# Coversheet on evidence assessment by ATAGI using the GRADE framework for MVA-BN (JYNNEOS) mpox vaccine

A summary of the use of the GRADE approach in the development of ATAGI and Australian Immunisation Handbook recommendations on the use of MVA-BN (JYEENOS) in healthy adults for mpox prevention

## Background

- MVA-BN (JYNNEOS) was approved by the US FDA, UK MHRA and other regulatory bodies for use in adults aged ≥18 years. It is available for use in Australia under s18A (emergency use provision) of the Therapeutic Goods Act 1989.
- To respond quickly to the most recent mpox (previously known as monkeypox) multi-country outbreak in 2022, the Australian Technical Advisory Group on Immunisation (ATAGI) clinical guidance on vaccination against mpox was released in 2022.
- In 2023, ATAGI undertook a GRADE assessment (completed in August) to support the updated recommendations based on previous ATAGI clinical guidance to allow for informed recommendations on the ongoing use of MVA-BN (JYNNEOS) for mpox prevention in Australia.
- The Australian Immunisation Handbook mpox chapter has been updated to include current ATAGI recommendations on the use of MVA-BN (JYNNEOS) in risk populations for mpox prevention.

## Research questions

1. Should healthy adults who are at high risk of exposure to monkeypox virus use MVA-BN vaccine?

**Table 1: Population, Intervention, Comparator, Outcomes (PICO) – MVA-BN vs placebo, no vaccine or comparator arm, healthy adults aged 18 years and over to receive mpox vaccine**

| | |
|---|---|
| Population | Vaccinia naïve healthy adults age ≥18 years old |
| Intervention | MVA-BN (brand names: JYNNEOS, Imvanex and Imvamune): 2 subcutaneous doses (1-month interval) of $1\times10^8$ $TCID_{50}$ |
| Comparator | Placebo or no vaccine |
| Outcomes | *Critical*<br>• Serious adverse events<br>*Important*<br>• Percentage of participants with seroconversion (monkeypox virus neutralising antibody seroconversion rate) 28 days post vaccination<br>• Effectiveness<br>• Efficacy<br>• Local adverse events<br>• Systemic adverse events<br>• Myo/pericarditis (clinically confirmed) |

*Abbreviation:* $TCID_{50}$= 50% tissue culture infectious dose

## Literature search

A literature search was undertaken using the databases Medline (1946 to 2023 April 03) and Embase (1974 to 2023 March 31) to identify studies assessing immunogenicity, efficacy and/or safety outcomes of the MVA-BN in adults. Details of the search methods are presented in Appendix B.

The citations were included for review if they met the following criteria:

- *Study design*: Clinical trials (randomised and non-randomised)
- *Population*: Adults aged 18 years old and over
- *Intervention*: MVA-BN
- *Comparator*: Placebo or no vaccine
- *Outcomes*: Effectiveness, efficacy, immunogenicity, safety

The initial literature search retrieved 256 records, of which 11 publications from 10 clinical trials met the above pre-defined inclusion criteria after title and full-text screening. Among the included studies, two were randomised placebo-controlled trials and eight were clinical trials without an unvaccinated comparator arm (including five randomised and three non-randomised).

## Inclusion criteria and rationale

**Table 2: Rationale for PICO and inclusion criteria**

| PICO | Rationale |
|---|---|
| Study type<br><br>Clinical trials | Both randomised and non-randomised phase II or III clinical trials investigating MVA-BN were included due to insufficient data. No efficacy or effectiveness studies with clinical outcomes were identified.<br>Emerging evidence from preprints and observational studies were not included in the current GRADE assessment due to significant methodological flaws and considerable variations (e.g. retrospective design, selection bias, self-reported data collection, small sample size, different dosing regimens, etc.). |
| Population<br><br>Healthy adults | The included population was selected based on the availability of existing evidence. No clinical trials were available in high-risk groups that are currently recommended to receive mpox vaccine during the most recent outbreaks (2022 onwards). |
| Intervention<br><br>MVA-BN | In alignment with current Australian practice, only participants who received standard formulation, dose and route of MVA-BN were included (i.e. a liquid formulation for subcutaneous administration at a dose of $1\times10^8$ infectious units of MVA-BN virus in a volume of 0.5 mL, given by a 2-dose schedule 1 month apart). |
| Comparator<br><br>Placebo, no vaccine or no comparator | Clinical trials with a placebo as comparator were included as they are most relevant to the PICO. However, due to the very low number of eligible studies, clinical trials without an unvaccinated arm or that were non-randomised were also included. |
| Outcomes | Included outcomes as stated above in Table 1. No clinical trials were identified that included vaccine efficacy or effectiveness against clinical outcomes. |
| | Ranking of importance of each important or critical outcome discussed iteratively, reaching consensus with the full ATAGI committee. |
| | General framework (depending on outcomes measured in studies available):<br><br>*Critical*<br>• Serious adverse events<br>*Important*<br>• Percentage of participants with seroconversion (monkeypox virus neutralising antibody seroconversion rate) 28 days post vaccination<br>• Effectiveness<br>• Efficacy<br>• Local adverse events<br>• Systemic adverse events<br>• Myo/pericarditis (clinically confirmed)<br><br>Note: some outcomes may be missing in GRADE projects due to absence of data from available studies. Additional outcomes specifically reported in studies were included due to relevance. |

