if prescribed 250mgs 4 x a day for 10 days (or until the Claimant went into labour) from 28, 29, 30 April or 4th May (as is admitted ought to have been the case) have prolonged labour in such a way as to avoid chorioamnionitis?

    ii) On the balance of probabilities, would oral Erythromycin, if prescribed 250mgs 4 x a day for 10 days (or until the Claimant went into labour) from 28, 29, 30 April or 4th May have avoided maternal acute chorioamnionitis developing 12-24 hrs before the birth of CYLP i.e. in the window 6pm to 6am on the night/early morning of 9-10th May?

    iii) On the balance of probabilities, would the addition of penicillin (if it would/should have been prescribed) from 28th April (in the dose suggested in the local guideline viz. oral 250mgs 4 times a day for 5 days) have avoided maternal acute chorioamnionitis developing 12-24 hrs before the birth of CYLP i.e. in the window 6pm to 6am on the night/early morning of 9-10th May.

    iv) If the answer to these questions is no, on the balance of probabilities would Erythromycin, or Erythromycin plus penicillin prescribed on any of the dates alleged have materially reduced the severity of the acute maternal chorioamnionitis that developed 12-24 hours before birth such that the foetal inflammatory response would have been avoided?

[7] Evidence

The nature of the evidence

46. The evidence is multifaceted and various in nature. The progress of the pregnancy, the delivery and neonatal care are well documented and accompanied by the results of testing and observation. I can be sure about these facts. Through the assistance of the medical professionals, I have evidence of the potential mechanisms for infection during PPROM and its potential sequence of consequences.

47. I have reviewed the literature and the synoptic and statistical studies by Cochrane. They provide a neutral record of what has happened in many other cases of similar type and seek to study and record the effect of medical interventions such as the taking of antibiotic medicine. That material has required careful analysis in order to understand its significance in this case and its relationship to accepted forms of medical guidance documents.

48. The parties' expert witnesses were either clinicians, neurologists or consultant microbiologists. The clinicians gave evidence which derived from their research, teaching and the care given to patients in hospitals. Theirs was evidence of what they would consider to be the best practice and what the effects of that practice might be. The microbiologists gave evidence of the range and types of bacteria which are typically found in the genital tract, their role and potential effects (beneficial and adverse). They explained the effects, and lack of effects, of antibiotic medicines and dose-response relationships, dependant on how the medicine was administered.

49. These sources of evidence are overlapping and interact with each other. I have not found any of these individual sources to be determinative. Rather, they provide a framework or mesh of material from which I can make findings.

Clinical & Neurology evidence

50. The evidence of Dr Kumar for the Claimant and Dr Thomas for the Defendant was agreed. It is evidence of neurologists. It is helpful to me in explaining the ways that the Claimant was affected by the PVL. They agree that the Claimant's current condition, that is, an asymmetrical bilateral cerebral palsy, is caused by PVL, which itself is the result of cytokine release produced in the course of acute chorioamnionitis. There is no evidence of any other pathological process which has led to her current condition. I accept their evidence and agreement, but it does not bear significantly on the causation issues and so I say no more about it.

51. Likewise, I was assisted by the written evidence and agreement for Dr Stoodley for the Claimant and Dr Likeman for the Defendant in respect of neuroradiology. I was shown relevant and comparative images. They aided my understanding but did not advance the resolution of the issues in either direction and so I need not refer to their evidence further.

52. The obstetrics experts were Professor Shennan for the Claimant and Professor Gupta for the Defendant. There is a large measure of agreement between them, and which I record as:

    i) Following PPROM, there is a risk of ascending infection;

    ii) Chorioamnionitis is polymicrobial;

    iii) GBS is not the predominant organism in causing chorioamnionitis;

    iv) The only other management to prevent progression of disease would be delivery;

    v) Antibiotics will reduce the risk of ascending infection in the context of PPROM;

    vi) A 10 day course of Erythromycin should have been commenced at the time a diagnosis was made i.e. on the evening of the 25th April, and no later than the following morning;

    vii) The purpose of Erythromycin is to improve preterm birth outcomes in general and not specifically to treat GBS or chorioamnionitis. The mechanism is not clear but other actions other than antimicrobial effects have been described that could be beneficial;

    viii) But it is not possible to determine whether chorioamnionitis would have been avoided, or not;

    ix) The exact microbiological cause of the chorioamnionitis is not known.

53. On those matters for which the obstetrics experts each give their own nuanced view, I do not regard the differences as material.

54. In his evidence in chief, Professor Shennan explained that the giving of antibiotics was advised against if membranes were intact. The balance of considerations is that there may be harm, and potential to mask infection, leaving the baby in a hostile environment. Conversely, antibiotics are routinely offered if membranes have ruptured and he considered that clinical evidence supported that approach.

55. Professor Shennan gave oral evidence on the use of the literature and statistical review. I return to that below.

56. Professor Gupta was cross-examined. The local guidance was put to him. The fact of a substantial presence of GBS in Mother's vaginal swab sample was established. Professor Gupta was challenged on the omission of penicillin in the treatment offered. The position which was arrived at, after a full exploration of that issue, is captured in this exchange:

"Q. I am positing to you a situation where we have Erythromycin and the addition of penicillin, so we have a combination of those drugs. They would certainly have improved the outcomes in the current case, wouldn't they?

A. I don't think they would have. Erythromycin was the standard evidence−based grade A to give for PPROM for 10 days. But the addition of penicillin is not in the guidance, not in the guidelines, the national guidance. So treating GBS specifically for that is not indicated despite what you find on your swab results, because it's only relevant −− GBS is only relevant for the neonate, and so you give intravenous intrapartum antibiotics for the treatment at the time of delivery, not before.

Q. Penicillin −− it may be −− I'm asking you these questions based upon your clinical practice. It may be that you haven't done this. Have you ever had a case of PPROM where you have been administering both Erythromycin and a penicillin?

A. I haven't, no.

Q. You haven't had that experience? Well, I'm not going to ask you then any further about it. I 'll leave it for others."

57. Dr Giles Kendall is a consultant in neonatal medicine at UCL where he is an Honorary Senior Lecturer. He was instructed on behalf of the Claimant. Dr Janet Rennie is a retired consultant in neonatal medicine at UCL and was instructed on behalf of the Defendant. I notice that these experts have published together: "Manual of Neonatal Intensive Care" 5th Edition (2013).

58. They agreed:

i) that the relationship between chorioamnionitis, foetal inflammatory response, and later brain injury is complex and not linear;

ii) that the purpose of prescribing intravenous benzylpenicillin intrapartum was to interrupt the vertical transmission of group B streptococcus, because Mother was known to be carrying this organism in her vagina. By then chorioamnionitis was established. The intrapartum antibiotic prophylaxis against neonatal

invasive GBS disease was effective. The Claimant's brain damage resulted from cytokine release associated with chorioamnionitis, not neonatal GBS disease.

59. These experts commented on the microbiological evidence in their responses to questions. They agreed with Dr Gray that the pathogenesis of chorioamnionitis is polymicrobial and that GBS is not the predominant organism in chorioamnionitis. The exact microbiological cause of chorioamnionitis is not known.

60. They agree that the purpose of Erythromycin is to improve preterm birth outcomes in general and not specifically to treat GBS or chorioamnionitis. The mechanism is not clear but actions other than antimicrobial effects have been described that could be beneficial. They agree that antibiotics will reduce the risk of ascending infection in the context of PPROM.

61. The differences between these experts appears to relate to matters where Dr Kendall does not feel comfortable expressing an opinion. His written opinion is very carefully drafted to stay close to the observed facts. He does not engage directly with the key issue which the court has to determine. His essential conclusion is as follows:

"It follows that the funisitis is causally related to LXLP's disability and that with alternative obstetric management that avoided the development of funisitis, Louisa would not have developed periventricular leukomalacia and would have had a normal neurodevelopmental outcome."

62. I do not find this to be helpful. It amounts to little more than a statement that funisitis is a precursor to PVL, which is agreed. It does not engage with the timeline of the case and does not assist the court with understanding what would have happened if pregnancy had been prolonged. Neither Dr Kendall's evidence in chief nor his cross-examination advanced matters in this regard.

63. Dr Rennie, given her long experience, is able to express an opinion on this key issue, namely the effect of prolonging pregnancy:

"If LXLP had still been exposed to chorioamnionitis but delivered a week or so later her brain injury would probably still have occurred. There is not a 1 to 1 relationship between chorioamnionitis and brain injury but genetic factors are thought to be relevant. LXLP was a baby who developed brain injury after a relatively short cytokine exposure time so I consider that the same response would have occurred a week later. If on the other hand LXLP had been born at either 29 or 30 weeks without exposure to cytokines then she would probably not have acquired PVL."

Medical literature and guidance

64. Professor Shennan provided a helpful explanation during his evidence in chief of the roles played by authoritative organisations in marshalling the current state of knowledge and understanding and in communicating that to medical practitioners. Those organisations are 'Cochrane', the Royal College of Gynaecologists ('RCOG') and the National Institute for Clinical Excellence ('NICE'). Each is independently created and managed by different groups, and all are highly respected.

65. Cochrane collates international evidence and reviews it systematically.

66. RCOG and NICE tend to be more clinically orientated and are very similar. They tend to follow each other. They are not always comprehensive because each organisation has a strict remit, thus leaving some areas for clinicians to interpret for themselves. They often form the basis of the protocols followed in NHS Trusts, though they may differ locally to address local circumstances.

