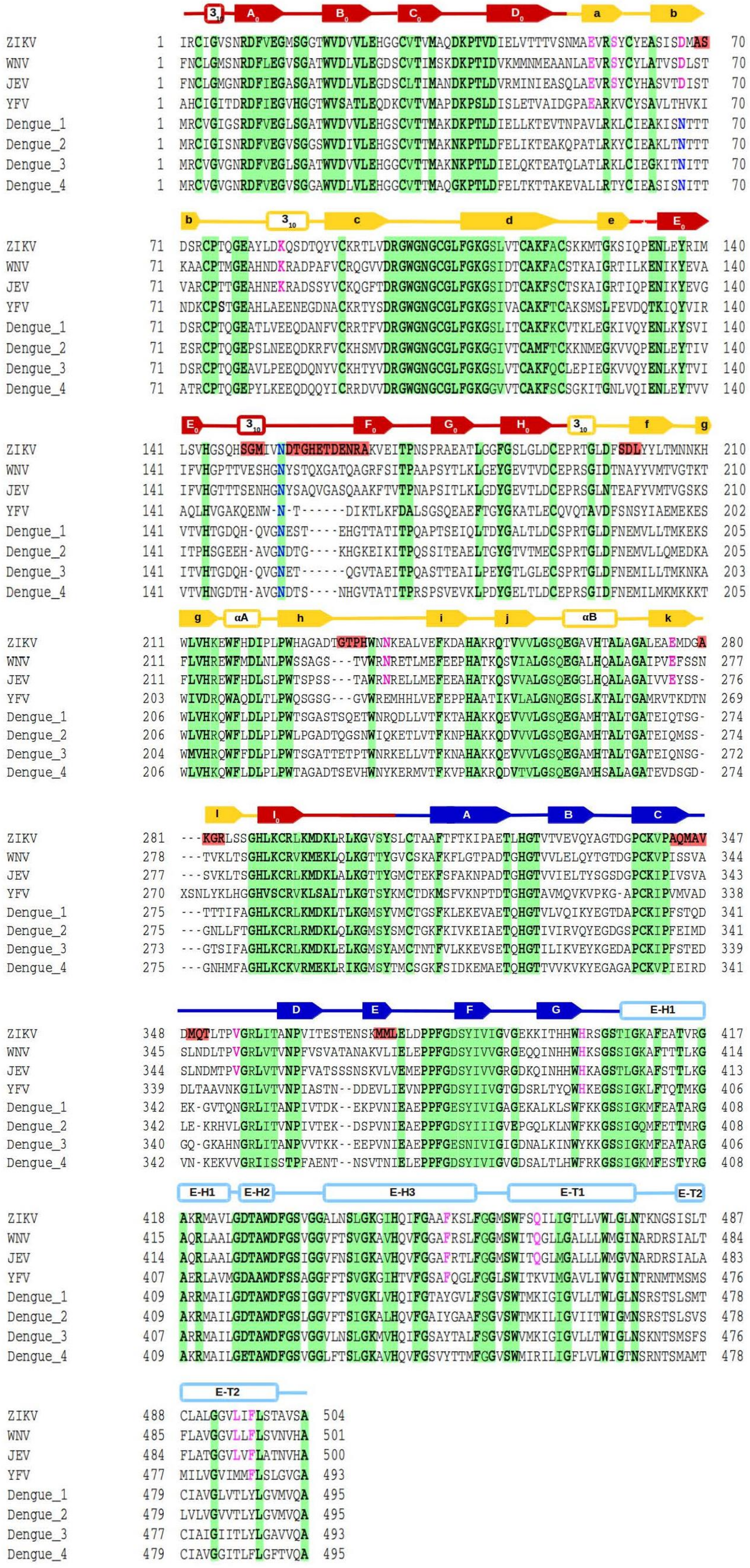

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ZIKV          1  IRCIGVSNRDFVEGMSGGTWVDVVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISDMAS   70
WNV           1  FNCLGMSNRDFLEGVSGATWVDLVLEGDSCVTIMSKDKPTIDVKMMNMEAANLAEVRSYCYLATVSDLST   70
JEV           1  FNCLGMGNRDFIEGASGATWVDLVLEGDSCLTIMANDKPTLDVRMINIEASQLAEVRSYCYHASVTDIST   70
YFV           1  AHCIGITDRDFIEGVHGGTWVSATLEQDKCVTVMAPDKPSLDISLETVAIDGPAEARKVCYSAVLTHVKI   70
Dengue_1      1  MRCVGIGSRDFVEGLSGATWVDVVLEHGSCVTTMAKDKPTLDIELLKTEVTNPAVLRKLCIEAKISNTTT   70
Dengue_2      1  MRCIGISNRDFVEGVSGGSWVDIVLEHGSCVTTMAKNKPTLDFELIKTEAKQPATLRKYCIEAKLTNTTT   70
Dengue_3      1  MRCVGVGNRDFVEGLSGATWVDVVLEHGGCVTTMAKNKPTLDIELQKTEATQLATLRKLCIEGKITNITT   70
Dengue_4      1  MRCVGVGNRDFVEGVSGGAWVDLVLEHGGCVTTMAQGKPTLDFELTKTTAKEVALLRTYCIEASISNITT   70

ZIKV         71  DSRCPTQGEAYLDKQSDTQYVCKRTLVDRGWGNGCGLFGKGSLVTCAKFACSKKMTGKSIQPENLEYRIM  140
WNV          71  KAACPTMGEAHNDKRADPAFVCRQGVVDRGWGNGCGLFGKGSIDTCAKFACSTKAIGRTILKENIKYEVA  140
JEV          71  VARCPTTGEAHNEKRADSSYVCKQGFTDRGWGNGCGLFGKGSIDTCAKFSCTSKAIGRTIQPENIKYEVG  140
YFV          71  NDKCPSTGEAHLAEENEGDNACKRTYSDRGWGNGCGLFGKGSIVACAKFTCAKSMSLFEVDQTKIQYVIR  140
Dengue_1     71  DSRCPTQGEATLVEEQDANFVCRRTFVDRGWGNGCGLFGKGSLITCAKFKCVTKLEGKIVQYENLKYSVI  140
Dengue_2     71  ESRCPTQGEPSLNEEQDKRFVCKHSMVDRGWGNGCGLFGKGGIVTCAMFTCKKNMEGKVVQPENLEYTIV  140
Dengue_3     71  DSRCPTQGEAVLPEEQDQNYVCKHTYVDRGWGNGCGLFGKGSLVTCAKFQCLEPIEGKVVQYENLKYTVI  140
Dengue_4     71  ATRCPTQGEPYLKEEQDQQYICRRDVVDRGWGNGCGLFGKGGVVTCAKFSCSGKITGNLVQIENLEYTVV  140

