

Supplementary Figure 1. Nucleotide alignment of clade 1 Ohio/03 and clade 2 Rich/07 HA proteins: In red are indicated the amino acid residues that differ between the two viruses present in the EIV bivalent LAIV. Residue numbers are indicated at the right as reference.

Ohio/03	ATGAAGACAA	CCATTATTTT	G*****ATA	CTACTGACCC	ATTGGGCCTA	CAGTCAAAAC	CCAATCAGTG	GCAACAACAC	74
Rich/07	ATGAAGACAA	CCATTATTTT	TATTTTATA	CTACTGACCC	ATTGGGCCTA	CAGTCAAAAC	CCAATCAGTA	ACAACAACAC	80
Ohio/03	AGCCACATTG	TGTCTGGGAC	GCCATGCAGT	AGCAAATGGA	ACATTGGTAA	AAACAATAAG	TGATGATCAA	ATTGAGGTGA	154
Rich/07	AGCCACATTG	TGTCTGGGAC	ACCATGCAGT	AGCAAATGGA	ACATTAGTAA	AAACAATAAG	TGATGATCAA	ATTGAGGTGA	160
Ohio/03	CAAATGCTAC	AGAATTAGTT	CAGAGCATTT	CAACGGGGAA	AATATGCAAC	AACTCATATA	GAATTCTAGA	TGGAAGAAAT	234
Rich/07	CAAATGCTAC	AGAATTAGTT	CAGAGCATTT	CAATGGGGAA	AATATGCAAC	AACTCATATA	GAATTCTAGA	TGGAAGAAAT	240
Ohio/03	TGCACATTAA	TAGATGCAAT	GCTAGGAGAC	CCCCACTGTG	ACGCTTTTCA	GTATGAGAAT	TGGGACCTCT	TTATAGAAAG	314
Rich/07	TGCACATTAA	TAGATGCAAT	GCTAGGAGAC	CCCCACTGTG	ACGTCTTTCA	GTATGAGAAT	TGGGACCTCT	TTATAGAAAG	320
Ohio/03	AAGCAGCGCT	TTCAGCAATT	GCTACCCATA	TGACATCCCT	GACTATGCAT	CGCTCCGATC	CATTGTAGCA	TCCTCAGGAA	394
Rich/07	AAGCAGCGCT	TTCAGCAATT	GCTACCCATA	TGACATCCCT	GACTATGCAT	CGCTCCGATC	AATTGTAGCA	TCCTCAGGAA	400
Ohio/03	CATTGGAATT	CACAGCAGAG	GGATTACAT	GGACAGGTGT	CACTCAAAAC	GGAA T AAGTG	GAGCCTGCAA	AAGGGGATCA	474
Rich/07	CATTGGAATT	CACAGCAGAG	GGATTACAT	GGACAGGTGT	CACTCAAAAC	GGAA G AAGTG	GAGCCTGCAA	AAGGGGATCA	480
Ohio/03	GCCGATAGTT	TCTTTAGCCG	ACTGAATTGG	CTAACAAAAT	CTGGAA G CTC	TTA C CCCACA	TTGAATGTGA	CAATGCCTAA	554
Rich/07	GCCGATAGTT	TCTTTAGCCG	ACTGAATTGG	CTAACAAAAT	CTGGAA A CTC	TTA T CCCACA	TTGAATGTGA	CAATGCCTAA	560
Ohio/03	CAATAAAAAT	TTCGACAAGC	TATACATCTG	GGGGATTCAT	CACCCGAG C T	CAAATCAAGA	GCAGACAAAA	TTGTACATCC	634
Rich/07	CAATAAAAAT	TTCGACAAGC	TATACATCTG	GGGGATTCAT	CACCCGAG T T	CAAATCAAGA	GCAGACAAAA	TTGTATATCC	640
Ohio/03	AAGAATCAGG	ACGAGTAACA	GTCTCAACAA	AAAGAAGTCA	ACAAACAATA	ATCCCTAACA	TCGGATCTAG	ACCGTGGGTC	714
Rich/07	AAGAATCAGG	ACGAGTAACA	GTCTCAACAA	AAAGAAGTCA	ACAAACAATA	ATCCCTAACA	TCGGATCTAG	ACCGTGGGTC	720
Ohio/03	AGAGGTCAAT	CAGGCAGGAT	AAGCATATAC	TGGACCATTG	TAAAACCTGG	AGATATCCTA	ATGATAAACA	GTAATGGCAA	794
Rich/07	AGAGGTCAAT	CAGGCAGGAT	AAGCATATAC	TGGACCATTG	TAAAACCTGG	AGATATCCTA	ATGATAAACA	GTAATGGCAA	800
Ohio/03	CTTAGTTGCA	CCGCGGGGAT	ATTTTAAATT	GAAAACAGGG	AAAAGCTCTG	TAATGAGATC	AGATGTACCC	ATAGA A ATT	874
Rich/07	CTTAGTTGCA	CCGCGGGGAT	ATTTTAAATT	GAAAACAGGG	AAAAGCTCTG	TAATGAGATC	AGATGTACCC	ATAGAC A ATT	880