67. Cochrane is different. A Cochrane review is a collation of medical evidence as reported in the medical literature, published in many countries. It is systematic and seeks to identify an overview. The relevant review for this case is *'Antibiotics for preterm rupture of membranes'.* Part of the method is to quantify the evidence as risk ratios, with specified confidence limits. These statistical measures are centred on the number '1'. A risk ratio of '1' means that the intervention has no observable effect; below '1' is an effect which is beneficial; above '1' is an effect which is not beneficial.

68. The ratios are based on a categorical end point, which is chosen in order to decide whether the intervention has had an effect. Professor Shennan explained that if a ratio is 0.9, it means there is a 10% reduction in the end point of interest, and the vast majority of interventions in the whole of clinical medicine have a modest reduction.

69. End points are a particular difficulty in studies of chorioamnionitis because of difficulty in measurement. Instead, proxies are used, such as maternal temperature. But a high temperature quite often occurs without chorioamnionitis, as subsequently shown by laboratory assessment of the placenta. This is an unavoidable limitation on the studies which are collated in the Cochrane reviews. There are other end points which may be considered, such as fatality or hysterectomy. Professor Shennan preferred to look at the risk ratio for a range of end points, not just chorioamnionitis. Dr Teare made the same point by reference to a study called ORACLE I. I accept their evidence in this respect: an intelligent view has to be taken of the totality of data, not a single end point.

70. Alongside the risk ratio is the confidence limit. Professor Shennan said this during his evidence in chief:

> "if the lower confidence interval is less than 0.5, it also means just for that one end point, you can't rule out that on the balance of probabilities it wouldn't have happened to a majority of people, because the truth is within these confidence intervals. So it's a bit of a nuance with how you interpret data."

71. I accept this observation, so far as it goes but I do not accept that 'truth' lies within the confidence limits. It is not a full appreciation of the meaning of the confidence intervals. Whether the confidence interval is broad or narrow provides important insight into the weight which can be given to the risk ratio. The interval is simply a statistical measure which looks at where 95% of the results will fall. In other words, the confidence limits capture all but 5% of the results, which might be considered to be outliers, but only for the specified end point. As is seen from the detail of the Cochrane Reviews, the indication given by the statistical measure differs as between different end points.

72. The literature informs the guidance. I therefore start with the literature, and with the most recent of the Cochrane Reviews, from 2013, rather than the 2003 or 2010 Reviews. I note that three authors of these reviews have remained consistent over this ten-year

period and so to the extent that there is notable change, it is in the context of a uniform method and authorship. This adds to my confidence in the consistency of method.

73. The literature and the analyses of that literature by Cochrane formed a significant part of the oral evidence given by the microbiological experts. I will therefore return to the literature in the context of the evidence which those experts gave about it. I now look at the scope of what has been provided to the court, and its relationship with the guidance.

74. The abstract to the 2013 Review is a precise and clear summary, which is also aided by a plain language version:

*"**Main results***

We included 22 trials, involving 6872 women and babies.

The use of antibiotics following PROM is associated with statistically significant reductions in chorioamnionitis (average risk ratio (RR) 0.66, 95% confidence interval (CI) 0.46 to 0.96, and a reduction in the numbers of babies born within 48 hours (average RR 0.71, 95% CI 0.58 to 0.87) and seven days of randomisation (average RR 0.79, 95% CI 0.71 to 0.89). The following markers of neonatal morbidity were reduced: neonatal infection (RR 0.67, 95% CI 0.52 to 0.85), use of surfactant (RR 0.83, 95% CI 0.72 to 0.96), oxygen therapy (RR 0.88, 95% CI 0.81 to 0.96), and abnormal cerebral ultrasound scan prior to discharge from hospital (RR 0.81, 95% CI 0.68 to 0.98). Co-amoxiclav was associated with an increased risk of neonatal necrotising enterocolitis (RR 4.72, 95% CI 1.57 to 14.23)."

Plain Language Summary

"Certain antibiotics given to women whose waters have broken early will improve babies' health. Babies born too soon are more likely to suffer ill health in the early days and sometimes throughout life. Early labour and birth (before 37 weeks) may be due to undetected infection as well as the waters breaking early. The review of 22 trials, involving 6872 women and their babies, found that, in the short term, certain antibiotics given to women, when their waters break early, increase the time babies stay in the womb. They reduced infection, but did not save more babies. One antibiotic (co-amoxiclav) increased the number of babies with a rare condition of inflammation of the bowel (necrotising enterocolitis). Although, in the longer term (at seven years of age) antibiotics seem to have little effect on the health of children, the short-term advantages are such that we recommend antibiotics should be given routinely."

75. The risk ratio of 0.66 which is cited in the Abstract for reductions in chorioamnionitis comes from an analysis of eleven studies which were undertaken between 1990 and 1997. As with all of the comparisons within the study, it is a particular comparison, looking at a particular outcome. The comparison is between any antibiotic versus a placebo and the 'end point' or outcome is chorioamniontis. For each study, the risk ratio and confidence limits are reported and given a weighting which is proportionate to the numerical size of the study, i.e. how many women were in the study.

76. The risk ratios are highly variable as between the studies. Four of the studies give risk ratios above '1', i.e. consistent with the antibiotic making chorioamnionitis more likely

(*Garcia-Burguillo* 1995; *Lockwood* 1993; *McGregor* 1991; *Svare* 1997). At the other end of the scale, some studies showed notably low risk ratios of 0.15, but with very broad confidence limits (0.02 to 1.14; *Kurki* 1992). When it is appreciated that the *Kurki* study included only one women out of 50 who received an antibiotic, and only seven out of 50 with a placebo, it becomes clear why the risk ratio is so weakly supported.

77. A similar observation may be made in respect of those studies which appear to support the hypothesis that risk favours the placebo rather than the antibiotic. So, in *Garcia-Burguillo* 1995, the risk ratio of 3 derives from a sample in which only one placebo was given within a group of 30 women.

78. As I have indicated, the weighting of the Cochrane analysis of the eleven studies is proportionate to total sample size. Therefore, the *Mercer* 1997 study was given greatest weight because it was based on a group of several hundred women. What the analysis does not do is allocate weight to each study based on the confidence limits, which in turn are based on the proportion of the study group which receives antibiotic/placebo.

79. For this reason, I am cautious in relying solely on the arithmetic average of the risk ratios obtained from the eleven studies.

80. Another of the comparisons which featured in evidence and submissions was any antibiotic versus placebo where the outcome is 'birth within 7 days'. In other words, is there a reduced risk of delivery within 7 days after rupture of membranes if antibiotics are given, compared with women to whom antibiotics are not given.

81. The aggregate risk ratio for this comparison is 0.79 with a confidence limit of 0.71-0.89. This comparison does not suffer from the low proportions of the sample groups receiving antibiotics and placebo which is a feature of the chorioamnionitis comparison which I have discussed above. This comparison has a strong weighting to a study by *Kenyon* 2001 which is by far the largest study, making up 27% of the total cohort. For that study the risk ratio is 0.91 with confidence limits of 0.87-0.91, i.e. quite close to '1', meaning no effect. The most favourable results are from three similar-sized and smaller studies with risk ratios of about 0.6 (*Fuhr* 2006; *Johnston* 1990; *Lockwood* 1993).

82. Given the weight attached to *Kenyon* 2001 in this comparison, it is worthwhile to set out the authors' detailed discussion of cerebral abnormality and PPROM:

"The decrease in the occurrence of major neonatal cerebral abnormality could also be due to prolongation of pregnancy alone, or to the effect of Erythromycin's reduction of intrauterine infection or inflammation on the fetal and neonatal brain. Again, there is evidence to implicate intrauterine infection or inflammation in foetal and neonatal cerebral damage. Histological chorioamnionitis, 21–23 and funisitis with raised concentrations of interleukin and interleukin in amniotic fluid have been associated with cerebral palsy. Additionally, raised concentrations of umbilical-cord interleukin have been found in neonates with ultrasonographic evidence of periventricular leucomalacia. The preliminary results of a study of more than 40 infants with very low birthweights showed a strong association between indicators of chorioamnionitis and damage to cerebral white matter. Additionally, concentrations of proinflammatory cytokines and CD40RO-positive T cells (a marker of exposure to antigen) were higher

in cord blood from infants with damage to white matter than in infants without such damage.

The importance of potential effects of pPROM on brain development in children is illustrated by the results of two clinical studies. In the first, Murphy and colleagues did a case-control study of 59 children with cerebral palsy who were singleton and less than 32 weeks of gestation at birth. They found that the three most important antenatal risk factors were prolonged (>24 h) rupture of the membranes (odds ratio 2·3 [95% CI 1·2–4·2]), chorioamnionitis (4·2 [1·4–12·0]), and maternal infection (2·3 [1·2–4·5]). Results of the second report showed a five-fold increase in the likelihood of severe neurological handicap in infants born after pPROM at between 24 and 34 weeks' gestation, compared with infants who had been born after spontaneous preterm labour, and that the risk of handicap was related to the duration of membrane rupture.

Since Erythromycin for pPROM seems to have some beneficial effect on the rate of ultrasound-identified cerebral abnormality, which is known to greatly underestimate cerebral damage, we plan to determine what effect Erythromycin given for pPROM has on childhood neuromotor and cognitive function, and whether disability is decreased.

Our results show that a cheap and widely available antibiotic, Erythromycin, when given to women with pPROM, has effects on the occurrence of major neonatal disease, and might therefore have a substantial health benefit on the long-term respiratory and neurological function of many children."

83. The conclusion is positive as to the effects of Erythromycin, but tentative about the extent of reduced risk and why it happens.

84. This work is now 25 years old. As Dr Gray pointed out in his evidence, and I accept, the effectiveness of antibiotics has been reduced in some instances as bacteria have become resistant, as in this case in respect of Erythromycin and GBS. Nevertheless, the conclusions in *Kenyon* and from the Cochrane review of the totality of the medical literature are that there are benefits from appropriate antibiotics in ameliorating effects of PPROM. That too is the evidence of Dr Gray to the extent that Erythromycin prolongs labour.