ZIKV        141  LSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLYYLTMNNKH  210
WNV         141  IFVHGPTTVESHGNYSTQXGATQAGRFSITPAAPSYTLKLGEYGEVTVDCEPRSGIDTNAYYVMTVGTKT  210
JEV         141  IFVHGTTTSENHGNYSAQVGASQAAKFTVTPNAPSITLKLGDYGEVTLDCEPRSGLNTEAFYVMTVGSKS  210
YFV         141  AQLHVGAKQENW-N-T------DIKTLKFDALSGSQEAEFTGYGKATLECQVQTAVDFSNSYIAEMEKES  202
Dengue_1    141  VTVHTGDQH-QVGNEST----EHGTTATITPQAPTSEIQLTDYGALTLDCSPRTGLDFNEMVLLTMKEKS  205
Dengue_2    141  ITPHSGEEH-AVGNDTG----KHGKEIKITPQSSITEAELTGYGTVTMECSPRTGLDFNEMVLLQMEDKA  205
Dengue_3    141  ITVHTGDQH-QVGNET------QGVTAEITPQASTTEAILPEYGTLGLECSPRTGLDFNEMILLTMKNKA  203
Dengue_4    141  VTVHNGDTH-AVGNDTS----NHGVTATITPRSPSVEVKLPDYGELTLDCEPRSGIDFNEMILMKMKKKT  205

ZIKV        211  WLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTALAGALEAEMDGA  280
WNV         211  FLVHREWFMDLNLPWSSAGS---TVWRNRETLMEFEEPHATKQSVIALGSQEGALHQALAGAIPVEFSSN  277
JEV         211  FLVHREWFHDLSLPWTSPSS---TAWRNRELLMEFEEAHATKQSVVALGSQEGGLHQALAGAIVVEYSS-  276
YFV         203  WIVDRQWAQDLTLPWQSGSG---GVWREMHHLVEFEPPHAATIKVLALGNQEGSLKTALTGAMRVTKDTN  269
Dengue_1    206  WLVHKQWFLDLPLPWTSGASTSQETWNRQDLLVTFKTAHAKKQEVVVLGSQEGAMHTALTGATEIQTSG-  274
Dengue_2    206  WLVHRQWFLDLPLPWLPGADTQGSNWIQKETLVTFKNPHAKKQDVVVLGSQEGAMHTALTGATEIQMSS-  274
Dengue_3    204  WMVHRQWFFDLPLPWTSGATTETPTWNRKELLVTFKNAHAKKQEVVVLGSQEGAMHTALTGATEIQNSG-  272
Dengue_4    206  WLVHKQWFLDLPLPWTAGADTSEVHWNYKERMVTFKVPHAKRQDVTVLGSQEGAMHSALAGATEVDSGD-  274

ZIKV        281  ---KGRLSSGHLKCRLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAGTDGPCKVPAQMAV  347
WNV         278  ---TVKLTSGHLKCRVKMEKLQLKGTTYGVCSKAFKFLGTPADTGHGTVVLELQYTGTDGPCKVPISSVA  344
JEV         277  ---SVKLTSGHLKCRLKMDKLALKGTTYGMCTEKFSFAKNPADTGHGTVVIELTYSGSDGPCKIPIVSVA  343
YFV         270  XSNLYKLHGGHVSCRVKLSALTLKGTSYKMCTDKMSFVKNPTDTGHGTAVMQVKVPKG-APCRIPVMVAD  338
Dengue_1    275  ---TTTIFAGHLKCRLKMDKLTLKGMSYVMCTGSFKLEKEVAETQHGTVLVQIKYEGTDAPCKIPFSTQD  341
Dengue_2    275  ---GNLLFTGHLKCRLRMDKLQLKGMSYSMCTGKFKIVKEIAETQHGTIVIRVQYEGDGSPCKIPFEIMD  341
Dengue_3    273  ---GTSIFAGHLKCRLKMDKLELKGMSYAMCTNTFVLKKEVSETQHGTILIKVEYKGEDAPCKIPFSTED  339
Dengue_4    275  ---GNHMFAGHLKCKVRMEKLRIKGMSYTMCSGKFSIDKEMAETQHGTTVVKVKYEGAGAPCKVPIEIRD  341

ZIKV        348  DMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRSGSTIGKAFEATVRG  417
WNV         345  SLNDLTPVGRLVTVNPFVSVATANAKVLIELEPPFGDSYIVVGRGEQQINHHWHKSGSSIGKAFTTTLKG  414
JEV         344  SLNDMTPVGRLVTVNPFVATSSSNSKVLVEMEPPFGDSYIVVGRGDKQINHHWHKAGSTLGKAFSTTLKG  413
YFV         339  DLTAAVNKGILVTVNPIASTN--DDEVLIEVNPPFGDSYIIVGTGDSRLTYQWHKEGSSIGKLFTQTMKG  406
Dengue_1    342  EK-GVTQNGRLITANPIVTDK--EKPVNIEAEPPFGESYIVIGAGEKALKLSWFKKGSSIGKMFEATARG  408
Dengue_2    342  LE-KRHVLGRLITVNPIVTEK--DSPVNIEAEPPFGDSYIIIGVEPGQLKLNWFKKGSSIGQMFETTMRG  408
Dengue_3    340  GQ-GKAHNGRLITANPVVTKK--EEPVNIEAEPPFGESNIVIGIGDNALKINWYKKGSSIGKMFEATARG  406
Dengue_4    342  VN-KEKVVGRIISSTPFAENT--NSVTNIELEPPFGDSYIVIGVGDSALTLHWFRKGSSIGKMFESTYRG  408

ZIKV        418  AKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTLLVWLGLNTKNGSISLT  487
WNV         415  AQRLAALGDTAWDFGSVGGVFTSVGKAVHQVFGGAFRSLFGGMSWITQGLLGALLLWMGINARDRSIALT  484
JEV         414  AQRLAALGDTAWDFGSIGGVFNSIGKAVHQVFGGAFRTLFGGMSWITQGLMGALLLWMGVNARDRSIALA  483
YFV         407  AERLAVMGDAAWDFSSAGGFFTSVGKGIHTVFGSAFQGLFGGLSWITKVIMGAVLIWVGINTRNMTMSMS  476
Dengue_1    409  ARRMAILGDTAWDFGSIGGVFTSVGKLVHQIFGTAYGVLFSGVSWTMKIGIGVLLTWLGLNSRSTSLSMT  478
Dengue_2    409  AKRMAILGDTAWDFGSLGGVFTSIGKALHQVFGAIYGAAFSGVSWTMKILIGVIITWIGMNSRSTSLSVS  478
Dengue_3    407  ARRMAILGDTAWDFGSVGGVLNSLGKMVHQIFGSAYTALFSGVSWVMKIGIGVLLTWIGLNSKNTSMSFS  476
Dengue_4    409  AKRMAILGETAWDFGSVGGLFTSLGKAVHQVFGSVYTTMFGGVSWMIRILIGFLVLWIGTNSRNTSMAMT  478

ZIKV        488  CLALGGVLIFLSTAVSA  504
WNV         485  FLAVGGVLLFLSVNVHA  501
JEV         484  FLATGGVLVFLATNVHA  500
YFV         477  MILVGVIMMFLSLGVGA  493
Dengue_1    479  CIAVGLVTLYLGVMVQA  495
Dengue_2    479  LVLVGVVTLYLGVMVQA  495
Dengue_3    477  CIAIGIITLYLGAVVQA  493
Dengue_4    479  CIAVGGITLFLGFTVQA  495
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Figure S1. **Sequence alignment of consensus sequences of ZIKV, WNV, JEV, YFV and DENV (related to Figure 3).** Conserved residues are shown in bold font and highlighted in green. Secondary structure elements of ZIKV are indicated above each set and are colored red, yellow and blue for E-DI, E-DII and E-DIII, respectively. Similar residue substitutions in ZIKV, WNV and JEV are represented in magenta font. Stretches of residues specific for ZIKV and different from other flaviviruses are highlighted in red. Conserved asparagine residues are shown in blue font.

