

Supplementary information for Reproducible and later vaccine strain selection can improve vaccine match to A/H3N2 seasonal influenza viruses

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S1. Genetic and antigenic assessment of vaccine match between dominant strain and vaccine and reproducibly selected strains per season for the United States of America

Table S1 Per season assessment of vaccine match between the dominant A/H3N2 strain in the United States of America and the WHO recommended vaccine strain, the reproducibly selected vaccine strains at WHO timing, and the reproducibly selected strain at three-month delayed timing. Vaccine match was assessed by the number of mutations in the classically defined epitope sites for H3, the number of mutations in novel antigenic variant sites¹, and the antigenic distance determined by antigenic cartography. Seasons for which comparison via antigenic cartography was not possible because HI tables could not be merged due to unclear labelling on antigens between 2004 and 2006, and differences in the use of antivirals between 2010 and 2011 have been indicated with NA.

Season	Number of epitope mutations			Number of mutations in novel antigenic variant sites			Antigenic distance		
	Vaccine strain	Reproducible selection strain	Delayed selection strain	Vaccine strain	Reproducible selection strain	Delayed selection strain	Vaccine strain	Reproducible selection strain	Delayed selection strain
2002-2003	13	7	7	2	2	2	4.594	5.152	5.152
2003-2004	14	1	1	2	0	0	5.342	0.000	0.000
2004-2005	7	6	2	4	3	1	NA	NA	NA
2005-2006	5	2	2	1	1	1	NA	NA	NA
2006-2007	5	2	1	0	0	0	NA	NA	NA
2007-2008	6	3	1	0	0	0	4.062	3.171	2.036
2008-2009	2	0	0	0	0	0	1.818	0.000	0.000
2009-2010	5	3	3	2	2	2	4.546	5.241	5.241
2010-2011	8	4	5	0	0	0	NA	NA	NA
2011-2012	6	6	6	0	0	0	3.463	2.171	2.171
2012-2013	2	4	4	1	1	1	2.579	1.668	1.668
2013-2014	3	0	2	1	0	0	2.737	1.246	2.047
2014-2015	6	5	5	2	1	1	5.127	3.038	3.038
2015-2016	8	0	0	1	0	0	2.069	0.000	0.000
2016-2017	4	2	2	0	0	0	3.002	1.061	1.061
2017-2018	5	5	5	0	0	0	1.364	2.241	2.241
2018-2019	10	10	10	2	2	2	3.165	1.999	1.999
2019-2020	11	2	11	2	0	2	3.271	0.767	3.271
2020-2021	10	8	9	1	1	1	2.192	2.192	2.192
2021-2022	10	5	7	2	1	2	0.929	2.575	1.394
2022-2023	4	4	5	1	1	1	1.454	2.343	2.228

S2. Genetic and antigenic assessment of vaccine match between dominant strain and vaccine and reproducibly selected strains per season for Europe

Table S2 Per season assessment of vaccine match between the dominant A/H3N2 strain in Europe and the WHO recommend vaccine strain, the reproducibly selected vaccine strains at WHO timing, and the reproducibly selected strain at three-month delayed timing. Vaccine match was assessed by the number of mutations in the classically defined epitope sites for H3, the number of mutations in novel antigenic variant sites¹, and the antigenic distance determined by antigenic cartography. Seasons for which comparison via antigenic cartography was not possible because HI tables could not be merged due to unclear labelling on antigens between 2004 and 2006, and differences in the use of antivirals between 2009 and 2011 have been indicated with NA.

