## Supplemental Table 1: Search strategy

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| Component Principle | PICOS Criteria | Search Strings | Inclusion Criteria | Exclusion Criteria |
| 1. Presence of antigenic drift | P: Not Limited  I: Not Limited  C: Not Limited  O: Not Limited  S: English; 2019-2021; full text available | (influenza or flu) AND antigenic AND drift | English Language  Any Geographical Location  Articles proving the phenomenon of antigenic drift in influenza viruses (e.g. genetic studies, systematic reviews, and meta-analyses)  Original research | Non-English Language  No Full Text  Non-influenza genetic drift  Articles not investigating the phenomenon, but describing other issues such as epidemiology, effectiveness, interventions and treatment comparisons, economic analyses  Strictly commentary and review articles  Disease Models |
| 2. Stages in egg-based influenza vaccine manufacture and candidate virus vaccine selection | P: Humans Only  I: Egg-based Vaccines  C: Not Limited  O: Publications outlining the stages of the manufacturing process  S: Descriptive Articles; English; 2019-2021; full text available | (stage or step or process or development) and (influenza OR flu) AND eggs AND (vaccine OR vaccination) AND (cvv OR candidate OR selection or manufacture OR manufacturing OR production OR inactivation OR purification OR harvesting OR incubation OR propagate OR propagation) | English Language  Human Influenza  Any Geographical Location  Articles outlining the stages of manufacturing or candidate vaccine virus selection  Egg-based manufacturing | Non-English Language  Non-human influenza  Articles with a different subject to the research question  Articles investigating only a single step of the candidate vaccine virus selection and vaccine production (e.g. virus characterization studies, methods to improve a step of production, diagnostics of methods, testing new methods in vitro or animal models  Strictly clinical studies interested in patient outcomes  Production only via non-egg mediums |
| 3. Egg-adaptation changes in influenza vaccine manufacturing process | P: Not Limited  I: Egg-based Vaccines  C: Not Limited  O: Not Limited  S: English; 2019-2021; full text available | (influenza OR flu) AND egg AND (adaptation OR drift OR mutation OR mismatch OR antigenic) AND (manufacture OR manufacturing OR process development OR inactivation OR purification OR harvesting OR incubation OR propagate OR propagation) | English Language  Human Influenza  Any Geographical Location  Articles indicating that egg-adaptation changes are linked to manufacturing processes or part of the process in eggs  Original research | Non-English Language  Non-Human Influenza  Articles with a different subject to the research question (e.g. virus characterization studies, methods to improve a step of production, diagnostics of methods, testing new methods in vitro or animal models)  Strictly clinical studies interested in patient outcomes  Strictly commentary or review articles  Production only via non-egg mediums |
| 4. Stage(s) in the manufacturing process most likely to impact influenza VE | P: Not Limited  I: Egg-based Vaccines  C: Not Limited  O: Not Limited  S: English; 2019-2021; full text available | (influenza OR flu) AND egg AND (manufacture OR manufacturing OR process development OR inactivation OR purification OR harvesting OR incubation OR propagate OR propagation) AND (effectiveness OR efficacy OR efficiency OR performance) | English Language  Human Influenza  Any Geographical Location  Articles relating manufacturing processes to VE  Egg-based vaccines (may not be exclusively egg-based vaccine articles) | Non-English Language  Non-Human Influenza  Articles with a different subject to the research question (e.g. virus characterization studies, methods to improve a step of production, diagnostics of methods, testing new methods in in vitro or animal models)  Strictly clinical studies interested in patient outcomes  Production only via non-egg mediums  Economic Analyses |