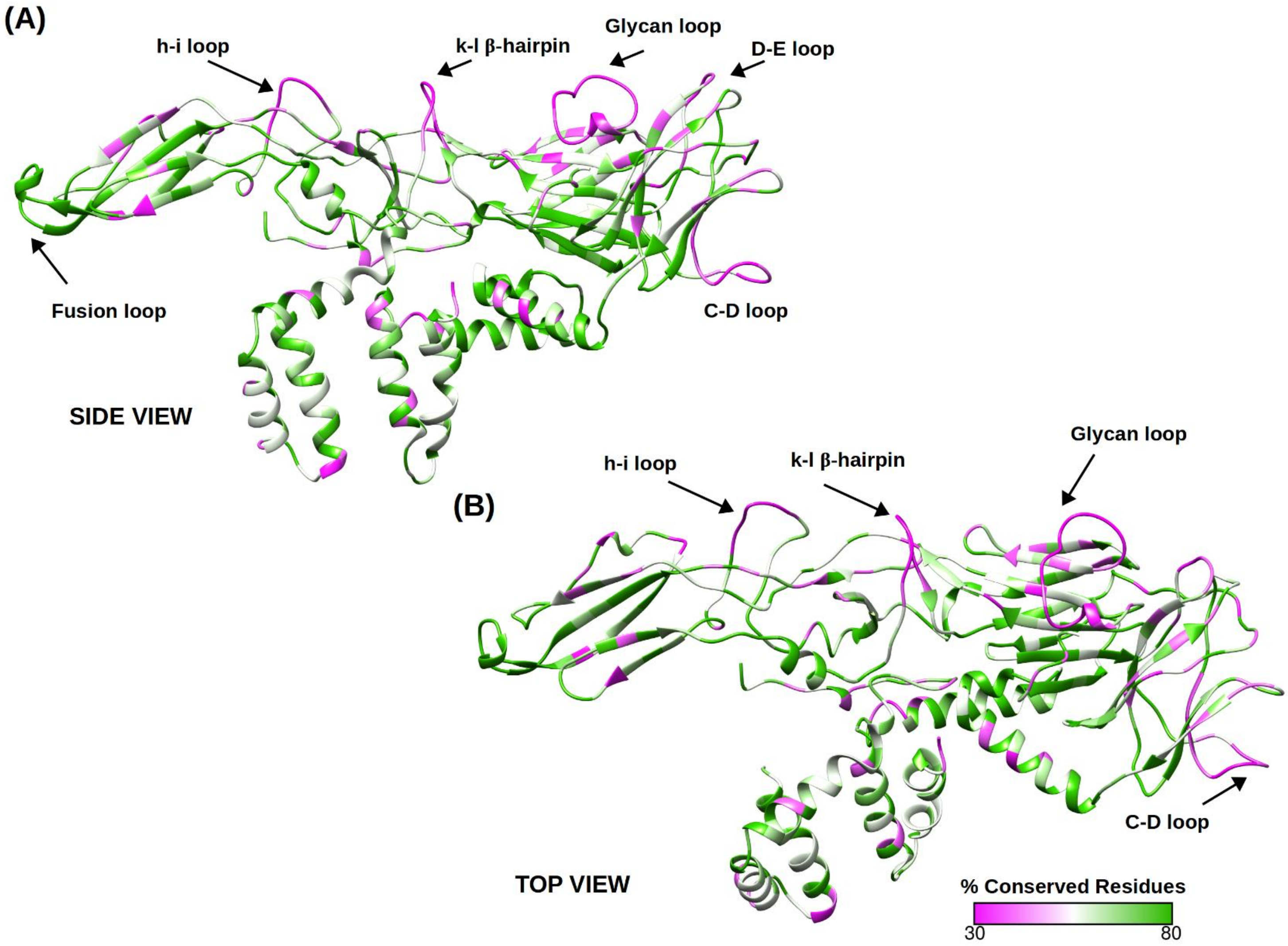

Figure S2. **Sequence conservation shown on ZIKV monomer (related to Figure 3).** Highly conserved regions are colored in green and less conserved regions are colored in magenta.