85. The 2003 Cochrane review is the evidential basis for the guidance documents on the issues in this case. It is referred to by Dr Gray in that regard.

86. The 2003 Cochrane Review reported on a sub-analysis of the 2750 women in four trials where Erythromycin was compared to placebo. There was a significant reduction in the number of babies born within 48 hours (RR 0.84, 95% CI 0.76 to 0.93), requiring oxygen therapy (RR 0.87, 95% CI 0.78 to 0.98) and with a positive blood culture (RR 0.70, CI 0.52 to 0.94). The relative risk of chorioamnionitis was reduced (RR 0.57, 95% CI 0.37 to 0.86) in women who received any antibiotic. Its comparison of '*Erythromycin versus placebo, Outcome Chorioamnionitis'* is based on three studies which produce an aggregate risk ratio of 1. In other words, the 2003 Cochrane review produces the result that Erythromycin has a nil effect on chorioamnionitis.

87. The RCOG published its first edition of the Green-top Guideline No. 44 *'Preterm Prelabour Rupture of Membranes'* in November 2006 (Minor amendment October 2010). In respect of managing and treating PPROM, the Guideline is heavily reliant on

the Cochrane Review (2003). The Guideline classifies this evidence as 'Ia', on a scale of I to IV, where I is randomised controlled trials and IV is opinion and experience. The recommendation is that "*Erythromycin should be given for 10 days following the diagnosis of PPROM*."

88. The supporting text to the recommendation goes on:

"*If group B streptococcus is isolated in cases of PPROM, antibiotics should be given in line with the recommendation for routine intrapartum prophylaxis. As indicated in the RCOG Green-top Guideline No.36: Prevention of early onset neonatal group B streptococcal disease, penicillin should be administered, or clindamycin in women who are allergic to penicillin."*

89. This advice is accompanied in the margin of the document by an indication that the evidence in support is Level IV, i.e. the lowest level.

90. Green-top Guideline No. 36 is concerned with risk of GBS infection of the mother and/or baby during delivery. It is substantively about intrapartum antibiotic prophylaxis, namely the giving of antibiotics during childbirth to prevent infection by GBS. However, it makes clear that treatment of GBS colonisation before the onset of labour is not recommended.

91. The key passage in Guideline No. 36 is:

"6.4 *How should women with preterm prelabour rupture of membranes be managed to reduce the risk of neonatal GBS disease?*

Antibiotic prophylaxis for GBS is unnecessary for women with preterm rupture of membranes.

Women who experience preterm rupture of membranes should be managed according to the RCOG Green-top Guideline Preterm Prelabour Rupture of Membranes. [Guideline 44, see above] *Antibiotic administration specifically for GBS colonisation is not necessary prior to labour and should not be given 'just in case'. If these women are known to be colonised with GBS, IAP should be offered. Induction of labour should be considered if there is suspicion of chorioamnionitis."*

92. There is Green-top Guideline No. 73 *Care of Women Presenting with Suspected Preterm Prelabour Rupture of Membranes from 24+0 Weeks of Gestation*, published in June 2019. It is expressed as supplementary to Guideline 36 and also supplementary to NICE Guideline 25. It post-dates the pregnancy and birth in this case and is therefore of limited assistance on breach of duty.

93. NICE Guideline 25 *Preterm labour and birth*, published on 20th November 2015 aims to reduce the risks of preterm birth for the baby and describes treatments to prevent or delay early labour and birth. It advises (emphasis in the original):

"**Antenatal prophylactic antibiotics for women with P-PROM**

1.4.1 Offer women with P-PROM oral Erythromycin 250 mg 4 times a day for a maximum of 10 days or until the woman is in established labour (whichever is sooner).

1.4.2 For women with P-PROM who cannot tolerate Erythromycin or in whom Erythromycin is contraindicated, consider oral penicillin for a maximum of 10 days or until the woman is in established labour (whichever is sooner).

1.4.3 Do not offer women with P-PROM co-amoxiclav as prophylaxis for intrauterine infection.

1.4.4 For guidance on the use of intrapartum antibiotics, see the NICE guideline on antibiotics for early-onset neonatal infection."

94. The Hospital maintains guidelines of its own. Chapter 12 of the Hospital *Guideline addresses Infection & Infection Risk Intrapartum and Postnatal*, dated August 2013 (v. 7). It indicates:

"*12.D.2.6 Pre-labour Rupture of the Membranes If there are no signs of infection in the woman, antibiotics should not be given to either the woman or the baby, even if the membranes have been ruptured for over 24 hours. If there is evidence of infection in the woman, a full course of broad-spectrum intravenous antibiotics should be prescribed. (NICE Intrapartum guidelines)"*

95. Chapter 15 is *Preterm Labour*, dated March 2012 (v. 6). It indicates:

"**15.E.2 Gestational age ≥ 23 < 34 weeks**

- *Admit to Hospital for the first 5 days and inform neonatologists*
- *Administer Betamethasone 12mg i.m. x 2 doses 24 hours apart*
- *On admission, women presenting with PPROM should be screened for urinary tract infections (urine culture) and group B streptococcus carriage (LVS + perianal swab). The microbiology form should include a request for sensitivity studies for GBS if this is isolated and appropriate antibiotic administered. GBS strains resistant to Erythromycin are increasing, currently up to 40%.*
- *Administer Erythromycin 250mg orally 6 hourly for 10 days if not in labour in order to prolong pregnancy and to decrease maternal and neonatal morbidity.*

  .....

- *Chase up and review microbiological results. If known to be GBS positive and pPROM is to be managed conservatively – offer Penicillin V 250mg qds for 5 days to eradicate GBS and repeat after 5 weeks if still undelivered. If allergic to penicillin consider clindamycin. Check sensitivity results. Do not use Augmentin (co-amoxiclav)"*

96. As was emphasised by Ms Rodway, the author of the Defendant's guidance document is the consultant who cared for the Claimant and her mother, Mr Ugwumadu.

Microbiological evidence

The experts

97. The Claimant called Dr Louise Teare MB BS, FRCPath, MBA, DiP HIC. She is a medically qualified clinical microbiologist. She has significant experience as an expert witness as demonstrated by the 50-60 medico-legal reports she writes each year. This is in the context of her master's degree in medical microbiology, Fellowship of the Royal College of Pathology and her long standing role in the Anglia Ruskin University Medical School. She has been and is a consultant on infection prevention and control.

98. The Defendant called Dr James Gray MB ChB MRCP(UK) FRCPath. He has been a Consultant Medical Microbiologist at Birmingham Children's and Women's Hospitals since July 1995. He was, until 2023, Editor in Chief of the *Journal of Hospital Infection*, and remains an editor of that and other learned journals.

99. A joint report was prepared in the usual way. They agreed:

i) The cause of chorioamnionitis is usually polymicrobial;

ii) The microbiological cause(s) of the chorioamnionitis was/were not established;

iii) Erythromycin in the context of PPROM is prescribed for additional beneficial anti-inflammatory effects;

iv) Chorioamnionitis due to GBS would have been avoided if penicillin and Erythromycin were given in combination.

100. While not a matter of agreement, it is worthwhile to set out this question and the responses because they capture much of the difference between the experts on the effects of the antibiotics:

"Do the experts agree that the aim of antibiotics in the context of PPROM is to prevent ascending infection occurring and not to 'treat' infection?

Dr Teare: The aim of antibiotics in the context of PPROM is to protect both the mother and baby from infection by reducing the microbial load, inflammatory response and subsequent development of CA, delay labour and allow for foetal maturation.

Dr Gray: There is no evidence that administration of low-dose Erythromycin to women with PPROM either prevents or treats ascending infection. There is evidence that administration of broader spectrum antibiotics (e.g. co-amoxiclav) can prevent ascending infection, but it has not been established that the benefits of these antibiotics outweigh the potential harms."

Dr Teare

101. The essence of Dr Teare's report is in her section 4, in which she sets out her opinion. She states her conclusions shortly in her sections 5 and 6. The opinion is succinctly stated in four pages, much of which is either explanatory or an extensive citation of the Serious Incident Report.

102. Dr Teare states the issue which she is addressing:

> "…whether giving antibiotics at the time of membrane rupture or at any other time before they actually were, could have avoided or reduced the severity of chorioamnionitis and subsequent funisitis, delaying the onset of labour and avoiding PVL."

103. Dr Teare considers that in a patient such as the Claimant, presenting with PPROM at 27 + 5 weeks' gestation, reducing the severity of chorioamnionitis would have a material contribution on reducing the likelihood of FIRS and on the balance of probabilities, prolong pregnancy. On the balance of probabilities, prolonging pregnancy beyond 32 weeks would have avoided PVL. She points to the guidelines which support this opinion by the recommendation of Erythromycin.

104. Dr Teare's view, per her report, is that, though the importance of Erythromycin has not been quantified, the immune modulating properties of Erythromycin in PPROM is more than minimal, on the balance of probabilities. When GBS are present and resistant to Erythromycin, a responsible body of opinion would have advised addition of penicillin.

105. In her evidence in chief, Dr Teare gave a plain language narrative. At the time of PPROM the bugs, as she called them, were not ready to multiply quickly and ascend to the amniotic cavity. Their metabolism had to change, their genes would be turned on to a new mode of rapid multiplication, aggressively colonizing the newly available space.

106. At the same time, the body is making its defences ready via its immune system. This was portrayed as a battle between the bacteria and the body's defences.