Season	Number of epitope mutations			Number of mutations in novel antigenic variant sites			Antigenic distance		
	Vaccine strain	Reproducible selection strain	Delayed selection strain	Vaccine strain	Reproducible selection strain	Delayed selection strain	Vaccine strain	Reproducible selection strain	Delayed selection strain
2002-2003	13	7	7	2	2	2	4.954	5.152	5.152
2003-2004	15	2	2	2	0	0	5.015	0.0	0.0
2004-2005	8	7	3	3	2	0	NA	NA	NA
2005-2006	4	1	1	1	1	1	NA	NA	NA
2006-2007	3	0	1	0	0	0	3.342	0.0	1.326
2007-2008	6	3	1	0	0	0	3.822	2.126	0.0
2008-2009	2	0	0	0	0	0	1.818	0.0	0.0
2009-2010	5	3	3	2	2	2	NA	NA	NA
2010-2011	8	4	5	0	0	0	NA	NA	NA
2011-2012	6	6	6	0	0	0	3.463	2.171	2.171
2012-2013	4	6	6	1	1	1	3.02	1.874	1.874
2013-2014	4	2	0	1	0	0	2.909	0.661	2.171
2014-2015	6	5	5	2	1	1	6.189	4.211	4.211
2015-2016	8	0	0	1	0	0	1.464	0.0	0.0
2016-2017	4	2	2	0	0	0	3.002	1.061	1.061
2017-2018	5	5	5	0	0	0	1.364	1.854	1.854
2018-2019	5	9	9	0	0	0	3.958	1.699	1.699
2019-2020	0	9	0	0	2	0	0.527	3.728	0.527
2020-2021	10	8	9	1	1	1	1.323	1.323	1.323
2021-2022	8	3	5	2	1	2	4.054	1.797	3.112
2022-2023	4	4	5	1	1	1	1.246	1.188	1.527

S3. Genetic and antigenic assessment of vaccine match between dominant strain and vaccine and reproducibly selected strains per Season for Australia and New Zealand

Table S3 Per season assessment of vaccine match between the dominant A/H3N2 strain in Australia and New Zealand and the WHO recommend vaccine strain, the reproducibly selected vaccine strains at WHO timing, and the reproducibly selected strain at three-month delayed timing. Vaccine match was assessed by the number of mutations in the classically defined epitope sites for H3, the number of mutations in novel antigenic variant sites¹ by antigenic cartography. Seasons for which comparison via antigenic cartography was not possible because HI tables could not be merged due to unclear labelling on antigens between 2004 and 2006, and differences in the species from which red blood cells were derived for the HI assay between 2007 and 2008 have been indicated with NA.

Season	Number of epitope mutations			Number of mutations in novel antigenic variant sites			Antigenic distance		
	Vaccine strain	Reproducible selection strain	Delayed selection strain	Vaccine strain	Reproducible selection strain	Delayed selection strain	Vaccine strain	Reproducible selection strain	Delayed selection strain
2003	14	8	8	2	2	2	4.954	5.152	5.152
2004	7	6	6	4	3	3	NA	NA	NA
2005	4	3	3	1	1	1	NA	NA	NA
2006	5	1	1	1	2	0	1.791	1.889	1.247
2007	5	1	2	0	0	0	NA	NA	NA
2008	2	1	1	0	0	0	NA	NA	NA
2009	6	4	4	2	2	2	5.192	6.15	6.15
2010	8	8	4	0	0	0	5.181	2.838	0.841
2011	8	0	0	0	0	0	2.641	0.0	0.0
2012	9	4	2	0	1	0	3.136	1.191	0.322
2013	4	2	2	1	0	0	1.877	0.677	0.677
2014	4	0	0	1	0	0	2.006	1.853	0.0
2015	8	5	0	1	1	0	2.454	4.268	0.0
2016	3	1	1	0	0	0	1.357	0.99	0.99
2017	5	2	1	0	0	0	1.764	1.037	0.931
2018	6	5	0	0	0	0	4.818	1.508	0.0
2019	11	5	4	0	0	0	2.647	3.076	2.227
2020	6	5	7	2	2	1	2.61	1.547	2.785
2021	12	7	4	2	2	2	2.957	3.311	3.265
2022	3	2	2	0	0	0	1.532	2.127	0.454
2023	6	4	4	0	0	1	1.706	3.041	0.585

References

1. Koel BF, Burke DF, Bestebroer TM, van der Vliet S, Zondag GCM, Vervaet G, et al. Substitutions Near the Receptor Binding Site Determine Major Antigenic Change During Influenza Virus Evolution. *Science* (1979). 2013 Nov 22;342(6161):976–9.