*Abbreviation*: MVA-BN=modified vaccinia Ankara – Bavarian Nordic.

## Risk of Bias assessment

Risk of Bias (RoB) was carried out on all included studies using the standard GRADE criteria. Two assessors independently undertook this analysis using the ROB 2 tool for assessing the included trials (Appendix A)

# Appendix A: Risk of Bias

**Table A1: Risk of bias assessment for clinical trial studies using RoB 2**

| Study | Outcome | Domain 1: Risk of bias arising from the randomisation process | Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Domain 3: Missing outcome data | Domain 4: Risk of bias in measurement of the outcome | Domain 5: Risk of bias in selection of the reported result | Overall risk of bias |
|---|---|---|---|---|---|---|---|
| von Krempelhuber (2010)[1] | Immunogenicity | Some concerns | Some concerns | Low | Low | Some concerns | Some concerns |
| | Safety | Some concerns | Some concerns | Low | Low | Some concerns | Some concerns |
| Frey (2013)[2] | Immunogenicity | Some concerns | High | High | Low | Some concerns | Some concerns |
| | Safety | Some concerns | High | High | Low | Some concerns | Some concerns |
| Greenberg (2013)[3] | Immunogenicity | High | High | Some concerns | Low | Some concerns | High |
| | Safety | High | High | Low | Some concerns | Some concerns | High |
| Frey (2014)[4] | Immunogenicity | Some concerns | Some concerns | Low | Low | Low | Low |
| | Safety | Some concerns | Some concerns | Some concerns | Low | Low | Some concerns |
| Frey (2015)[5] | Immunogenicity | Some concerns | Some concerns | Some concerns | Low | Low | Some concerns |
| | Safety | Some concerns | Some concerns | Some concerns | Low | Low | Some concerns |
| Greenberg (2015)[6] | Immunogenicity | High | High | Low | Low | Some concerns | High |
| | Safety | High | High | Low | Some concerns | Some concerns | High |
| Overton (2015)[7] | Immunogenicity | High | High | Low | Low | Some concerns | High |
| | Safety | High | High | Low | Some concerns | Some concerns | High |
| Zitzmann-Roth (2015)[8] | Safety | Some concerns | Low | Low | Low | Some concerns | Low |
| Jackson (2017)[9] | Immunogenicity | Low | High | Some concerns | Low | Some concerns | High |
| | Safety | Low | High | Low | Some concerns | Some concerns | Some concerns |
| Ilchmann (2022)[10] | Immunogenicity | Some concerns | Some concerns | Low | Low | Some concerns | Some concerns |
| Overton (2023)[11] | Immunogenicity | Low | Some concerns | Low | Low | Some concerns | Low |
| | Safety | Low | Some concerns | Low | Low | Some concerns | Low |

## Appendix B: Literature search strategy

**Table B1: MVA-BN vs placebo, no vaccine or comparator arm, healthy adults aged 18 years and over to receive mpox vaccine (as of 31.03.2023)**