107. The role of antibiotics, Dr Teare explained, was to hold back the progression of the bacteria and provide an advantage to the immune system. The bacterial burden and inflammation are reduced. Clinical infection occurs when the bacterial genes made them virulent, and the bacteria overcome the immune system.

108. Dr Teare's evidence in chief then turned from the plain narrative to specific effects of erythromycin. Erythromycin is reasonably effective against mycoplasmas and ureaplasmas and this is particularly important in this situation because these are organisms that are known to be associated with a particularly aggressive inflammatory response. The reduction of inflammation is important because it increases latency – the time in utero.

109. Dr Teare was cross-examined.

110. Dr Teare accepted that the Cochrane reviews show risk reduction with prescription of Erythromycin, which means that there is a statistically significant risk reduction for chorioamnionitis, but not prevention of chorioamnionitis. Her opinion was that there would be a material contribution to avoiding and, or, reducing the severity of chorioamnionitis and therefore delaying the onset of labour and avoiding PVL.

111. There were two steps in reaching this outcome. First, Erythromycin and penicillin would have suppressed but not eradicated some bacteria, with associated anti-inflammatory effects. Secondly, therefore, the chorioamnionitis would have been less severe.

112. Only some of the bacteria would be controlled by antibiotics. She could not say whether antibiotics would reduce the actual microbial load, but they would certainly change its make-up. This means that the microbiome in the vagina would adjust as some bacteria are suppressed and others will increase. Antibiotic combinations and doses will affect microorganisms differently.

113. What is not known is which bacteria are implicated in chorioamnionitis, though GBS is highly significant and played an important role. A vast array of microorganisms can potentially cause chorioamnionitis. One situation is different to the next.

114. Likewise, the causal mechanism is not known in the sense that there is a wide range of routes by which microbes are capable of invading foetal membranes, all of which are possible, though ascending infection is the most usual and likely pathway. Every woman is different, and every microbiome is different and so it is very difficult to understand the precise casual relationship between ureaplasmas and whether or not infection occurs. Moreover, severity of infection and inflammation is highly variable.

115. Gomez et al (2007) was put to Dr Teare, for which the abstract records the results of a study of antibiotic administration to patients with PPROM as follows:

> "Forty-six patients with preterm PROM whose first amniocentesis was performed between 18 and 32 weeks (median 27.4 weeks) were included in the study. The overall prevalence of intra-amniotic inflammation in the first amniocentesis was 39% (18/46). Seven had a positive amniotic fluid culture for microorganisms. At the time of the second amniocentesis, six of the seven patients with a positive amniotic fluid culture had microorganisms. Of 18 patients with intra-amniotic inflammation at admission, only three showed no evidence of inflammation after antibiotic treatment. Among patients with no evidence of intra-amniotic inflammation at admission, 32% (9/28) developed inflammation despite therapy. Five of these nine patients had positive amniotic fluid cultures."

116. Dr Teare emphasized that the objective is not to treat infection, but to reduce inflammatory burden and therefore to delay labour, prolonging the pregnancy. But the literature provides no indication of the potential to prolong labour beyond 7 days. Rather, for a large cohort of 4145 women, more than half of those with antibiotics went on to give birth within 7 days. These data, collated by Cochrane show that antibiotics reduce the risk of giving birth by up to 7 days. Thus, the risk of development of chorioamnionitis would have been reduced.

Dr Gray

117. Dr Gray's report sets out a detailed chronology of the clinical history of the pregnancy, with specific reference to the medical records and citing the key test results. Similarly, he records the neonatal chronology in detail.

118. Dr Gray's opinion proceeds as follows.

119. The cause (pathogenesis) of chorioamnionitis is generally held to be from more than one microorganism (polymicrobial) including those which are not sensitive to penicillin. Dr Gray provided literature in support of this summary (Tita, A.T.N. and Andrews, W.W. 'Diagnosis and Management of Clinical Chorioamnionitis' *Clin*

Perinatol 2010 37(2): 339-354). This explains that the genital mycoplasmas, *Ureaplasma urealyticum* and *Mycoplasma hominis* (genital mycoplasmas), constitute the most frequent microbes occurring in up to 47% and 30% respectively of cases of culture-confirmed chorioamnionitis. Their role in the pathogenesis of chorioamnionitis and neonatal complications, once controversial, is now increasingly accepted. Other common isolates in women with chorioamnionitis include anaerobes such as *Gardnerella vaginalis* (25%) and bacteroides (30%), as well as aerobes including *Group B streptococcus* (GBS, 15%) and gram-negative rods including *Escherichia coli* (8%).

120. However, GBS is most commonly associated with chorioamnionitis, and its presence elevates the risk of chorioamnionitis. He gives his opinion on the potential role of penicillin in this case, as follows:

> "[5.14] This case is slightly unusual in that, by coincidence, the timings of the onset of PPROM, swab results availability and development of chorioamnionitis would have meant that if a 10-day course of treatment with penicillin had been prescribed, the Claimant would still have been receiving, or would only just have stopped, receiving penicillin at the time of onset of labour. It is widely accepted that antibiotic therapy does not permanently eliminate GBS from the maternal genital tract. However, I would expect that administration of a penicillin antibiotic at a dose and frequency equivalent to Erythromycin 250 mg four times daily) would have suppressed GBS in the genital tract such that CYLP would not have developed chorioamnionitis due to GBS on 09.05.2016 or 10.05.2016. Even if penicillin therapy had been discontinued a little before 09.05.2016, I do not consider that there would have been a sufficiently high dose of GBS in the lower genital tract for it to be involved in the development of chorioamnionitis on 09.05.2016 or 10.05.2016.
>
> [5.15] Taking account of my opinion that GBS was an important contributor to the development of chorioamnionitis, it is my opinion that if CYLP had been treated with penicillin (even at a low dose, equivalent to the low dose of Erythromycin that is recommended in guidelines), she would not, on the balance of probabilities, have developed choriomnionitis associated with GBS when she did. However, it cannot be said that CYLP would have avoided chorioamnionitis at all for several reasons: a) because it is unlikely that presence of GBS was the sole reason why chorioamnionitis developed; b) because GBS might have been replaced with other bacteria that also had a propensity to cause chorioamnionitis; and c) because if the pregnancy had continued for longer, there would have been an increasing chance that the GBS that had been suppressed but not eliminated by low-dose penicillin, would have recolonised the vagina (either from surviving GBS in the genital tract or from a gastrointestinal source). It would be a matter for obstetricians to advise on when the Claimant would have been born had chorioamnionitis been avoided on around 10.05.2016."

121. The vaginal swab showed the presence of GBS but other bacteria may have been present which had potential to cause chorioamnionitis, almost none of which would be sensitive to penicillin and a small proportion sensitive to Erythromycin. But, the presence of microorganisms in the vagina does not necessarily indicate they will cause chorioamnionitis.

122. Dr Gray was cross-examined.

123. Dr Gray's evidence remained that there was no evidence that Erythromycin prevents the development of chorioamnionitis, and that it was biologically implausible that it would. However, he agreed that the totality of the evidence showed other benefits, including prolongation of pregnancy.

124. Like Dr Teare, Dr Gray considered that the relative contribution of types of bacteria to chorioamnionitis was unclear.

125. Both of the antibiotics under consideration, Erythromycin and penicillin, are narrow-spectrum. Penicillin is narrower than Erythromycin and has no anti-inflammatory effect. He would advise use of Erythromycin for PPROM because it strikes the best balance between benefit and harm. He would not advise use of penicillin to a patient with PPROM, who was GBS positive and had no evidence of infection.

126. Dr Gray was examined closely on paragraphs 5.14 and 5.15 of his report. The totality of his evidenced remained as drafted: GBS played a role in Mother's development of chorioamnionitis, and was an important contributor. But, if penicillin had been given, any microbiologist would recognise that it would have potentially disrupted the normal balance of bacteria in the vagina, and left the potential for other virulent bacteria, such as E. coli from around the vulva and anus to enter the genital tract, colonise, and have at least the same potential to cause chorioamnionitis as the group B strep would have done. Dr Gray explained the scenario to me in this way:

"So I think what happens is that exposing the mother to penicillin will change the vaginal flora , and it will reduce the number of Lactobacilli that are present because they are one of the few bacteria which remain sensitive to penicillin.

So by removing or reducing the number of Lactobacilli , less acid is produced, the vaginal pH increases from its normal sort of 3 to 4 to a level that's closer to neutral, or even reaches neutral. So the vagina becomes a less hostile environment for any bacteria that are around to establish themselves in the vagina, and almost perversely, it also creates an environment that would actually favour the group B strep being able to multiply once the suppressive effect of the antibiotic is removed.

So I think what it's fair to say is that the vaginal flora would be altered in a way that would last for some time after the antibiotics were administered, and by some time, I mean more than a few days, I mean a week or two, before there would be any chance of the vaginal flora being able to re−establish itself into its sort of pre−antibiotic state.

And during that time, the group B strep is still going to be around, and even if it wasn't around in the genital tract, it's still going to be around in the region −− in the anatomical region of the genital tract.

A worse scenario would be that the vaginal flora was changed so much that actually there was a greater risk of developing chorioamnionitis.

But what I cannot envisage is a situation where administering penicillin for five days would lead to an ongoing state where there was a reduced risk of developing chorioamnionitis."

"Failure to administer Erythromycin, in my opinion, would not have changed the outcome, because the chorioamnionitis would have happened in any event.

The failure to give penicillin, if the court were to find that group B strep was a significant contributor to the chorioamnionitis, and I understand that there is a difference of opinion between the various disciplines of experts on the role of group B strep in this case, but if the court were to find that group B strep were a factor, then if the penicillin had been given in a timescale that meant that the mother was receiving penicillin or had just stopped receiving penicillin before 9 May when she did develop chorioamnionitis, then I would agree that the development of chorioamnionitis caused by group B strep at that time would not have happened."