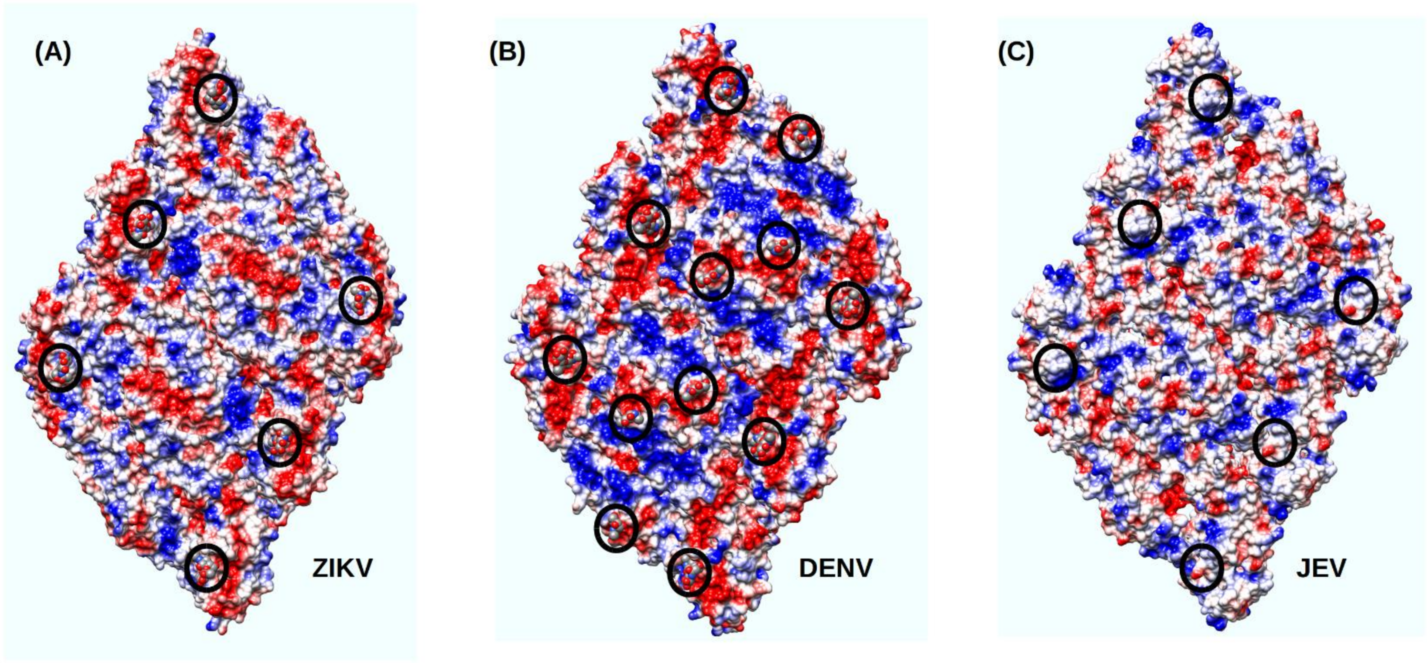

Figure S3. Electrostatic surface plots of ZIKV, DENV and JEV (related to Figure 5). Electrostatic surface potential between +10 (blue) and -10 (red) kb T ec^{-1} (kb=Boltzmann's constant, T is temperature of calculation in K and ec is the charge of the electron) plotted on surface of ZIKV, DENV and JEV. The glycosylation sites are marked by black circles.

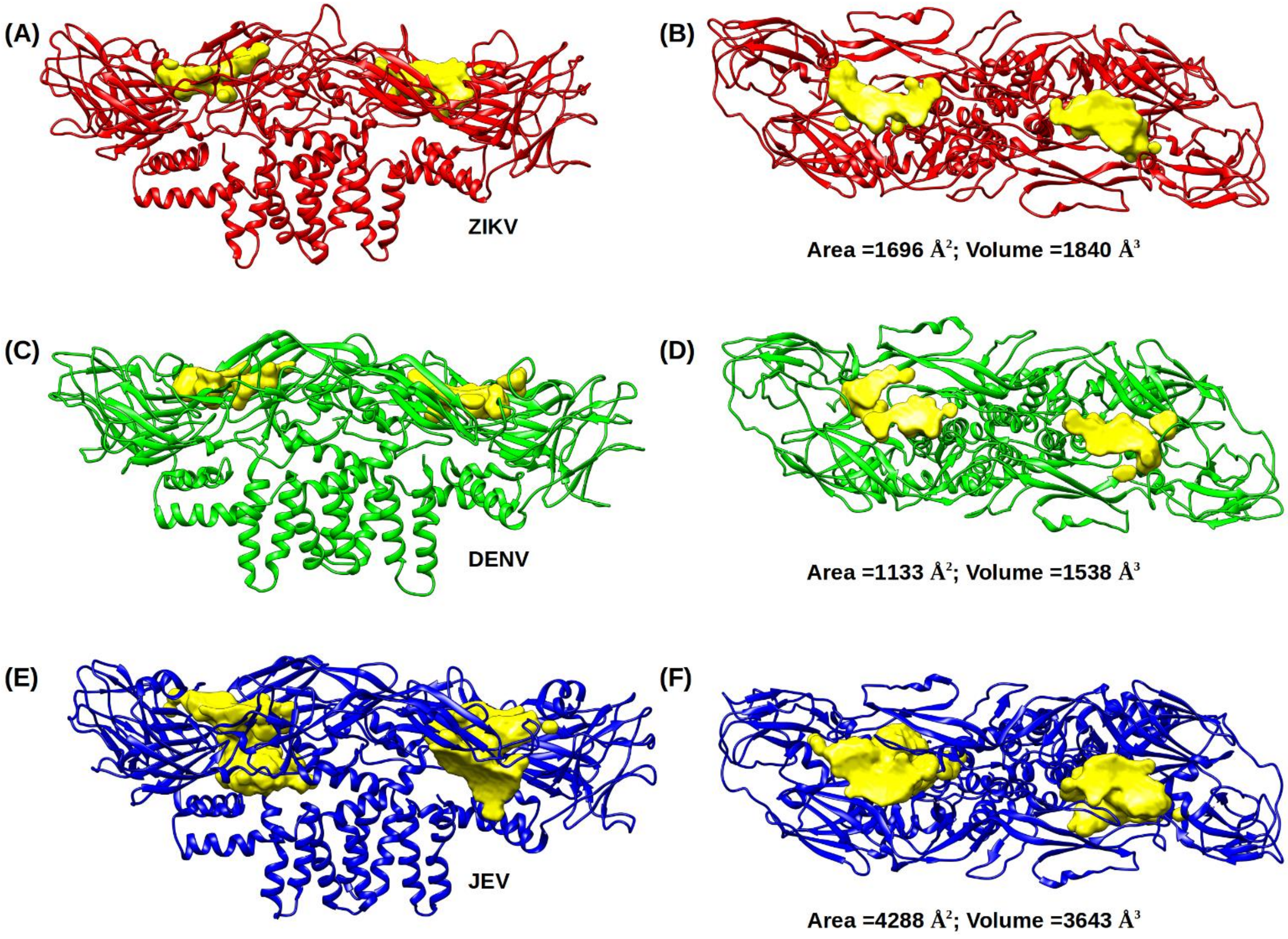

Figure S4. Accessible pockets enclosed by E-M heterodimers in ZIKV, DENV and JEV (related to Figure 5). Panels A, C and E are side views of the dimers and panels B, D and F represent top views of the pockets enclosed by the dimers.