Ohio/03	GTGTGTCTGA	ATGTATTACA	CCAAATGGAA	GCATCTCCAA	CGA C AAGCCA	TTCCAAAATG	TGA C AAAAGT	TACATATGGA	954
Rich/07	GTGTGTCTGA	ATGTATTACA	CCAAATGGAA	GCATCTCCAA	CGA A AAGCCA	TTCCAAAATG	TAA C AAAAGT	TACATATGGA	960
Ohio/03	AAATGCCCCA	AGTATATCAG	GCAAAACACT	TTAAAG C TGG	CCACTGGGAT	GAGGAATGTA	CCAGAAAAGC	AAATCAGAGG	1,034
Rich/07	AAATGCCCCA	AA T TATATCAG	GCAAAACACT	TTAAAG T TGG	CCACTGGAA T	GAGAAATGTA	CCAGAAAAGC	AAATCAGAGG	1,040
Ohio/03	AATCTT C GGA	GCAATAGCGG	GATTCATCGA	AAACGGCTGG	GAAGGAATGG	TTGATGGGTG	GTATGGGTTC	CGATA T CAAA	1,114
Rich/07	AATCTT T GGG	GCAATAGCGG	GATTCATCGA	AAACGGCTGG	GAAGGAATGG	TTGATGGGTG	GTATGGGTTC	CGATA C CAA	1,120
Ohio/03	ACTCTGAAGG	AACAGG G CAA	GCTGCAGATC	TAAAGAGCAC	TCAA G CAGCC	ATCGACCAGA	TTAATG G AAA	GTTAAACAGA	1,194
Rich/07	ACTCTGAAGG	AACAGG A CAA	GCTGCAGATC	TAAAGAGCAC	TCAA A CAGCC	ATCGACCAGA	TTAATG A AAA	GTTAAACAGA	1,200
Ohio/03	GTGATTGAAA	GAACCAATGA	GAAATTCAT	CA A ATAGAGA	AGGAATTCTC	AGAAGTAGAA	GGAAGAATTC	AGGACTTGG	1,274
Rich/07	GTGATTGAAA	GAACCAATGA	AAAATTCAT	CAGATAGAGA	AGGAATTCTC	AGAAGTAGAA	GGAAGAATTC	AGGACTTGG	1,280
Ohio/03	GAAATATGTA	GAAGACACCA	AAATAGACCT	ATGGTCTTAC	AATGCAGAAAT	TGCTGGTGGC	TCTAGAAAAT	CAACATACAA	1,354
Rich/07	GAAATATGTG	GAAGACACCA	AAATAGACCT	ATGGTCTTAC	AATGCAGAAAT	TGCTGGTGGC	TCTAGAAAAT	CAACATACAA	1,360
Ohio/03	TTGACTTAAC	AGATGCAGAA	ATGAATAAAT	TATTTGAGAA	GACTAGACGC	CAGTTAAGAG	AAAACGCAGA	AGACATGGGA	1,434
Rich/07	TTGACTTAAC	AGATGCAGAA	ATGAATAAAT	TATTCGAGAA	GACTAGACGC	CAGTTAAGAG	AAAACGCAGA	AGACATGGGA	1,440
Ohio/03	GGTGGATGTT	TCAAGATTTA	CCACAAATGT	GATAATGCAT	GCATTGGATC	AATAAGAAAT	GGGACATATG	ACCATTACAT	1,514
Rich/07	GGTGGATGTT	TCAAGATTTA	CCACAAATGT	GATAATGCAT	GCATTGGATC	AATAAGAAAT	GGGACATATG	ACCATTACAT	1,520
Ohio/03	ATACAGAGAT	GAAGCATTAA	ACAACCGATT	TCAGATCAAA	GGTGTAGAGT	TGAAATCAGG	CTACAAAGAT	TGGATACTGT	1,594
Rich/07	ATACAGAGAT	GAAGCATTAA	ACAACCGATT	TCAAATCAAA	GGTGTGAGT	TGAAATCAGG	CTACAAAGAT	TGGATACTGT	1,600
Ohio/03	GGATTT C ATT	CGCCATATCA	TGCTTCTTAA	TTTGCCTTGT	TCTATTGGGT	TT C ATTATGT	GGGCTTGCCA	AAAAGGCAAC	1,674
Rich/07	GGATTT T ATT	CGCCATATCA	TGCTTCTTAA	TTTGCCTTGT	TCTATTGGGT	TT T ATTATGT	GGGCTTGCCA	AAAAGGCAAC	1,680
Ohio/03	ATCAGATGCA	ACATTTGCAT	TTGA	1,698					
Rich/07	ATCAGATGCA	ACATTTGCAT	TTGA	1,708					

Supplementary Figure 2. Nucleotide alignment of clade 1 Ohio/03 and clade 2 Rich/07 NA proteins: In red are indicated the amino acid residues that differ between the two viruses present in the EIV bivalent LAIV. Residue numbers are indicated at the right as reference.