127. I now turn to the Hospital's investigation, report and response.

Serious Incident Report

128. The Hospital has a procedure to address serious incidents. A serious incident was declared by the Hospital on 11th July 2016. Evidence was gathered and a Serious Incident Panel was convened by the Medical Director. They met on three occasions and issued a twelve page report on 5th October 2016. It is a thorough, transparent, open and well-structured report.

129. The report addresses the differences between local and national guidelines and identifies that as a factor in the case. In respect of Mother's positive GBS swab, "*The panel considered that whilst the unit guidance was not followed, the management was more in keeping with national RCOG guidance*."

130. The panel asked the clinical director for comments on the national guidance on routine antibiotic therapy for PPROM. The response was detailed:

"Early studies of antibiotics to treat or prevent ascending infection, prolong pregnancy, and reduce neonatal morbidity in women with PPROM showed significant prolongation of pregnancy but no effect on infant morbidity or mortality. However, the Oracle trial and subsequent meta-analysis dominated by Oracle showed improvement in neonatal outcome with oral erythromycin but the findings were controversial as they arose from previously unspecified subgroup analysis of women with PPROM and may be due to chance.

It is well documented that many pathologic process is unrelated to infection, could cause PPROM. Furthermore, ongoing research in the department at the time demonstrated that oral clindamycin significantly reduced the risk of preterm delivery in women with bacterial vaginosis (BV) who were at the greatest risk of PPROM. Erythromycin on the other hand was effective against BV organisms. Therefore, at Saint George's hospital it was considered that routine antibiotic therapy for PPROM wrongly presumed infectious aetiology in many cases and exposed a substantial number of uninfected foetuses/ mothers to antibiotics with potential for alteration of natural flora, childhood allergies, and the development of resistant organisms. It was therefore decided to wait further evidence and better understanding of the risks and benefits.

Based on a CDC (Centre for Disease Control and Prevention) recommendation the unit adopted a departmental policy to treat women with PROM who were also GBS positive

with penicillin and clindamycin as this organism accounted for many of the foetal morbidity and mortality [sic] whilst the frequency of erythromycin-resistant strains of GBS rose with routine use of erythromycin, currently reported to be over 40%.

In the interim the RCOG and NICE issued guidelines recommending routine 10 days course of oral erythromycin for PPROM. The department reviewed the policy on average every three years until 2015 and the majority view of obstetricians and neonatologists remained in favour of our local guidance.

However, in a recent case clinicians failed to follow the departmental guidance and administer penicillin to a woman with PPROM who was also GBS positive. The department therefore revisited the issue at its multidisciplinary governance meeting in June 2016 and acknowledged the risk of confusion of staff by having a different local guidance. Therefore a majority of clinical staff supported the switch to the NICE/ RCOG guidance"

131. Professor Shennan said of this response:

"… the purpose of antibiotics is not [to] treat an infection but to prevent ascending infection occurring. The rationale given in [the report] was that routine antibiotic therapy for PPROM wrongly presumes infectious aetiology; this is not the case, it is given to prevent subsequent infection and its consequences. … In this case the value of antibiotics was to improve preterm birth outcomes, not specifically related to GBS."

132. The report finds that the patient was not listened to with regards to leaking.

[8] Findings & Analysis

133. The history of the pregnancy, the chronology and the basic clinical facts are not in dispute and I found facts accordingly at paragraphs 17 to 27, above.

134. To recap, membranes broke on 25th April 2016. On 26th April an ultrasound scan showed normal amniotic fluid volume. The low vaginal swab taken on 27th April isolated GBS on 28th April 2016. The GBS was prevalent. On 30th April, GBS resistance to Erythromycin and sensitivity to penicillin was identified. On 28th April the C-reactive protein result was normal.

135. Mother was either in touch with the Hospital or at the Hospital on 29th, 4th, 7th and 9th May. During this period, she continued to show symptoms of ruptured membranes. The understanding of the microbiology remained unchanged: GBS resistance to Erythromycin and sensitivity to penicillin.

136. Chorioamnionitis only developed in the 12 to 24 hours prior to delivery.

Penicillin

137. Was it a breach of duty to not offer oral penicillin from 28th April 2016 in addition to Erythromycin, by reason of the GBS positive result?

138. The Claimant has strong points in her favour on this issue. Amongst them is the admission of the breach of duty in respect of Erythromycin. The Defendant's acceptance in that regard follows guidance documents at both national and local level,

i.e. at the Hospital. Such documents may capture, in summary form, the best available evidence. They incorporate a balancing of relevant factors, articulate the preferred courses of action, and indicate where caution is needed.

139. From the point of view of deciding whether there has been a breach of duty, such guidance documents are evidence. Like all evidence, the weight to be given to it is case-specific and sensitive to context. As Professor Shennan explained, and nobody contradicted him, national guidance documents are held in high regard as guidance and are often followed by hospital trusts in crafting their own protocols. However, no element of guidance is a rule. If it were, it would no longer have the characteristics of guidance and the importance of medical observation, experience and care for the individual person in their particular circumstances would be diminished.

140. The guidance documents recognise their own role, and the boundaries to their role. This awareness is expressed in the RCOG Green Top guidelines by classifying the strength of the underlying evidence and therefore of the advice given (see paragraphs 87 to 89 above). It would be an unfortunate backward step if those drafting important national medical guidance were influenced so that they changed the terms of their guidance through concern that a court may over-interpret their purpose and effect.

141. In respect of dealing with PPROM, the medical profession is faced with an event which it may only observe by remote means and indicators. Though that is a common circumstance in medicine, and is obvious, it is the necessary starting point in understanding the nature of the challenges in decision making. To these uncertainties are added the variabilities in the microbiome which Dr Teare and Dr Gray both described. A further overlay is lack of precision in effect of different types and dose of antibiotic. With these fundamental features of the task of caring for the Claimant in mind, it is unsurprising that the range of reasonable responses is not a narrow one.

142. However, the professions do know that a rupture event may lead and progress to adverse consequences for both a mother and her baby and so the guidance documents speak in terms of management. In turn, the management options in terms of the future development of infection are not clear cut, and management of GBS is a good example of that.

143. As Professor Gupta emphasised in his evidence, national guidance does not guide practitioners to offer penicillin in the same way that it guides the use of Erythromycin. National guidance indicates use of penicillin during labour, intravenously to address GBS: "*Antibiotic administration specifically for GBS colonisation is not necessary prior to labour and should not be given 'just in case'."* – see paragraph 91 above.

144. The Claimant also, correctly, emphasises the fact of the local guidance and the fact that it was drafted by the clinician who was caring for the Claimant. That local guidance was to do that which the Hospital did not do: prescribe oral penicillin. The debate in this regard is twofold: what is the impact of national guidance, which is different to the local guidance, and what is the strength of the reasons not to offer penicillin? The particular circumstance in the Hospital was that GBS had some resistance to Erythromycin. Penicillin was the alternative to address that particular hazard, namely GBS-related infection and related inflammation.

145. I found Professor Gupta's evidence to be helpful in this regard. He was pressed hard on these issues during his evidence. With a considered approach to his evidence, he preferred the national guidance over the local. He was able to support that with reference to the established practice and guidance of treating GBS specifically at the time of delivery, and by intravenous method. The national guidance deliberately and clearly distinguishes between the need to protect the mother against risk of infection in cases of PPROM. The Guidance to give antibiotics (RCOG No.36) where GBS is isolated in cases of PPROM is to give them in line with the recommendation for routine intrapartum prophylaxis and was limited to those circumstances to protect the baby from GBS infection, and not otherwise. I accept Professor Gupta's view and find that the national guidance is the best available evidence in this case by which to gauge the duty to the Claimant, by reference to the test I have summarised at paragraphs 31 to 34 above.

146. Moreover, he confirmed during his evidence that he had never given Erythromycin and penicillin together. I find that his evidence is confirmatory of the Defendant's position.

147. This does not mean that the local Hospital guideline is wrong, nor does it mean that if the local were to be followed in preference to the national in another case, with some adverse effect, that would be a breach of duty. Each guideline is there with the intention of providing the medical professional with a well-informed starting point for managing the particular circumstances which they encounter, for the particular patient.

148. The Serious Incident Report considered the local and national guidance and the two differing approaches taken on this point. The Panel thought the differences were confusing. With respect to the Panel, it may be confusing, but that is a consequence of the difficult choice to be made. Each approach is associated with credible arguments going each way. The response from the Clinical Director (paragraph 130 above) is illustrative of the internal debate with the Hospital, as the evidence evolved over the years.

149. I find that Dr Gray's evidence is more fully and completely reasoned that Dr Teare's evidence, both in writing and orally, and I accept his evidence on the potential role of penicillin. I find that administering penicillin orally at the doses proposed would not lead to an ongoing state where there was a reduced risk of developing chorioamnionitis.

150. I also note and accept the view which was widespread amongst the experts that the cause of chorioamnionitis is usually polymicrobial. I find that the range of bacteria in issue is broad and variable. I find that penicillin would not, in any event, be active against the whole of that broad and variable range of bacteria.

151. Per *Bolitho*, I find that Professor Gupta considered the balance of risks and benefits and I accept his opinion on that balance and his reliance on national guidance. I find that Dr Gray was correct in his identification of the risks associated with use of penicillin as I set out above at paragraph 126. Against these findings, I have given considerable weight to the fact of the local Hospital guidance and to the local circumstances in respect of GBS which were evidently recognised by the author of that guidance. However, I have reached the conclusion overall that to act in accordance with national guidance, and not to follow local Hospital guidance, was not a breach of duty. My conclusion is reinforced by what I accept and find as good reasons to avoid disruption of the balance of bacteria in the genital tract, with its own attendant risks. Those good reasons also include the

dilemma of dealing with GBS resistance, which the Hospital was grappling with, as shown by the Serious Incident Report.