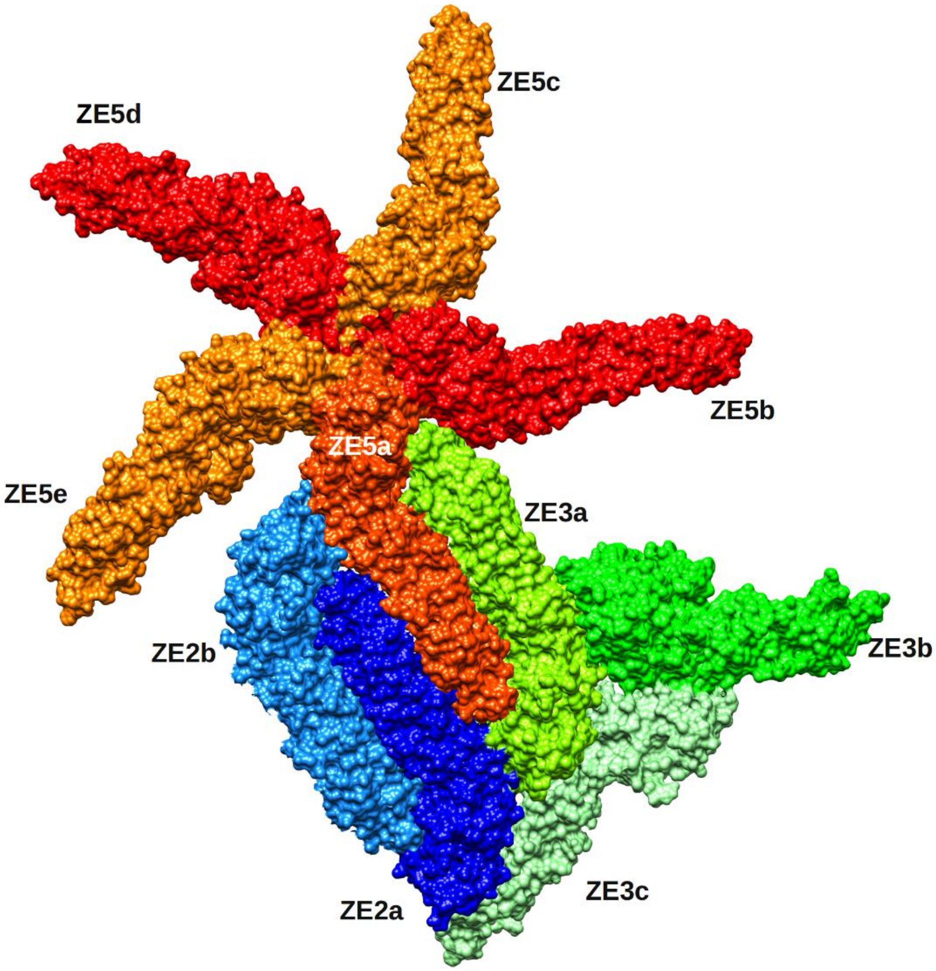

Figure S5. Labelling of the ZIKV E monomer chains described in Tables S2, S3 and S4 (related to Figure 5). ZIKV E monomer chains at a 5-fold axis (red) are labelled ZE5a, ZE5b, ZE5c, ZE5D and ZE5e; at a 3-fold axis (green) are labelled as ZE3a, ZE3b and ZE3c; and at a 2-fold axis (blue and light blue) are labelled ZE2a and ZE2b, respectively.

Supplementary Tables

Table S1. Secondary structure (SS) elements in ZIKV E and M proteins and their interactions (related to Figure 1). E protein domains 1, 2 and 3 are labelled E-DI, E-DII and E-DIII and the transmembrane domain as TM. Highly conserved residues are underlined. E protein domains (Domain/SS) E-DI, E-DII, E-DIII, and transmembrane (TM); M protein and the hinge region are colored in red, yellow, blue, light blue, brown and green, respectively.

Domain/SS	**Residue range**	**Interactions/Residue Environment**
E-DI		
N-term	1-9	2-fold
A_0	10-15	
B_0	19-24	E-M
C_0	30-35	
Loop C_0-D_0	36-40	3-fold
D_0	41-46	
E_0	136-143	
Loop E_0-F_0	144-164	**Glycosylation Loop,** 2-fold
F_0	165-169	
G_0	174-181	3-fold
H_0	184-190	
I_0	288-294	
3_{10} helix	4-6,149-151,193-195	
DI-DII Hinge		
Loop D_0-a	47-50	
Loop e-E_0	129-134	3-fold
Loop H_0-f	191-199	3-fold
Loop l-I_0	281-288	E-M
E-DII		
a	54-58	
b	63-73	
c	91-98	
Loop c-d	99-109	**Fusion loop,** 2-fold
d	110-121	
e	126-128	
f	200-206	
g	210-215	E-M
Helix-A	215-220	E-M
h and Loop h-i	224-243	E-M
i	244-247	E-M
Loop i-j	247-253	E-M and 2-fold
j	253-257	
j-Helix-B	258-260	2-fold
Helix-B	261-269	2-fold, E-M
Helix-B-k	270-272	E-M
K	273-277	
Loop k-l	278-280	E-M
l	281-285	2-fold

DI-DIII Hinge		
Loop L_0-A	295-305	5-fold and 3-fold
E-DIII		
A	313-319	2 and 5-fold
B	327-332	2 and 5-fold
C	338-344	5-fold
Loop C-D	345-360	3 and 5-fold
D	361-366	
E	372-375	
Loop E-F	376-383	
F	384-389	5-fold
Loop F-G	390-395	5-fold
G	396-401	
TM		
E-H1	406-424	
E-H2	425-429	
Loop E-H2-H3	430-436	
E-H3	437-457	
E-H3-T1	458-461	E-M
E-T1	462-478	E-M
E-T2	484-499	
M		
N-term	1-22	E-M
M-H1	22-39	E-M
M-H2	40-50	
M-H3	57-72	

Table S2. Interactions less than 3.2 Å at the 5-fold axis (related to Figure 5). The E monomer chains at the 5-fold axis are indicated as ZE5a, ZE5b, ZE5c, ZE5d and ZE5e for ZIKV; DE5a, DE5b, DE5c, DE5d and DE5e for DENV; JE5a, JE5b, JE5c, JE5d and JE5e for JEV (Figure S5). Secondary structure elements are labelled as described in Table S1. E protein domains (E-D/SS) E-DI, E-DII, E-DIII, and transmembrane (TM); M protein and the hinge region are colored in red, yellow, blue, light blue, brown and green respectively.

ZIKV					
No.	Residue 1	E-D/SS	Residue 2	E-D/SS	Type
1.	Val303ZE5a	Loop L_0-A	Lys316ZE5e	A	Hydrophobic
2.	Ser304ZE5a	Loop L_0-A	Phe314ZE5e	A	Hydrophobic
3.	Ser304ZE5a	Loop L_0-A	Thr313ZE5e	A	Polar
4.	Ser304ZE5a	Loop L_0-A	Gln313ZE5e	A	Polar
5.	Cys308ZE5a	Loop L_0-A	Lys394ZE5e	Loop F-G	Polar (Backbone)
6.	Thr309ZE5a	Loop L_0-A	Lys394ZE5e	Loop F-G	Polar
7.	Thr313ZE5a	A	Ser304ZE5b	Loop L_0-A	Polar (Backbone)
8.	Phe314ZE5a	A	Ser304ZE5b	Loop L_0-A	Hydrophobic
9.	Lys316ZE5a	A	Val303ZE5b	Loop L_0-A	Hydrophobic
10.	Gln331ZE5a	B	Ser304ZE5b	Loop L_0-A	Polar
11.	Gln344ZE5a	C	Met349ZE5e	Loop C-D	Hydrophobic
12	Asp348ZE5a	Loop C-D	Thr351ZE5b	Loop C-D	Polar
13.	Asp348ZE5a	Loop C-D	Thr3531ZE5b	Loop C-D	Polar
14.	Met349ZE5a	Loop C-D	Leu353ZE5b	Loop C-D	Hydrophobic
15.	Met349ZE5a	Loop C-D	Gln344ZE5b	C	Hydrophobic
16.	Gln350ZE5a	Loop C-D	Thr351ZE5b	Loop C-D	Polar
17.	Gln350ZE5a	Loop C-D	Gln350S/ZE5b	Loop C-D	Polar
18.	Thr351ZE5a	Loop C-D	Thr351ZE5b/ZE5e	Loop C-D	Polar
19.	Thr351ZE5a	Loop C-D	Gln350ZE5e	Loop C-D	Polar
20.	Thr351ZE5a	Loop C-D	Asp348ZE5e	Loop C-D	Polar
21.	Leu352ZE5a	Loop C-D	Gln350ZE5e	Loop C-D	Hydrophobic
22.	Leu352ZE5a	Loop C-D	Met349ZE5e	Loop C-D	Hydrophobic
23.	Thr353ZE5a	Loop C-D	Asp348ZE5e	Loop C-D	Polar
24.	Pro354ZE5a	Loop C-D	Tyr386ZE5e	F	Polar (Backbone)
25.	Tyr386ZE5a	F	Pro354ZE5b	Loop C-D	Polar (Backbone)
26.	Val391ZE5a	F	Glu393ZE5e	Loop F-G	Hydrophobic