Ohio/03	ATGAATCCAA	ATCAAAAAGAT	AATAGCAATT	GGATTTGCAT	CATTGGGGAT	ATTAATCATT	AATGTCATTC	TCCATGTAGT	80
Rich/07	ATGAATCCAA	ATCAAAAAGAT	AATAACAATT	GGATCTGCAT	CATTGGGGAT	ATTAATCATT	AACGTCATTC	TCCATGTAGT	
Ohio/03	CAGCATTATA	GTAACAGTAC	TGGTCCTCAA	TAACAATGAA	ACAGATCTGA	ACTGCAAAGG	GACGATCATA	AGAGAGTGCA	160
Rich/07	CAGCATTATA	GTAACAGTAC	TGGTCCTCAA	TAACAATAGA	ACAGGTCTGA	ACTGCAAAGG	GACGATCATA	AGAGAGTACA	
Ohio/03	ATGAAACAGT	AAGAGTAGAA	AAAATTACTC	AATGGTATAA	TACCAGTACA	ATTAAGTACA	TAGAGAGACC	TTCAAATGAA	240
Rich/07	ATGAAACAGT	AAGAGTAGAA	AAAATTACTC	AATGGCATAA	TACCAGTGCA	ATTAAGTACA	TAGAGAGACC	TCAAATGAA	
Ohio/03	TACTACATGA	ACAACACTGA	ACTACTTTGT	GAGGCCAAG	GCTTTGCACC	ATTTTCCAAA	GATAATGGAA	TACGAATTGG	320
Rich/07	TACTACATGA	ACAACACCGA	ACCACTTTGT	GAGGCCAAG	GCTTTGCACC	ATTTTCCAAA	GATAATGGAA	TACGAATTGG	
Ohio/03	GTCGAGAGGC	CATGTTTTTG	TGATAAGAGA	ACCTTTTGTA	TCATGTTTCGC	CCTCAGAATG	TAGAACCTTT	TTCCTCACAC	400
Rich/07	GTCGAGAGGC	CATGTTTTTG	TGATAAGAGA	ACCTTTTGTA	TCATGTTTCGC	CCTCAGAATG	TAGAACCTTT	TTCCTCACAC	
Ohio/03	AGGGCTCATT	ACTCAATGAC	AAACATTCTA	ACGGCACAGT	AAAGGACCGA	AGTCCGTATA	GGACTTTGAT	GAGTGTCAGA	480
Rich/07	AGGGCTCATT	ACTCAATGAC	AAACATTCTA	ACGGCACAGT	AAAGGATCGA	AGTCCATATA	GGACTTTGAT	GAGTGTCAA	
Ohio/03	ATAGGGCAAT	CACCTAATGT	ATATCAAGCT	AGGTTTGAAT	CGGTAGCATG	GTCAGCAACA	GCATGCCATG	ATGGAAAAA	560
Rich/07	ATAGGGCAAT	CACCTAATGT	GTATCAAGCT	AGGTTTGAAT	CGGTGGCATG	GTCAGCAACA	GCATGCCATG	ATGGAAAAA	
Ohio/03	ATGGATGACA	GTTGGAGTCA	CAGGGCCCGA	CAATCAAGCA	ATTGCAGTAG	TGAACTATGG	AGGTGTTCCG	GTTGATATTA	640
Rich/07	ATGGATGACA	ATTGGAGTCA	CAGGGCCCGA	CAATCAAGCA	ATTGCAGTAG	TGAACTATGG	GGGTGTTCCG	GTTGATATTA	
Ohio/03	TTAATTCATG	GGCAGGGGAT	ATTTTAAGAA	CCCAAGAATC	ATCATGCACC	TGCATTAAAG	GAGACTGTTA	TTGGGTAATG	720
Rich/07	TTAATTCATG	GGCAGGGGAC	ATCTTAAGAA	CCCAAGAATC	ATCATGCACC	TGCATTAAAG	GAAACTGTTA	TTGGGTAATG	
Ohio/03	ACTGATGGAC	CGGCAAATAG	GCAAGCTAAA	TATAGAAATAT	TCAAAGCAAA	AGATGGAAGA	GTAATTGGAC	AGACTGATAT	800