152. I now turn to the causation issues. My finding on breach of duty in respect of penicillin has an impact on the scope of the causation issues which the court has to determine. However, and notwithstanding my conclusion in this regard, I have considered the causation issues on the Claimant's case, namely that both antibiotics should have been offered. I do so for three reasons. Firstly, the Claimant's parents wish to know what the court's conclusions are on the basis of the Claimant's case as a whole. After nearly ten years, they reasonably want to know '*what would have happened if?'*, and not solely on a part of the Claimant's case. Secondly, while it is possible to separate out the evidence which relates solely to Erythromycin, there are interactions with evidence of the effects of other antibiotics which it is more straightforward to address as a whole. Thirdly, if I were to be wrong in my conclusion as to breach of duty in respect of penicillin, I provide findings and analysis for that counterfactual.

Causation

153. I have accepted the generality of Professor Shennan's evidence as to the use of the Cochrane meta-analyses (and Dr Teare's evidence to the same effect). By that I mean that I accepted his approach of looking at the risk ratios for a range of end points, rather than focussing overly on whether or not chorioamnionitis is prevented. For the reasons which he explained, he is correct to say that it is a difficult end point to establish and observe. A range of other end points are more reliably observed and measured. An overview is required. Professor Shennan was also correct not to go so far as to say that the chorioamnionitis end point should be set aside. It too is part of the picture.

154. I find that there are significant indications that Erythromycin has net-beneficial effects on outcomes for babies born after their mother has experienced PPROM. Those indications are found within both the literature which I have been taken to, and which I have reviewed, and also from meta-analysis. There is good support for the conclusion that some antibiotics reduce infection during PPROM and there is similarly good support for the short-term prolongation of pregnancy, or put another way; increased latency. The support is good because it comes from a significant number of individual studies which are different and diverse in terms of the cohort studied. While the size of some studies is small, they may nevertheless contribute to the totality of the evidence and in a way which can be moderated by reference to confidence intervals.

155. However, the evidence is far from all one-way. As the competing cross-examinations of witnesses on the literature showed, there are results from cohorts of patients which can be deployed to argue the merits in both directions. In my review of the literature, I have identified features which illustrate both variability and uncertainties as between cohorts and for different end points. In my judgment, these features are to be expected because the cohort is self-selecting and the many other variables which may affect outcomes are not within the control of those reporting the results. These are results from the real world, as the medical professions find it, not a laboratory in which the variables can be controlled.

156. The risk ratios alone are a tool and not an answer. Paraphrasing Lord Nicholls in *Gregg v Scott* at [27 and 28], though the statistical evidence may be the main tool available to understand what would have happened to a claimant, prospectively, the statistics are

necessarily retrospective records, and for different patients. They do not show whether the claimant would conform to trend, or not.

157. As for the national guidance documents, I have already addressed their role in guiding clinical decisions. Their further role is to do the reading and analysis to help the busy clinician and that is what then informs the recommendations. I, of course, accept that Cochrane, RCOG and NICE have undertaken careful and expert review and assessment of the evidence base. These materials, along with the expert evidence I have heard, amount to a broad and consistent consensus that Erythromycin improves outcomes where there is PPROM. I find that the national guidance reflects the primary research studies, the meta-analysis of those studies and the aggregate of clinical experience. None of that material supports a proposition that Erythromycin prevents chorioamnionitis, and that is not the Claimant's case. Rather, I find that Erythromycin has a sufficient range of beneficial effects in a sufficient proportion of cases, with sufficient evidence of a lack of adverse effects, to warrant its use to assist in managing PPROM.

158. However, the national guidance documents cannot provide evidence for, nor establish, a position which goes beyond the evidence base which underpins them. In this case, it would be a fallacy to equate a recommendation in national guidance with causation.

159. I find that there is no body of evidence which establishes that Erythromycin assists with latency such that it extends pregnancy beyond about a week. Erythromycin alone would not, on the balance of probability, have delayed the onset of labour in the Claimant's case beyond a week and that delay alone would not have avoided the cytokine response and the resultant PVL (Dr Rennie; paragraph 63 above).

160. Dr Teare was a witness who very much emphasised the importance of delay in the onset of labour: *"On the balance of probabilities, prolonging pregnancy beyond 32 weeks would have avoided PVL.":* paragraph 103 above. The difficulty with this evidence is the lack of support within the literature and the guidance to the effect that such a prolongation was at all likely in the Claimant's case. I appreciate that Dr Kendall has had positive experiences of treating PPROM and managing it successfully with the assistance of antibiotics. However, that is not the same proposition as to whether it was likely that an extended prolongation beyond a week would occur in the case of the Claimant and Mother. I have found that it is unlikely that this would have happened.

161. Rather, it became clear during Dr Teare's oral evidence that it was her opinion that there was assistance to be had from treatment with Erythromycin which reduced the risk of PVL. So far as it goes, I accept that is so, to the degree indicated by the literature I have reviewed. In my judgment, the purpose of national guidance is to point medical practitioners to a course of action which is beneficial in sufficient cases for it to be worthwhile, to some degree. However, that position does not, of itself, mean that to not prescribe Erythromycin causes PVL, or may be the likely cause of PVL, or a likely contributor. It does not, and cannot, lead to the conclusion that but for the prescription of Erythromycin the sequence of events leading to PVL would not, on the balance of probabilities, have occurred. The prolongation of pregnancy argument advanced by the Claimant falls a long way short of establishing causation to the civil standard of proof. Dr Rennie was clear that a prolongation of a week would have made no material difference, and I have accepted that evidence and make findings accordingly.

162. Per Lord Hope in *Gregg v Scott* and *Zgonec-Rozej v Periera* (paragraph 42 above) the evidence which comprises the reported studies to be found in the medical literature, the meta-analyses and the national guidance do not support a conclusion that but for the prescription of Erythromycin the Claimant would not have suffered her injury. This is consistent with the evidence as to the range of potential causes of infection and inflammation. The microbiological experts agree that the microbiome is variable as between patients, each with its own complex bacterial composition. This was demonstrated in Dr Teare's evidence that:

    i) The Cochrane review shows risk reduction but not prevention of chorioamnionitis;

    ii) Only some bacteria would be controlled by antibiotics, and others would adjust their number accordingly;

    iii) Which bacteria cause chorioamnionitis is not known, though GBS are significant;

    iv) The routes via which bacteria might invade foetal membranes are numerous;

    v) The vaginal microbiome is variable between individuals.

163. These observations were consistent with Dr Gray's evidence. The matters of agreement between the obstetrics and neonatal experts are also consistent with these five points. I find each of the points at i) to v) above as facts.

164. On these facts, the Claimant is not able to demonstrate that Erythromycin would have prevented the Claimant's injury. The Claimant faces a situation which is analogous to that described in *Williams* at [40]; see paragraph 39 above. There are numerous potential and credible causes of the chorioamnionitis. By the end of the microbiologist's evidence, it was clear that they were unable to say Erythromycin would be likely to eliminate potential and credible causes in the Claimant's particular case such that chorioamnionitis would not occur anyway. This is consistent with the agreement between Professors Shennan and Gupta, namely that it is not possible to determine whether chorioamnionitis would have been avoided, or not, and the exact microbiological cause of the chorioamnionitis is not known.

165. For this further reason, the Claimant is unable to show causation in respect of Erythromycin alone.

166. This aspect of the case focusses on what is <u>not</u> known, and the range of potential causes. However, I have not approached this analysis solely on that basis. I have found that there is no body of evidence which demonstrates that antibiotics would prolong labour beyond one week. Put another way, I have found that prolongation for one week is the maximum likely length of any prolongation. The evidence which I have accepted, from Dr Rennie, is that a prolongation of one week would not suffice to prevent PVL in the Claimant's case. This leads me to the conclusion that the balance of the evidence in this case shows the Claimant's injury would have happened in any event.

167. For similar reasons, I reach the same conclusion if oral penicillin were prescribed in addition to Erythromycin. Though I accept that GBS is significantly implicated in

chorioamnionitis, the points in paragraph 162 i) to iv) remain to be overcome. In my judgment, it has not been shown on the balance of probabilities that a combination of antibiotics, including penicillin, would have prevented the Claimant's injury and causation has not been shown on this basis.

168. Given these findings, an analysis of material contribution does not arise. However, Miss Rodway submitted that the injury was indivisible and she relies upon material contribution, so I address it.

169. Firstly, I do not find the concept of indivisible injury to be of assistance in this case. The Claimant's injury does not have the characteristics of an indivisible injury, namely those which I record at paragraph 37.i) above: *"A characteristic of divisible disease is that severity is influenced by the total amount of the agent that has caused the disease. But, once contracted, an indivisible disease is not influenced by the total amount of the agent which caused it"*. The Claimant's case is the opposite of indivisible disease. The Claimant argues that the severity of the injury would be reduced if the bacterial load was reduced.

170. If I were wrong, and this case did have the characteristics of an indivisible disease, then I would still find the concept of little assistance. The question of 'infection or not' is a complex and overlapping set of factors and interactions as the totality of the expert evidence amply demonstrates. Which antibiotics may, or may not, help to some degree is just one factor. This is a very long way from exposure to a hazardous environment in which the degree of exposure plays a role in the injury as in the dust and asbestos cases.