27.	Gly392ZE5a	Loop F-G	Glu393ZE5e	Loop F-G	Hydrophobic
28.	Glu393ZE5a	Loop F-G	Val391ZE5b	F	Hydrophobic
29.	Glu393ZE5a	Loop F-G	Gly392ZE5b	Loop F-G	Hydrophobic
30.	Lys394ZE5a	Loop F-G	Thr309ZE5b	Loop F-G	Polar
31.	Lys394ZE5a	Loop F-G	Cys308ZE5b	Loop F-G	Hydrophobic
DENV					
No.	Residue 1	E-D/SS	Residue 2	E-D/SS	Type
1.	Asn37DE5a	Loop C_0-D_0	Glu311DE5e	A	Polar
2.	Ser298DE5a	Loop L_0-A	Lys307S	A	Polar
3.	Lys307DE5a	A	Ser298DE5b	Loop L_0-A	Polar
4.	Glu311DE5a	A	Asn37DE5b	Loop C_0-D_0	Polar
5.	Glu338DE5a	C	Lys388DE5e	G	Polar
6.	Glu343DE5a	Loop C-D	His346DE5b	Loop C-D	Hydrophobic
7.	Glu343DE5a	Loop C-D	Arg345DE5b	Loop C-D	Hydrophobic
8.	Glu343DE5a	Loop C-D	Val347DE5b	Loop C-D	Hydrophobic
9.	Glu343DE5a	Loop C-D	Arg345DE5b	Loop C-D	Hydrophobic
10.	Arg345DE5a	Loop C-D	Glu343DE5e	Loop C-D	Polar
11.	His346DE5a	Loop C-D	Glu343DE5e	Loop C-D	Hydrophobic
12.	Val347DE5a	Loop C-D	Glu343DE5e	Loop C-D	Hydrophobic
13.	Lys388DE5a	G	Glu338DE5b	C	Polar
JEV					
No.	Residue 1	E-D/SS	Residue 2	E-D/SS	Type
1.	Thr299JE5a	Loop L_0-A	Phe310JE5e	A	Polar (Backbone)
2.	Thr299JE5a	Loop L_0-A	Asn313JE5e	A	Polar
3.	Thr300JE5a	Loop L_0-A	Phe310JE5e	A	Polar (Backbone)
4.	Met303JE5a	Loop L_0-A	Ile392JE5e	G	Hydrophobic
5.	Phe310JE5a	A	Thr299JE5b	Loop L_0-A	Polar (Backbone)
6.	Asn313JE5a	A	Thr299JE5b	Loop L_0-A	Polar
7.	Asn346JE5a	Loop C-D	Asn346JE5e/JE5b	Loop C-D	Polar
8.	Thr349JE5a	Loop C-D	Tyr382JE5e	F	Hydrophobic
9.	Tyr382JE5a	F	Thr349JE5b	Loop C-D	Polar
10.	Arg387JE5a	Loop F-G	Asp389JE5e	Loop F-G	Polar
11.	Arg387JE5a	Loop F-G	Gln391JE5e	G	Polar
12.	Arg387JE5a	Loop F-G	Asp389JE5e	Loop F-G	Polar
13.	Arg387JE5a	Loop F-G	Gly388JE5e	Loop F-G	Hydrophobic
14.	Gly388JE5a	Loop F-G	Arg387JE5b	Loop F-G	Hydrophobic

15.	Asp389JE5a	Loop F-G	Arg387JE5b	Loop F-G	Polar
16.	Lys390JE5a	Loop F-G	Arg387JE5b	Loop F-G	Polar
17.	Gln391JE5a	G	Arg387JE5b	Loop F-G	Polar
18.	Ile392JE5a	G	Met303JE5b	Loop L_0-A	Hydrophobic

Table S3. Interactions less than 3.2 Å at 3-fold axes (related to Figure 5). The E monomer chains at the 3-fold axis are indicated as ZE3a, ZE3b and ZE3c for ZIKV; DE3a, DE3b and DE3c for DENV; and JE3a, JE3b and JE3c for JEV (Figure S5). Secondary structure elements are labelled as described in Table S1. E protein domains (E-D/SS) E-DI, E-DII, E-DIII, and transmembrane (TM); M protein and the hinge region are colored in red, yellow, blue, light blue, brown and green respectively.