## Supplemental Table 2: Highest rated evidence for each component principle of the research question

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| Component Principle | Author/Date | Title | Expert score | Lit review | From experts | Journal |
| 1. Antigenic drift | Bragstad K. 2008 | The evolution of human influenza A viruses from 1999 to 2006: a complete genome study | 4.5 | YES | NO | Virology Journal |
| Hardy I. 2001 | Molecular evolution of influenza A/H3N2 viruses in the province of Quebec (Canada) during the 1997-2000 period | 4.5 | YES | NO | Virus Research |
| Venter M. 2012 | Evolutionary dynamics of 2009 pandemic influenza A virus subtype H1N1 in South Africa during 2009-2010 | 4.5 | YES | NO | Journal of Infectious Diseases |
| Shen J. 2009 | Evolutionary trends of A(H1N1) influenza virus hemagglutinin since 1918 | 4.5 | YES | NO | PLOS |
| Skowronski D. 2016 | A perfect storm: impact of genomic variation and serial vaccination on low influenza vaccine effectiveness during the 2014-2015 season | 4.5 | YES | NO | Clinical Infectious Diseases |
| Vijaykrishna D. 2015 | The contrasting phylodynamics of human influenza B viruses | 4.5 | YES | NO | eLife |
| Flannery B. 2016 | Enhanced genetic characterization of influenza A(H3N2) viruses and vaccine effectiveness by genetic group, 2014-2015 | 4.5 | YES | YES(1) | Journal of Infectious Diseases |
| Li J. 2005 | Annual report of the National Influenza Surveillance Scheme, 2004 | 4.5 | YES | NO | Communicable Diseases Intelligence |
| Sleigh MJ. 1981 | Antigenic drift in the hemagglutinin of the Hong Kong influenza subtype: correlation of amino acid changes with alterations in viral antigenicity | 4.5 | YES | NO | Virology |
| Tenforde MW. 2021 | Effect of antigenic drift on influenza vaccine effectiveness in the United States - 2019-2020. An official publication of the Infectious Diseases Society of America | 4.5 | YES | NO | Clinical Infectious Diseases |
| 2. CVV selection and manufacturing stages | Ampofo W. & WHO Writing Group 2011 | Improving influenza vaccine virus selection: Report of a WHO informal consultation held at WHO headquarters, Geneva, Switzerland, 14–16 June 2010. | 5 | YES | YES(1) | WHO website |
| Milian E. 2015 | Current and emerging cell culture manufacturing technologies for influenza vaccines | 5 | YES | YES(1) | Vaccines |
| Tosh P. 2010 | Influenza vaccines: From surveillance through production to protection | 5 | YES | YES(1) | Vaccines |
| FDA | FDA Website: The making of a vaccine | 5 | YES | YES(1) | FDA website |
| Gerdil C. 2003 | The annual production cycle for the influenza vaccine | 5 | YES | YES(1) | Vaccines |
| Robertson J. 2011 | The development of vaccine viruses against pandemic A(H1N1) influenza. | 5 | YES | YES(1) | Vaccines |
| Weir J. 2016 | An overview of the regulation of influenza vaccines in the United States | 5 | YES | YES(2) | Vaccines |
| Treanor J. 2004 | Weathering the Influenza Vaccine Crisis | 5 | YES | YES(1) | Vaccines |
| Trombetta C. 2019 | Challenges in the development of egg-independent vaccines for influenza. | 5 | YES | YES(1) | Vaccines |
| Shin D. 2015 | Comparison of immunogenicity of cell-and egg-passaged viruses for manufacturing MDCK cell culture-based influenza vaccines. | 5 | NO | YES(1) | Virology |
| Wahid R. 2016 | Chemistry, manufacturing and control (CMC) and clinical trial technical support for influenza vaccine manufacturers. | 5 | NO | YES(1) | Virology |
| 3. Egg adaptations during influenza vaccine manufacture | Rocha J. 1993 | Comparison of 10 influenza A (H1N1 and H3N2) haemagglutinin sequences obtained directly from clinical specimens to those of MDCK cell- and egg-grown viruses | 5 | YES | NO | Journal of General Virology |
| Zost S. 2017\* | Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains | 4.5 | YES | YES(4) | PNAS |
| Skowronski D. 2014\* | Low 2012-13 influenza vaccine effectiveness associated with mutation in the egg- adapted H3N2 vaccine strain not antigenic drift in circulating viruses | 4.5 | YES | YES(3) | PLOS One |
| Robertson J. 1987 | Structural changes in the hemagglutinin which accompany egg adaptation of an influenza A (H1N1) virus | 4 | NO | YES(2) | Virology |
| Meyer W. 1993 | Influence of host cell-mediated variation on the international surveillance of influenza A (H3N2) viruses | 4 | YES | NO | Virology |
| Stevens J. 2010 | Receptor specificity of influenza A H3N2 viruses isolated in mammalian cells and embryonated chicken eggs | 4 | YES | NO | Virology |
| Gubareva L. 1994 | Codominant mixtures of viruses in reference strains of influenza virus due to host cell variation | 4 | YES | NO | Virology |
| Nicolson C. 2016 | The ability of a non-egg adapted (cell-like) A(H1N1)pdm09 virus to egg-adapt at HA loci other than 222 and 223 and its effect on the yield of viral protein | 4 | YES | NO | PLOS One. |
| Wang M. 1989 | Extensive heterogeneity in the hemagglutinin of egg-grown influenza viruses from different patients | 4 | YES | NO | Virology |
| Wu NC. 2019 | Preventing an antigenically disruptive mutation in egg-based H3N2 seasonal influenza vaccines by mutational incompatibility | 4 | NO | YES(1) | Cell Host & Microbe |
| 4. Steps in manufacturing most likely to influence VE | Dugan V. 2017 | Morbidity and mortality weekly report update: Influenza activity - United States, October 1-November 25, 2018 | 4 | YES | NO | CDC Website |
| Zost S. 2017\* | Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains | 4 | YES | NO | PNAS |
| Wu N. 2017 | A structural explanation for the low effectiveness of the seasonal influenza H3N2 vaccine | 4 | YES | NO | PLOS Pathogens |
| Petrie J. 2018 | Epidemiological studies to support the development of next generation influenza vaccines | 4 | YES | NO | Vaccines |
| Park YW. 2020 | Comparison of antigenic mutation during egg and cell passage cultivation of H3N2 influenza virus | 4 | NO | YES(1) | Clinical and Experimental Vaccine Research |
| Ampofo W. 2015 | Strengthening the influenza vaccine virus selection and development process: Report of the 3rd WHO Informal Consultation for Improving Influenza Vaccine Virus Selection held at WHO headquarters, Geneva, Switzerland, 1–3 April 2014 | 3.5 | YES | NO | Vaccine |
| Hampson A. 2017 | Improving the selection and development of influenza vaccine viruses – Report of a WHO informal consultation on improving influenza vaccine virus selection, Hong Kong SAR, China, 18–20 November 2015 | 3.5 | YES | NO | WHO website |
| Skowronksi D. 2014\* | Low 2012–13 Influenza vaccine effectiveness associated with mutation in the egg-adapted H3N2 vaccine strain not antigenic drift in circulating viruses | 3.5 | YES | YES(2) | PLOS One |
| Raymond D. 2016 | Influenza immunization elicits antibodies specific for an egg-adapted vaccine strain | 3,5 | YES | NO | Nature |

\*References supported component principles three and four.