CLAIMS:

1. An invention not claimed in any divisional application~~A programmable nuclease for use in a method of treating an acute microbial infection of a subject, wherein the microbial infection is caused by microbes of a first species or strain and the nuclease is programmable to cut a target site comprised by the genomes of microbes that have infected the subject, whereby microbes of the first species or strain are killed, or growth or proliferation of the microbes is reduced, the treatment method comprising exposing the subject to the nuclease wherein the nuclease is programmed to cut the target site, whereby genomes of the microbes comprised by the subject are cut and acute microbial infection of the subject is treated, wherein the method comprises reducing the infection at least 100-fold by the first 30 minutes of the treatment~~.

~~2. A programmable nuclease for use in a method of durably treating a microbial infection of a subject, wherein the microbial infection is caused by microbes of a first species or strain and the nuclease is programmable to cut a target site comprised by the genomes of microbes that have infected the subject, whereby microbes of the first species or strain are durably killed, or growth or proliferation of the microbes is reduced, the treatment method comprising exposing the subject to the nuclease wherein the nuclease is programmed to cut the target site, whereby genomes of the microbes comprised by the subject are cut and microbial infection of the subject is durably treated.~~

~~3. The nuclease of claim 2, wherein the nuclease and/or a nucleic acid that programs the nuclease to recognise and cut the target site is administered to the subject at a first time (T1) and at a second time (T2) wherein T2 is at least 1 hour after T1.~~

~~4. The nuclease of claim 2 or 3, wherein the method comprises reducing the infection at least 100-fold by the first 30 minutes of the treatment.~~

~~5. The nuclease of any preceding claim, wherein the method comprises maintaining reduction of the infection by at least 100-fold for at least 60 minutes after exposing the subject to the programmed nuclease.~~

~~6. The nuclease of any preceding claim, wherein the method comprises reducing the infection such that the reduction in infection persists for 30 minutes immediately after the first 30 minutes of the treatment.~~

7. The nuclease of any preceding claim, wherein the method comprises administering to the subject a RNA or a nucleic acid that encodes an RNA for expression of the RNA in the subject, wherein the RNA complexes with the nuclease to program the nuclease to cut the target site in microbes comprised by the subject.

8. The nuclease of claim 7, wherein
    a. the nuclease is administered simultaneously or sequentially with the RNA or nucleic acid to the subject; or
    b. the subject comprises the nuclease prior to administration of the RNA or nucleic acid to the subject.

9. The nuclease of claim 7 or 8 wherein a plurality of viruses are administered to the subject, wherein each virus comprises a copy of the nucleic acid, wherein the viruses infect the microbes comprised by the subject to deliver thereto the nucleic acid.

10. The nuclease of claim 9, wherein the ratio of administered viruses : microbes comprised by the subject is from 10 to 150.

11. The nuclease according to any preceding claim, wherein the subject is a human or animal, and wherein the infection is an infection of the lungs, abdomen or urinary tract; or wherein the subject has undergone surgery, is on an immunosuppressant medication or is suffering from a chronic disease.

12. The nuclease according to any preceding claim, wherein the nuclease is for use in a method of treating a pathogenic bacterial infection in the subject caused by bacteria (first bacteria) of a first species or strain, the method comprising selectively killing first bacteria comprised by the subject by cutting a target site comprised by the genomes of the first bacteria, wherein the cutting is carried out using the programmable nuclease that is programmed to cut the target site, wherein the subject is suffering from a further disease or condition other than the pathogenic bacterial infection and the method comprises administering a therapy to the subject for treating or preventing the further disease or condition, wherein the nuclease treats the infection and the therapy is efficacious in the presence of the programmed nuclease to treat or prevent the disease or condition.

13. The nuclease of claim 12, wherein (i) the subject is a cancer patient and the therapy comprises administration of a haematopoietic stem cell transplant, chemotherapeutic agent, immune checkpoint inhibitor, immune checkpoint agonist or an immune cell enhancer; adoptive cell

~~therapy; radiation or surgery; or (ii) the therapy is a tissue, organ or cell transplant.~~

~~14. The nuclease of any preceding claim, wherein the treatment of the infection treats or prevents in the subject a condition selected from vaginosis, meningitis, pneumonia, urinary tract infection, cystitis, nephritis, gastroenteritis, a skin infection, impetigo, erysipelas, cellulitis, septicaemia or sepsis in the subject.~~

~~15. The nuclease according to any preceding claim, wherein the infection is reduced by at least 90% for 1 hour or more, optionally by the first 30 minutes (optionally by the first 15 minutes) of the treatment.~~