ZIKV					
No.	Residue 1	E-D/SS	Residue 2	E-D/SS	Type
1.	Asp37ZE3a	Loop C_0-D_0	Lys294ZE3b	Loop L_0-A	Polar
2.	Asp37ZE3a	Loop C_0-D_0	Arg175ZE3b	G_0	Polar
3.	Gln131ZE3a	Loop e-E_0	Gln350ZE3c	Loop C-D	Polar
4.	Arg175ZE3a	G_0	Asp37ZE3c	Loop C_0-D_0	Polar
5.	Glu177ZE3a	G_0	Val303ZE3c	Loop L_0-A	Hydrophobic
6.	Arg193ZE3a	Loop H_0-f	Pro354ZE3c	Loop C-D	Hydrophobic
7.	Arg193ZE3a	Loop H_0-f	Leu352ZE3c	Loop C-D	Hydrophobic
8.	Lys294ZE3a	Loop L_0-A	Asp37ZE3c	Loop C_0-D_0	Polar
9.	Val303ZE3a	Loop L_0-A	Glu177ZE3b	G_0	Hydrophobic
10.	Gln350ZE3a	Loop C-D	Glu131ZE3b	Loop e-E_0	Polar
11.	Leu352ZE3a	Loop C-D	Arg193ZE3b	Loop H_0-f	Hydrophobic
12.	Pro354ZE3a	Loop C-D	Arg193ZE3b	Loop H_0-f	Hydrophobic
DENV					
No.	Residue 1	E-D/SS	Residue 2	E-D/SS	Type
1.	Gln52DE3a	Loop D_0-a	Glu383DE3b	Loop F-G	Polar
2.	Gln131DE3a	Loop e-E_0	Glu343DE3b	Loop C-D	Polar
3.	Glu133DE3a	Loop e-E_0	Glu338DE3b	Loop C-D	Polar
4.	Glue133DE3a	Loop e-E_0	Arg345DE3b	Loop C-D	Polar
5.	Pro166DE3a	Loop F_0-G_0	Glu338DE3b	Loop C-D	Polar (Backbone)
6.	Gln167DE3a	Loop F_0-G_0	Val382DE3b	Loop F-G	Hydrophobic
7.	Ser168DE3a	Loop F_0-G_0	Met301DE3b	Loop L_0-A	Hydrophobic
8.	Ile170DE3a	G_0	Met297DE3b	Loop L_0-A	Hydrophobic
9.	Glu172DE3a	G_0	Met297DE3b	Loop L_0-A	Polar (Backbone)
10.	Met297DE3a	Loop L_0-A	Glue172DE3c	G_0	Polar (Backbone)
11.	Met297DE3a	Loop L_0-A	Ile170DE3c	G_0	Hydrophobic
12.	Met301DE3a	Loop L_0-A	Ser168DE3c	Loop F_0-G_0	Hydrophobic
13.	Glu338DE3a	Loop C-D	Glu133DE3c	Loop e-E_0	Polar
14.	Glu338DE3a	Loop C-D	Pro166DE3c	Loop F_0-G_0	Polar (Backbone)

15.	Glu343DE3a	Loop C-D	Gln131DE3c	Loop e-E_0	Polar
16.	Arg345DE3a	Loop C-D	Glu133DE3c	Loop e-E_0	Polar
17.	Val382DE3a	Loop F-G	Gln167DE3c	Loop F_0-G_0	Hydrophobic
18.	Glu383DE3a	Loop F-G	Gln52DE3c	Loop D_0-a	Polar
JEV					
No.	Residue 1	E-D/SS	Residue 2	E-D/SS	Type
1.	Glu133JE3a	Loop e-E_0	Met348JE3c	Loop C-D	Hydrophobic
2.	Thr177JE3a	G_0	Thr299JE3c	Loop L_0-A	Polar
3.	Glue185JE3a	H_0	Thr299JE3c	Loop L_0-A	Polar
4.	Thr299JE3a	Loop L_0-A	Thr177JE3b	G_0	Polar
5.	Thr299JE3a	Loop L_0-A	Glu185JE3b	H_0	Polar
6.	Met348JE3a	Loop C-D	Glu133JE3b	Loop e-E_0	Hydrophobic

Table S4. Interactions less than 3.2 Å at 2-fold (E-E, E-M and M-M interactions) (related to Figure 5). The E-M monomer chains at the 2-fold axis of ZIKV, DENV and JEV are indicated as ZE2a-ZM2a, ZE2b-ZM2b, DE2a-DM2a, DE2b-DM2b, JE2a-JM2a, and JE2b-JM2b, respectively (Figure S5). Secondary structure elements are labelled as described in Table S1. E protein domains (E-D/SS) E-DI, E-DII, E-DIII, and transmembrane (TM); M protein and the hinge region are colored in red, yellow, blue, light blue, brown and green respectively.

ZIKV					
No.	Residue 1	E-D/SS	Residue 2	E-D/SS	Type
E-E Interactions					
1.	Asp98ZE2a	Loop c-d	Ser7ZE2b	N-term	Polar
2.	Trp101ZE2a	Loop c-d	Ser149ZE2b	Loop E_0-F_0	Polar
3.	Trp101ZE2a	Loop c-d	Lys316ZE2b	A	Hydrophobic
4.	Trp101ZE2a	Loop c-d	Thr327ZE2b	B	Hydrophobic
5.	Gly259ZE2a	j-αB	His266ZE2b	αB	Polar (Backbone)
6.	Ser260ZE2a	j-αB	Gly263ZE2b	αB	Polar (Backbone)
7.	Ser260ZE2a	j-αB	Ser260ZE2b	j-αB	Polar
8.	Gly263ZE2a	αB	Ser260ZE2b	j-αB	Polar (Backbone)
9.	Gly263ZE2a	αB	Gln261ZE2b	j-αB	Polar (Backbone)
10.	His266ZE2a	αB	Gly259ZE2b	j-αB	Polar (Backbone)
11.	Ser285ZE2a	l	His249ZE2b	Loop i-j	Polar
12.	Thr327ZE2a	B	Trp101ZE2b	Loop c-d	Hydrophobic
E-M Interactions					
1.	Glu26ZE2a	B_0	Arg15ZM2a	M-N-term	Polar
2.	His214ZE2a	g-αA-h	His7ZM2a	M-N-term	Polar
3.	Glu216ZE2a	g-αA-h	Arg10ZM2a	M-N-term	Polar
4.	Trp217ZE2a	g-αA-h	Pro5ZM2a	M-N-term	Polar (Backbone)
5.	Asp220ZE2a	g-αA-h	Asn34ZM2b	M-H1	Polar
6.	Asp220ZE2a	g-αA-h	Arg38ZM2a	M-H1	Polar
7.	Glu240ZE2a	Loop h-i	Arg23ZM2b	M-H1	Polar
8.	Ala241ZE2a	Loop h-i	Ala1ZM2a	M-N-term	Hydrophobic
9.	Glu244ZE2a	i	Ser22ZM2b	M-N-term	Polar
10.	Glu244ZE2a	i	Arg23ZM2b	M-H1	Polar
11.	Ala268ZE2a	αB	His7ZM2a	M-N-term	Hydrophobic

