CLAIMS

1. A modified Zika virus in which expression of viral proteins is reduced compared to a parent virus, in which the reduction in expression is the result of recoding the envelope (E) region, the nonstructural protein 3 (NS3) region, both the E and NS3 regions, or prM, in which one or both of the E protein-encoding sequence and the NS3 protein-encoding sequence are recoded by reducing the codon pair bias, and in which the modified virus has a safety factor of at least 10^2, in which the safety factor is defined by the ratio of LD_{50}/PD_{50}.

2. A modified Zika virus according to Claim 1, in which reducing the codon-pair bias comprises identifying a codon pair in the parent protein-encoding sequence having a codon-pair score that can be reduced, and reducing the codon-pair bias by substituting the codon pair with a codon pair that has a lower codon-pair score.

3. A modified Zika virus according to Claim 1, in which reducing the codon-pair bias comprises rearranging the codons of a parent protein-encoding sequence.

4. A modified Zika virus according to Claim 1, in which one or both of the E protein-encoding sequence and the NS3 protein-encoding sequence are recoded by also increasing the number of CpG or UpA di nucleotides compared to a parent virus.

5. A modified Zika virus according to Claim 1, in which each of the recoded prM/E protein-encoding sequence and the recoded NS3 protein-encoding sequence have a codon pair bias less than, -0.05, −0.1, or less than −0.2, or less than −0.3, or less than −0.4.

6. A modified Zika virus according to Claim 1, in which the parent virus is a natural isolate.

7. A modified Zika virus according to Claim 1, in which the parent virus is a mutant of a natural isolate.

8. A Zika vaccine composition for inducing a protective immune response in a subject, which comprises a modified virus according to any preceding claim.

9. A modified Zika virus according to any of Claims 1 to 7 for use in a method of eliciting a protective immune response in a subject, in which a prophylactically or therapeutically

effective dose of a vaccine composition comprising the modified virus is to be administered to the subject.

10. A modified Zika virus for use according to Claim 9, in which at least one adjuvant is to be further administered to the subject.

11. A modified Zika virus for use according to Claim 9, in which the immune response is cross-protective against a heterologous Zika virus.

12. A method of making a modified Zika virus genome comprising:

obtaining the nucleotide sequence encoding the envelope protein of a Zika virus and the nucleotide sequence encoding the nonstructural 3 proteins of a Zika virus;

recoding the envelope (E) protein encoding nucleotide sequence to reduce protein expression and recoding the nonstructural protein 3-encoding nucleotide sequence to reduce protein expression, and

substituting a nucleic acid having the recoded E protein-encoding nucleotide sequence and a nucleic acid having the recoded nonstructural protein 3-encoding nucleotide sequence into a parent Zika virus genome to make a modified Zika virus genome; whereby expression of the recoded E protein-encoding nucleotide sequence and expression of the recoded nonstructural protein 3-encoding nucleotide sequence is reduced compared to the parent virus, in which one or both of the E protein-encoding sequence and the NS3 protein-encoding sequence are recoded by reducing the codon pair bias, and in which the modified Zika virus has a safety factor of at least 10^2, in which the safety factor is defined by the ratio of LD_{50}/PD_{50}.

13. A modified Zika virus in which expression of viral proteins is reduced compared to a parent virus, in which the reduction in expression is the result of recoding envelope (E) region, the nonstructural protein 3 (NS3) region, both the E and NS3 regions, or prM, in which one or both of the E protein-encoding sequence and the NS3 protein-encoding sequence are recoded by reducing the codon pair bias, and in which the modified virus has a safety factor of at least 10^2, in which the safety factor is defined by the ratio of LD_{50}/PD_{50}, for use in a method of eliciting an immune response in a subject in need thereof, in which:

a prime dose of the modified Zika virus, or an attenuated Zika produced by a method other than codon-pair deoptimization, is to be administered to a subject in need thereof; and

one or more boost dose of the modified Zika virus, or the attenuated Zika by methods other than codon-pair deoptimization, is to be administered to the subject in need thereof;

in which at least the prime dose or the one or more boost dose is the modified Zika virus.

14. A modified Zika virus for use according to Claim 13, in which a first of the one or more boost dose is to be administered about 2 weeks after the prime dose.

15. A modified Zika virus for use according to Claim 13 or 14, in which one or both of the E protein-encoding sequence and the NS3 protein-encoding sequence are recoded by increasing the number of CpG or UpA di nucleotides compared to a parent virus.

16. A modified Zika virus for use according to Claim 13 or 14, in which reducing the codon-pair bias comprises identifying a codon pair in the parent protein-encoding sequence having a codon-pair score that can be reduced, and reducing the codon-pair bias by substituting the codon pair with a codon pair that has a lower codon-pair score.

17. A modified Zika virus for use according to Claim 13 or 14, in which reducing the codon-pair bias comprises rearranging the codons of a parent protein-encoding sequence.

18. A modified Zika virus for use according to Claim 13 or 14, in which each of the recoded prM/E protein-encoding sequence and the recoded NS3 protein-encoding sequence have a codon pair bias less than, -0.05, −0.1, or less than −0.2, or less than −0.3, or less than −0.4.

19. A modified Zika virus according to any of Claims 1 to 7, in which a NS5 region is recoded.

20. A modified Zika virus according to any of Claims 1 to 7, in which the Zika is a modified Zika virus in which expression of viral proteins is reduced compared to a parent virus, in which the reduction in expression is the result of recoding the envelope (E) region, the nonstructural protein 3 (NS3) region, both the E and NS3 regions, or prM.

21. A Zika vaccine composition for inducing a protective immune response in a subject, comprising a modified virus according to Claim 20.

22. A Zika vaccine composition according to Claim 21 for use in a method of eliciting a protective immune response in a subject, in which a prophylactically or therapeutically effective dose of the vaccine composition is to be administered to the subject.

23. A Zika vaccine composition for use according to Claim 22, in which at least one adjuvant is to be administered to the subject.

24. A Zika vaccine composition for use according to Claim 22, in which the immune response is cross-protective against a heterologous Zika virus.