| **MEDLINE** | **EMBASE** |
|---|---|
| Database: MEDLINE(R): All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946–2023 March 31> | Database: Embase: <1974 to 2023 March 31> |
| Search strategy: | Search strategy: |
| --- | --- |
| 1 exp Monkeypox/ (1523) | 1 exp monkeypox/ (2736) |
| 2 exp Monkeypox virus/ (978) | 2 exp Monkeypox virus/ (1489) |
| 3 monkeypox$.tw. (2789) | 3 monkeypox$.tw. (3081) |
| 4 mpox$.tw. (353) | 4 mpox$.tw. (327) |
| 5 mpx$.tw. (838) | 5 mpx$.tw. (1265) |
| 6 exp Smallpox/ (6135) | 6 exp smallpox/ (6475) |
| 7 exp Variola virus/ (2028) | 7 exp Smallpox virus/ (1440) |
| 8 exp Vaccinia virus/ (10870) | 8 exp Vaccinia virus/ (11710) |
| 9 smallpox$.tw. (7773) | 9 smallpox$.tw. (6290) |
| 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (22430) | 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (23139) |
| 11 exp Immunization/ (206968) | 11 exp immunization/ (364475) |
| 12 exp Immunization Programs/ (15984) | 12 exp vaccine/ (406658) |
| 13 exp Vaccines/ (274010) | 13 (immuni$ or vaccin$).tw. (786048) |
| 14 (immuni$ or vaccin$).tw. (655370) | 14 11 or 12 or 13 (930139) |
| 15 11 or 12 or 13 or 14 (755779) | 15 10 and 14 (16468) |
| 16 10 and 15 (15467) | 16 exp smallpox vaccine/ (4969) |
| 17 exp Smallpox Vaccine/ (3983) | 17 15 or 16 (17430) |
| 18 16 or 17 (16124) | 18 (modified adj3 vaccinia adj3 ankara adj3 (bavarian adj2 nordic$)).tw. (25) |
| 19 (modified adj3 vaccinia adj3 ankara adj3 (bavarian adj2 nordic$)).tw. (26) | 19 (mva adj3 (bavarian adj2 nordic$)).tw. (24) |
| 20 (mva adj3 (bavarian adj2 nordic$)).tw. (15) | 20 mva-bn$.tw. (154) |
| 21 mva-bn$.tw. (79) | 21 (live adj3 ("non replicat$" or non-replicat$ or nonreplicat$)).tw. (37) |
| 22 (live adj3 ("non replicat$" or non-replicat$ or nonreplicat$)).tw. (26) | 22 (replicat$ adj3 deficien$).tw. (3002) |
| | 23 18 or 19 or 20 or 21 or 22 (3193) |

| | |
|---|---|
| 23 (replicat$ adj3 deficien$).tw. (2451)<br>24 19 or 20 or 21 or 22 or 23 (2561)<br>25 18 and 24 (154)<br>26 (Imvanex$ or Imvamune$ or Jynneos$).tw. (69)<br>27 25 or 26 (202)<br>28 exp Immunogenicity, Vaccine/ (3264)<br>29 immunogen$.tw. (89987)<br>30 exp Antibody Formation/ (63543)<br>31 (antibod$ adj3 (respons$ or form$)).tw. (68972)<br>32 (immun$ adj3 (respon$ or protect$)).tw. (377940)<br>33 exp Treatment Outcome/ (1232969)<br>34 exp Vaccine Efficacy/ (703)<br>35 efficac$.tw. (1068769)<br>36 effective$.tw. (2467865)<br>37 exp Safety/ (88480)<br>38 exp Safety-Based Drug Withdrawals/ (416)<br>39 exp Product Surveillance, Postmarketing/ (18065)<br>40 exp Drug Evaluation/ (42051)<br>41 exp Population Surveillance/ (74369)<br>42 exp Adverse Drug Reaction Reporting Systems/ (8756)<br>43 (adverse adj3 (effect$ or event$)).tw. (452904)<br>44 (safe or safety or aefi or aesi).tw. (1002783)<br>45 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 (5270107)<br>46 27 and 45 (134)<br>47 exp animals/ not humans/ (5107928)<br>48 46 not 47 (98) | 24 17 and 23 (172)<br>25 (Imvanex$ or Imvamune$ or Jynneos$).tw. (189)<br>26 24 or 25 (332)<br>27 exp vaccine immunogenicity/ (6400)<br>28 immunogen$.tw. (120422)<br>29 exp antibody production/ (62187)<br>30 (antibod$ adj3 (respons$ or form$)).tw. (81297)<br>31 (immun$ adj3 (respon$ or protect$)).tw. (499194)<br>32 exp drug efficacy/ (1011542)<br>33 efficac$.tw. (1588377)<br>34 effective$.tw. (3257546)<br>35 exp drug safety/ (553663)<br>36 exp post marketing surveillance/ (39079)<br>37 exp drug surveillance program/ (26694)<br>38 exp adverse drug reaction/ (630746)<br>39 (adverse adj3 (effect$ or event$)).tw. (727754)<br>40 (safe or safety or aefi or aesi).tw. (1543283)<br>41 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 (6761783)<br>42 26 and 41 (215)<br>43 (exp animal/ or nonhuman/) not exp human/ (7123373)<br>44 42 not 43 (158) |

# References


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