12.	Leu269ZE2a	αB	Trp19ZM2a	M-N-term	Polar
13.	Gly271ZE2a	αB-k	Thr18ZM2a	M-N-term	Hydrophobic
14.	Gly271ZE2a	αB-k	Leu12ZM2a	M-N-term	Hydrophobic
15.	Ala272ZE2a	αB-k	Thr18ZM2a	M-N-term	Hydrophobic
16.	Ala272ZE2a	αB-k	Trp19ZM2a	M-N-term	Hydrophobic
17.	Ser286ZE2a	l-L_0	Thr14ZM2a	M-N-term	Polar
18.	Gly459ZE2a	E-H3-E-T1	Tyr74ZM2b	M-C-term	Hydrophobic
19.	Ser461ZE2a	E-H3-E-T1	Glu24ZM2a	M-H1	Polar
20.	Phe463ZE2a	E-T1	Tyr74ZM2b	M-C-term	Hydrophobic
M-M Interactions					
1.	Val2ZM2a	M-N-term	Arg31ZM2b	M-H1	Hydrophobic
2.	Arg10ZM2a	M-N-term	Asn39ZM2b	M-H1	Polar
3.	Arg10ZM2a	M-N-term	Asn39ZM2b	M-H1	Polar
4.	His28ZM2a	M-H1	Tyr74ZM2b	M-C-term	Polar
5.	Arg31ZM2a	M-H1	Val2ZM2b	M-N-term	Polar (Backbone)
6.	Arg38ZM2a	M-H1	Arg10ZM2b	M-N-term	Polar
7.	Asn39ZM2a	M-H1	Arg10ZM2b	M-N-term	Polar
8.	Leu53ZM2a	M-H2-M-H3	Gln59ZM2b	M-H3	Hydrophobic
9.	Ser55ZM2a	M-H2-M-H3	Gln59ZM2b	M-H3	Polar
10.	Gln59ZM2a	M-H3	Tyr63ZM2b	M-H3	Polar
11.	Leu69ZM2a	M-H3	Ser75ZM2b	M-C-term	Hydrophobic
12.	Tyr74ZM2a	M-C-term	His28ZM2b	M-H1	Polar
13.	Ser75ZM2a	M-C-term	Leu69ZM2b	M-H3	Hydrophobic
DENV					
No.	Residue 1	E-D/SS	Residue 2	E-D/SS	Type
E-E Interactions					
1.	Asp98DE2a	Loop c-d	Gln316DE2b	A	Polar
2.	Asp98DE2a	Loop c-d	Ile6DE2b	N-term	Hydrophobic
3.	Asp98DE2a	Loop c-d	Ser7DE2b	N-term	Polar
4.	Asp98DE2a	Loop c-d	Gly5DE2b	N-term	Hydrophobic
5	Trp101DE2a	Loop c-d	Lys310DE2b	A	Hydrophobic
6.	Phe108DE2a	d	Thr315DE2b	A	Hydrophobic
7.	Gly109DE2a	d	Gln316DE2b	Loop A-B	Hydrophobic
8.	Lys241DE2a	i	Glu269DE2b	k	Polar
9.	Ser255DE2a	j-αB	Gly258DE2b	αB	Hydrophobic
10.	Ser255DE2a	j-αB	Glu257DE2b	αB	Polar

11.	Gly258DE2a	αB	Ser255DE2b	j-αB	Hydrophobic
12.	His261DE2a	αB	Leu253DE2b	j	Polar (Backbone)
13.	Glu269DE2a	αB-k	Lys241DE2b	i	Polar
14.	Lys310DE2a	A	Trp101DE2b	Loop c-d	Hydrophobic
15.	Thr315DE2a	A	Gly109DE2b	d	Hydrophobic
E-M Interactions					
1.	Glu26DE2a	Loop B_0-C_0	Ala15DM2a	M-N-term	Hydrophobic
2.	Trp206DE2a	g	Trp19DM2a	M-N-term	Hydrophobic
3.	His209DE2a	g	His7DM2a	M-N-term	Polar
4.	His209DE2a	g	Met10DM2a	M-N-term	Hydrophobic
5.	Trp212DE2a	αA	His7DM2a	M-N-term	Polar
6.	Lys241DE2a	i	Trp19DM2b	M-N-term	Polar
7.	Pro243DE2a	i	Glu17DM2b	M-N-term	Hydrophobic
8.	Gln256DE2a	j-αB	Val2DM2a	M-N-term	Hydrophobic
9.	Ala263DE2a	αB	Val5DM2a	M-N-term	Hydrophobic
10.	Gly266DE2a	αB-k	Thr18DM2a	M-N-term	Hydrophobic
11.	Ala267DE2a	αB-k	Trp19DM2a	M-N-term	Hydrophobic
12.	Thr280DE2a	Loop l-L_0	Thr16DM2a	M-N-term	Polar
13.	Ile414DE2a	E-H1	Glu13DM2a	M-N-term	Polar (Backbone)
14.	Ser449DE2a	E-H3-E-T1	Gly9DM2a	M-N-term	Polar (Backbone)
15.	Gly450DE2a	E-H3-E-T1	Gly9DM2a	M-N-term	Hydrophobic
16.	Ala495DE2a	E-C-term	Thr18DM2a	M-N-term	Polar (Backbone)
M-M Interactions					
1.	Ala3DM2a	M-N-term	Ala3DM2b	M-N-term	Hydrophobic
2.	Val5DM2a	M-N-term	Arg31DM2b	M-H1	Hydrophobic
3.	Gln59DM2a	M-H3	Gln59DM2b	M-H3	Polar
JEV					
No.	Residue 1	E-D/SS	Residue 2	E-D/SS	Type
E-E Interactions					
1.	Trp101JE2a	Loop c-d	Lys312JE2b	A	Hydrophobic
2.	Phe108JE2a	d	Asp316JE2b	A	Hydrophobic
3.	Lys209JE2a	g	Val253JE2b	j	Hydrophobic
4.	Val253JE2a	j	Lys209JE2b	g	Hydrophobic
5.	Ser257JE2a	j-αB	Gly260JE2b	αB	Polar (Backbone)
6.	Gln258JE2a	j-αB	Gly260JE2b	αB	Hydrophobic
7.	Gly260JE2a	αB	Ser257JE2b	j-αB	Polar (Backbone)

8.	Gly260JE2a	αB	Gln258JE2b	j-αB	Hydrophobic
9.	His263JE2a	αB	Gly256JE2b	j-αB	Hydrophobic
10.	Lys312JE2a	A	Trp101JE2b	Loop c-d	Hydrophobic
11.	Asp316JE2a	A	Phe108JE2b	d	Hydrophobic
E-M Interactions					
1.	Glu26JE2a	Loop B_0-C_0	Lys15JM2a	M-N-term	Polar
2.	His214JE2a	g	His7JM2a	M-N-term	Hydrophobic
3.	His214JE2a	g	Ser10JM2a	M-N-term	Polar
4.	Glu216JE2a	αA	Arg38JM2b	M-H1	Polar
5.	Trp217JE2a	αA	Gln5JM2a	M-N-term	Polar (Backbone)
6.	Trp217JE2a	αA	His7JM2a	M-N-term	Hydrophobic
7.	Asp220JE2a	αA	Arg38JM2b	M-H1	Polar
8.	Glu241JE2a	i	Trp19JM2b	M-N-term	Hydrophobic
9.	Glu241JE2a	i	Leu20JM2b	M-N-term	Hydrophobic
10.	Glu244JE2a	i	Glu17JM2b	M-N-term	Hydrophobic
11.	Glu244JE2a	i	Thr16JM2b	M-N-term	Polar
12.	Leu266JE2a	αB-k	Trp19JM2a	M-N-term	Hydrophobic
13.	Ala267JE2a	αB-k	Trp19JM2a	M-N-term	Hydrophobic
M-M Interactions					
1.	Ser1JM2a	M-N-term	Lys31JM2b	M-H1	Polar
2.	Phe63JM2a	M-H3	Phe63JM2b	M-H3	Hydrophobic
3.	Tyr74JM2a	M-C-term	Leu69JM2b	M-H3	Hydrophobic