171. Secondly, prolongation of pregnancy is, as I have found, associated with improved outcomes. But those improved outcomes cover a broad spectrum, as the review of the literature shows. It is not possible, in my judgment, to equate a general conclusion of improved outcomes, with its many potential meanings, to a reduction in severity of PVL and brain injury. The evidence does not sufficiently support that specific conclusion. As I have sought to emphasise, there is a difference between evidence of generally improved outcomes in cohort studies and a conclusion that it is worthwhile to prescribe Erythromycin and a conclusion that there would be a reduction is severity of PVL in a particular case. The link which Miss Rodway seeks to make in this regard, is not sufficiently supported because: (1) the underlying data show significant variability as between studies and within them; (2) extrapolation from the general to the specific is a tenuous basis for finding material contribution; (3) the underlying data and the national guidance documents are founded on what did happen in particular cases, whereas the issues in this case are prospective; (4) the expert evidence which I have accepted in this case and the associated findings do not indicate a finding that the Claimant's PVL and brain injury would have been less severe if antibiotics were prescribed.

[9] Conclusions

172. This case is about medical treatment of two patients: the Claimant and her mother. But it is also about the way in which they were treated as people, at a very significant time in their lives. Mother felt that she was not being listened to by the consultant who was in charge of her care, as the Serious Incident Report records. I trust that remains a lesson learnt at the Hospital. In the factual context of the Hospital not listening to Mother, having departed from its own guideline and given the very serious condition which the Claimant and her parents now live with, the parents' wish to bring this claim is not

surprising. Mother formed the understandable impression that medication was omitted which would have changed the outcome. The evidence which I have heard shows that is not in fact so, and for the reasons I have sought to explain, the claim must therefore be dismissed.

173. I am grateful to all counsel for their written and oral submissions which were of considerable assistance. Their conduct of the trial was exemplary, consistent with their duties, while maintaining a productive and practical atmosphere. Similarly, I record my thanks to solicitors for their careful preparation of the materials.

GLOSSARY

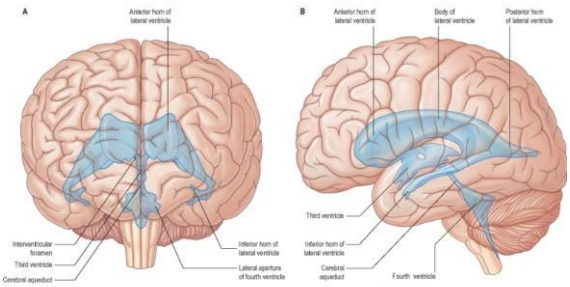
<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td>Acidosis</td><td>See metabolic, and respiratory acidosis.</td></tr>
<tr><td>Aerobic bacteria</td><td>Microorganisms that require oxygen to survive, grow and carry out metabolic processes.</td></tr>
<tr><td>Amniotic fluid</td><td>The fluid in the uterus surrounding the fetus. Also termed liquor.</td></tr>
<tr><td>Amniocentesis</td><td>Taking a sample of fluid around the baby (the amniotic fluid) usually with a needle passed through the abdomen. It is used to detect fetal cells and sometimes signs of infection.</td></tr>
<tr><td>Amnisure</td><td>A non-invasive and highly sensitive test for amniotic fluid used to detect rupture of the fetal membranes.</td></tr>
<tr><td>Anaerobic bacteria</td><td>Microorganisms that thrive in environments with little or no oxygen.</td></tr>
<tr><td>Antibiotic prophylaxis</td><td>The use of antibiotics to prevent an infection occurring, rather than to treat an existing one.</td></tr>
<tr><td>Apgar score</td><td>A method of assessing the newborn; the system was designed to recognise babies who needed assistance. The score is assigned as zero, 1 or 2 for each of five parameters. The maximum possible total score is 10.
<table>
<tr><th></th><th>Score</th><th>0</th><th>1</th><th>2</th></tr>
<tr><td>A</td><td>Appearance</td><td>Pale or blue</td><td>Body pink but extremities blue</td><td>Pink</td></tr>
<tr><td>P</td><td>Pulse rate</td><td>Absent</td><td><100</td><td>>100</td></tr>
<tr><td>G</td><td>Grimace</td><td>Nil</td><td>Some</td><td>Cry</td></tr>
<tr><td>A</td><td>Activity (muscle tone)</td><td>Limp</td><td>Some flexion</td><td>Well flexed</td></tr>
<tr><td>R</td><td>Respiratory effort</td><td>Absent</td><td>Hypoventilation</td><td>Good</td></tr>
</table></td></tr>
<tr><td>Apnoea</td><td>Not breathing.</td></tr>
</table>

Axons	A long slender projection of a nerve cell or neurone that transmits electrical impulses (action potentials) to other neurons, muscles and other organs.
Bacteroides	A type of gram-negative anaerobic bacteria.
Beta-Lactam antibiotics	β-lactams inhibit bacterial cell wall synthesis. They require a cell wall to work. Members include: penicillin, amoxicillin and co-amoxiclav.
Cerebral palsy	A disorder of movement and posture resulting a non-progressive injury to the developing brain. The severity varies but children with CP often have difficulty walking and reduced fine motor skills. Muscle tone can be increased (spastic CP) , and some children have involuntary movements (Dyskinetic CP). Patterns include: - Quadriplegia – affecting all of the body - Hemiplegia – affecting left or right half of the body - Diplegia – affecting upper or lower half of the body
Cerebrospinal fluid (CSF)	CSF is a watery fluid formed in the choroid plexus of the lateral ventricles, which then circulates into "cisterns" in the brain and into the subarachnoid space around the spinal cord and into the lumbar cistern (where it can be sampled via a lumbar puncture). CSF then circulates over the brain and is reabsorbed via the arachnoid granulations.
Chorioamnionitis	Inflammation of the fetal membranes; this can be divided into: - Histological chorioamnionitis where on histological analysis (from the assessment of the placenta sent to the labs after delivery), there is evidence of inflammation on placental microscopy with inflammatory cells seen in the fetal membranes without clinical signs in the mother - Clinical chorioamnionitis where there are signs and symptoms such as maternal fever, uterine tenderness, maternal tachycardia, purulent or foul-smelling amniotic fluid. Histological staging (location): - Stage 0 (preacute chorioamnionitis): neutrophils in the subchorial intervillous space beneath the chorionic plate - Stage 1 (early): neutrophils in chorion laeve of the extraplacental membranes - Stage 2 (intermediate): neutrophils within chorionic or amnionic mesoderm - Stage 3 (advanced): stage 2, plus necrosis of amnionic epithelium or neutrophil necrosis Grade (severity): - Grade 1 (mild to moderate): anything less than severe, as described below Grade 2 (severe): confluent neutrophils or > 3 foci or > 200 neutrophil

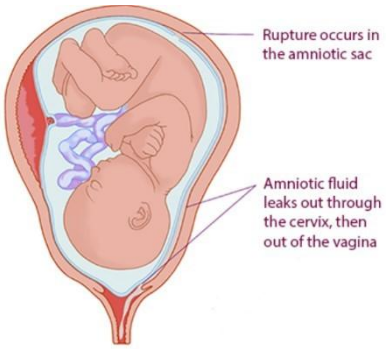
Co-amoxiclav (Augmentin)	A combination of amoxicillin (a penicillin) and clavulanic acid which broadens the spectrum of bacteria treated by amoxicillin alone, by overcoming a specific antibiotic resistance.
Cochrane	An organisation formed to synthesise medical research findings to facilitate evidence-based choices about health interventions involving health professionals, patients and policy makers.
Colonising bacteria	Existing on or in the body without causing harm.
95% Confidence interval	A range of values applied in statistics where there is a 95% chance that the true result lies within this range.
Coronal view on imaging	A view of the brain/body imaging viewed from the front (the subject is 'looking' at the viewer face on).
Corpus callosum	Bundle of nerve fibres which connect the two hemispheres of the brain.
Cortex	The outer layer of the brain, which contains layers of nerve cells. Can be referred to as "grey matter". The layer is folded, forming sulci and gyri. Underneath the grey matter lies white matter, the myelinated axons (processes) of the nerve cells.
C-reactive protein (CRP)	A non-specific inflammatory marker that can rise in response to infection which can be measured in the blood.
CTG cardiotocograph	A method used to graph the fetal heart rate and the uterine contractions in pregnancy. Some machines have the ability to graph the maternal heart rate as well, on a third channel.
Cytokines	Proteins which are produced in response to infection/inflammation which help to co-ordinate and regulate the immune response to infection. Cytokines can be characterised as pro-inflammatory or antiinflammatory.
Diplegia	Paralysis affecting symmetrical parts of the body (for example both legs).
Dystonia	Involuntary muscle contractions resulting in twisting or repetitive or abnormal posturing.
Encephalopathy	An abnormal neurological state. There are scoring systems for the term newborn examining the baby's conscious level, arousability, tone, reflexes, and whether or not seizures (fits) are present.
Erythromycin	A macrolide antibiotic.
Fetal inflammatory response syndrome (FIRS)	Fetal inflammatory response syndrome (FIRS) is a condition characterised by inflammation of the umbilical cord (funisitis) and elevated fetal pro-inflammatory cytokines.
Forewater rupture	Rupture of the membranes low down over the head (presenting part). There tends to be a larger initial leak (a gush).
Funisitis	Evidence of inflammatory cells in the Wharton's jelly of the umbilical cord. This would be identified on post-delivery pathological assessment of the umbilical cord. Funisitis staging (location):

<table>
<tr><td></td><td>- Stage 1 (early): fetal inflammatory cells within chorionic plate vessel walls (fetal vasculitis) or umbilical vein vessel wall (umbilical vein vasculitis)
- Stage 2 (intermediate): fetal inflammatory cells within umbilical arteries (umbilical artery vasculitis) or vein
- Stage 3 (advanced): necrotising funisitis (perivascular bands of necrotic Wharton jelly containing dense neutrophils)