Rich/07	ACTGATGGAC	CGGCAAATAG	GCAAGCTAAA	TATAGGATAT	TCAAAGCAAA	AGATGGAAGA	GTAATTGGAC	AGACTGATAT	
Ohio/03	AAGTTTCAAT	GGGGGACACA	TAGAGGAGTG	TTCTTGTTAC	CCCAATGAAG	GGAAGGTGGA	ATGCATATGC	AGGGACAATT	880
Rich/07	AAGCTTCAAT	GGGGGACACA	TAGAGGAGTG	TTCTTGTTAC	CCCAATGAAG	GGAAGGTGGA	ATGCATATGC	AGGGACAATT	
Ohio/03	GGACTGGAAC	AAATAGACCA	ATTCTGGTAA	TATCTTCTGA	TCTATCGTAC	ACAGTTGGA	TATTTGTGTGC	TGGCATTCCC	960
Rich/07	GGACTGGAAC	AAATAGACC	AATCTGGTAA	TATCTTCTGA	TCTATCGTAC	ACAGTTGGA	TATTTGTGTGC	TGGCATTCCC	
Ohio/03	ACTGACACTC	CTAGGGGAGA	GGATAGTCAA	TTCACAGGCT	CATGTACAAG	TCCTTTGGGA	AATAAAGGAT	ACGGTGTAAA	1,040
Rich/07	ACTGACACTC	CTAGGGGAGA	GGATAGTCAA	TTCACAGGCT	CATGTACAAG	TCCTTTGGGA	AATAAAGGAT	ACGGTGTAAA	
Ohio/03	AGGTTTCGGG	TTTCGACAAG	GAACTGACGT	ATGGGCCGGA	AGGACAATTA	GTAGGACTTC	AAGATCAGGA	TTCGAAATAA	1,120
Rich/07	AGGTTTCGGG	TTTCGACAAG	GAACTGACGT	ATGGGCCGGA	AGGACAATTA	GTAGGACTTC	GAGATCAGGA	TTCGAAATAA	
Ohio/03	TAAAAATCAG	GAATGGTTGG	ACACAGAACA	GTAAGACCA	AATCAGGAGG	CAAGTGATTA	TCGATGACCC	AAATTGGTCA	1,200
Rich/07	TAAAAATCAG	GAATGGTTGG	ACACAGAACA	GTAAGACCA	AATCAGGAGG	CAAGTGATTA	TCGATGACCC	AAATTGGTCA	
Ohio/03	GGATATAGCG	GTTCTTTCAC	ATTGCCGTT	GAACTAACAA	AAAAGGGATG	TTTGGTCCCC	TGTTTCTGGG	TTGAAATGAT	1,280
Rich/07	GGATATAGCG	GTTCTTTCAC	ATTGCCGATT	GAACTAACAA	AAAAGGGATG	TTTGGTCCCC	TGTTTCTGGG	TTGAAATGAT	
Ohio/03	TAGAGGTAAA	CCTGAAGAAA	CAACAATATG	GACCTCTAGC	AGCTCCATTG	TGATGTGTGG	AGTAGATCAT	AAAATTGCCA	1,360
Rich/07	TAGAGGTAAA	CCTGAAGAAA	CAACAATATG	GACCTCTAGC	AGCTCCATTG	TGATGTGTGG	AGTAGATCAT	AAAATTGCCA	
Ohio/03	GTTGGTCATG	GCACGATGGA	GCTATTCTTC	CCTTTGACAT	CGATAAGATG	TAA	1,413		
Rich/07	GTTGGTCATG	GCACGATGGA	GCTATTCTTC	CCTTTGACAT	CGATAAGATG	TAA			

Supplementary Figure 3. Correlation between HAI titers (Figure 7) and clinical scores (Figure 8) at day 7 after challenge with Clade 1 KY/14 (A) and Clade 2 Rich/07 (B) WT viruses.