~~16. The nuclease according to any preceding claim, wherein the method comprises reducing the infection at least 100-fold by the first 30 minutes (optionally by the first 15 minutes) of the treatment; and wherein reduction of the infection by at least 100-fold is maintained for at least 60 minutes after exposing the subject to the programmed nuclease.~~

~~17. The nuclease according to any preceding claim, wherein the method treats or prevents septicaemia and/or sepsis in the subject, wherein the subject is a human and at the start of the treatment, the subject has a temperature of <36 °C or >38 °C; a heart rate of >90/min, a respiratory rate of >20 breaths/min or $PaCO_2$ <4.3 kPa; and white blood cell count of <4000/mm³ or >12,000/mm³.~~

~~18. The nuclease of claim 17, wherein at the start of the treatment, the subject has presence of two or more of the following: abnormal body temperature, abnormal heart rate, abnormal respiratory rate, abnormal blood gas and abnormal white blood cell count.~~

~~19. The nuclease of any preceding claim, wherein the subject is a human or animal and the microbes are bacteria, wherein blood infection of the subject by the bacteria is reduced at least 100- or 1000-fold by the first 30 minutes of the treatment.~~

~~20. The nuclease according to any preceding claim, wherein the microbes are bacteria.~~

~~21. The nuclease according to any preceding claim, wherein the nuclease is a Cas nuclease, a meganuclease, a TALEN (Transcription activator-like effector nuclease) or zinc finger nuclease.~~

~~22. A plurality of viruses, phage or phagemids for producing phage for use with the nuclease of any preceding claim in the method of treatment, wherein each virus, phage or phagemid comprises a copy of a nucleic acid as defined in any one of claims 7 to 9, wherein the viruses or phage are~~

capable of infecting microbes comprised by the subject to deliver thereto the nucleic acid.

23. A composition comprising a plurality of nucleic acids for programming the nuclease of any one of claims 1 to 21 in the method of treatment, wherein each nucleic acid is a nucleic acid as defined in any one of claims 7 to 9.

24. A CRISPR/Cas system comprising a nuclease according to any one of claims 1 to 21 for use in the method of treatment, wherein the nuclease is a Cas nuclease and the system comprises one or more guide RNAs or DNA encoding one or more guide RNAs, wherein each guide RNA is capable of programming the Cas nuclease to cut a target site comprised by the genomes of the microbes.

25. A guide RNA or a DNA encoding a guide RNA for use in the system of claim 24 for use in the method of treating an acute microbial infection in the subject, optionally septicaemia or sepsis wherein the subject is a human or animal.

26. A nucleic acid vector comprising the guide RNA or DNA recited in claim 24 or 25.

27. The vector of claim 26 wherein the vector is a phage, phagemid, viriophage, virus, plasmid or transposon.

28. An anti-sepsis or anti-septicaemia composition for administration to a human or animal for treating sepsis or septicaemia, the composition comprising a plurality of vectors, wherein each vector is according to claim 26 or 27.

29. A method of treating an acute microbial infection of a subject, wherein the method is as defined by any preceding claim.

30. Use of a nuclease, plurality of viruses, phage, phagemids, system, guide RNA, DNA or vector of any one of claims 1 to 27, in the manufacture of a composition for carrying out a method of treatment as defined by any preceding claim.

31. The method of claim 29 or the use of claim 30, wherein the nuclease and/or a nucleic acid that programs the nuclease to recognise and cut the target site is administered to the subject or substrate at a first time (T1) and at a second time (T2) wherein T2 is at least 1 hour after T1.

32. The method or use of any one of claims 29 to 31, wherein the infection is reduced at least 100-fold by the first 30 minutes (optionally by the first 15 minutes) of the treatment.

33. The method or use of any one of claims 29 to 32, wherein the reduction of the infection is maintained by at least 100-fold for at least 60 minutes after exposing the subject to the programmed nuclease.

34. The method or use of any one of claims 29 to 33, wherein the reduction in infection persists for 30 minutes immediately after the first 30 minutes of the treatment.

35. The nuclease, viruses, phage, phagemids, system, guide RNA, DNA, vector, composition, method or use of any preceding claim, wherein the microbes are *E coli* bacteria (optionally EHEC *E coli*) or *C difficle* bacteria.

36. The nuclease, viruses, phage, phagemids, system, guide RNA, DNA, vector, composition, method or use of any preceding claim, wherein the microbes are *E coli* bacteria (optionally EHEC *E coli*) *Klebsiella* or *Pseudomonas* bacteria, the subject is a human and the infection is a lung infection.