Funisitis grading (severity):
- Grade 1 (mild to moderate): anything less than severe, as described below
Grade 2 (severe): confluent fetal inflammatory cells with attenuation / degeneration of smooth muscle</td></tr>
<tr><td>Germinal matrix, and germinal haemorrhage (GMH</td><td>The germinal matrix (GM) is a highly cellular and vascular structure in the developing brain. In very early fetal life the GMH is situated along the entire wall of the ventricular system, but as the fetus matures and the cells migrate out to populate the cortex the GMH regresses, with a major site over the head of the caudate nucleus. The structure is prone to bleeding in preterm babies, termed GMH.</td></tr>
<tr><td>Gestation, gestational age</td><td>Number of weeks and days of a pregnancy, for example 29+5. For babies born preterm the expression "corrected gestational age" refers to the gestational age at birth added to the days /weeks since birth.</td></tr>
<tr><td>Gliosis</td><td>Scarring within the brain following injury or damage.</td></tr>
<tr><td>GMFCS (Gross Motor Functional Classification Score)</td><td>A standardised tool used to describe the movement abilities of children with cerebral palsy:
<table><tr><th>Level</th><th>General heading description</th></tr><tr><td>Level I</td><td>Walks without limitations</td></tr><tr><td>Level II</td><td>Walks with limitations</td></tr><tr><td>Level III</td><td>Walks using a hand-held mobility device</td></tr><tr><td>Level IV</td><td>Self mobility with limitations; may use powered wheelchair</td></tr><tr><td>Level V</td><td>Transported in a manual wheelchair</td></tr></table></td></tr>
<tr><td>Group B Streptococcus (GBS)</td><td>A type of bacteria commonly found in the intestine and lower genital tract of healthy adults. It can lead to severe infection in newborns most commonly acquired during delivery or after rupture of membranes.</td></tr>
<tr><td>Hindwater rupture</td><td>Rupture of the membranes higher up. There tends to be a smaller volume leak rather than a gush (compare for forewater rupture).</td></tr>
<tr><td>HVS</td><td>High vaginal swab. A technique to collect samples from the upper part of the vagina for detection of bacteria. Usually involves a speculum.</td></tr>
<tr><td>Hypocarbia</td><td>Low levels of carbon dioxide below the expected normal range for the context measured in the blood as part of blood gas analysis.</td></tr>
<tr><td>Hypoglycaemia</td><td>Low levels of blood glucose below the expected normal range for the context.</td></tr>
</table>

Hypoxia	Low oxygen tension. The body need oxygen to make the essential energy currency of the cell - adenosine triphosphate (ATP), which is not stored in significant amounts. Without oxygen cells make ATP from stored glycogen (anaerobic metabolism), and lactic acid accumulates. Acids are H+ (proton) donors so the pH falls. See metabolic acidosis, and ischaemia.
Hypoxic ischaemic encephalopathy	A neonatal encephalopathic illness, often characterised by seizures, which was caused by a hypoxic ischaemic brain injury.
Inflammatory Response	The body's immune system reacting to any kind of insult (eg. trauma, irritant, infection). The purpose is to isolate damage and destroy harmful agent.
Intrapartum antibiotic prophylaxis (IAP)	Antibiotics given to a mother during labour to prevent transmission of bacteria to the baby and reduce the risk of early onset neonatal sepsis.
Intraventricular haemorrhage (IVH)	Bleeding into the lateral ventricles of the brain (see below for definition). In a preterm baby the blood generally arises from a large GMH with release of blood from the germinal matrix into the CSF (fluid) of the lateral ventricles.
Ischaemia	Lack of blood supply to an organ, or the whole body. When less blood is supplied to an organ the tissues cannot get the oxygen delivered to them which they need for making ATP (see hypoxia).
Lateral (cerebral) ventricles	The lateral ventricles are cerebrospinal fluid (CSF) containing spaces deep within the brain, one on each side of the brain. They communicate with the other parts of the ventricular system into which CSF circulates.  FIG. 16.1 The ventricular system. **A**, Anterior view; **B**, left **lateral** view.
Liquor	See amniotic fluid.
Low birthweight	Birthweight below 2.5 kg.
LVS	Low vaginal swab taken to send for microbiological assessment. Does not usually involve a speculum.
Macrolide	A class of antibiotic which includes Erythromycin which are considered to have immune modulation effects in addition to antimicrobial properties.
Metabolic acidosis	The pH of the body is normally maintained within tight limits. pH is a value which is calculated from the hydrogen ion concentration on a minus log scale. When hydrogen ions increase, pH decreases. An acidosis is associated with an accumulation of hydrogen ions, which causes a fall in pH. Acids are proton (H+ ion) donors. The body has "buffer" systems to

	cope with fluctuations of hydrogen ions, but these can be overwhelmed. An important cause of a metabolic acidosis in the newborn is caused by an accumulation of lactic acid produced by anaerobic metabolism (i.e metabolism without oxygen). See hypoxia, hypoxic ischaemia, and respiratory acidosis.
Microbiome	Refers to the collective genetic material (genes) of all the microbes in a community. The microbiome determines how microbes influence immunity, metabolism, and susceptibility to infection.
Microbiota	Microbiota refers to the community of microorganisms (bacteria, viruses, fungi) that live on or inside the human body.
Microcephaly	A head circumference smaller by more than two standard deviations below the mean than that expected for age and out of proportion to body size. This may be caused by genetic conditions or a failure of normal brain growth following brain injury.
Microglia	Resident immune cell within the central nervous system able to produce cytokines and clear dead cells and debris.
MSU (mid stream urine)	A urine sample for microbiological assessment.
Mycoplasma	Mycoplasma refers to a group of very small, cell wall deficient bacteria that cause a range of human infections. Because they have no cell wall, antibiotics that target protein synthesis such as macrolides must be used. Beta-lactams (eg penicillin based antibiotics) will not work.
Myelin	A lipid rich material made by mature oligodendrocytes that ensheathes nerve fibres and increases the rate at which electrical impulses (action potentials) transmit along the axon.
Necrotising enterocolitis	A serious intestinal disease primarily affecting premature or very low birth weight infants. It involves inflammation and death of intestinal cells which can lead to perforation and serious abdominal infections.
Odds ratio	The odds ratio is defined as the ratio of the odds of an outcome taking place in the presence of a treatment, and the odds of the outcome in the absence of a treatment. An effective treatment will have an odds ratio of less than 1. When considering the odds ratio it is important to consider the statistical significance of the result.
Oligodendrocyte	Glial (non-neuronal) cell in the central nervous system responsible for producing the myelin sheath that insulates neuronal axons which speeds up nerve transmission. During fetal development there are three stages: oligodendrocyte progenitor cells, immature oligodendrocytes (non-myelinating), and mature oligodendrocytes (myelinating).
Oligohydramnios	Reduced volume of liquor (diagnosed by measuring the pools with ultrasound).
Parenchymal lesion	A lesion in the substance (the parenchyma) of the brain.
Penicillin	A beta-lactam class of antibiotic.
Periventricular flare	A descriptive term used in neonatal brain ultrasound describing increased echoreflectivity within the white matter around the lateral ventricles. This

	may resolve or be precursor of more extensive cystic white mater – see periventricular leukomalacia.
Periventricular leukomalacia	Term used to describe reduction in the white matter of the periventricular cortex, which is often "scarred" (gliosis). Cystic PVL (cPVL) refers to a specific appearance on ultrasound scanning of the brain in which cysts (or "holes") are seen in the periventricular white matter. The cysts usually resolve over time leading to the later appearance of gliosis on MR imaging.
Periventricular white matter	The myelinated (white matter) part of the brain in the regions around the lateral ventricles. Contains the myelinated axons of the cortical neurons on their way to the spinal cord (see cortex).
Posterior fornix	The deepest recess of the vaginal vault.
Prematurity	Preterm birth is birth at less than 37 weeks of gestation (term is 40 weeks). This can be subdivided: - Late preterm 34-36 weeks - Moderately preterm 32-34 weeks - Very preterm 28-32 weeks Extremely preterm before 28 weeks
Preterm prelabour rupture of membranes (PPROM)	Rupture of membranes at <37 weeks of gestation which occurs without labour starting. 
Prolonged rupture of membranes (PROM)	Rupture of the membranes more than 18-24 hours (definitions vary) before delivery, at term (see PPROM).
RCT (Randomised Controlled Trial)	A scientific study that randomly assigns participants to at least two groups. One group is an intervention group and there is a control group. The difference in the outcomes in each group enable the intervention effectiveness to be assessed.
Relative risk	The ratio of the probability of an event occurring in the exposed group to the probability of the event occurring in the unexposed group. Causative exposures will have a relative risk of more than 1, protective exposures (eg treatment) will have a relative risk of less than 1.
Sagittal view imaging	A view of the brain viewed from the side.
Speculum	A small instrument which is inserted into the vagina to allow visualisation of liquor pooling in the vagina, and (if possible) the cervix.
Sulcation	The brain is folded to increase the surface area, with gyri (which are the ridges) and sulci (which are the furrows). The folding increases as the fetus matures.

Surfactant	A compound secreted by the lining cell of lungs to reduce the surface tension and make the lung easier to inflate. Although produced from 24 weeks it is often not in sufficient quantities until ~ 32 weeks. Exogenous surfactant can be administered into the lungs via the trachea to make the lung easier to ventilate.
Ureaplasma	Ureaplasma is a genus of cell wall deficient bacteria related to
Ventriculomegaly	Enlargement of the lateral cerebral ventricles.
Very low birthweight	Birthweight below 1500g.
White matter	The part of the brain containing the myelinated axons that transmit neural impulses (see definitions of axon and myelin).