



## ATAGI statement on the intradermal use of Imojev Japanese encephalitis vaccine

Version 1

22 December 2022

This statement should be read in conjunction with the existing ATAGI clinical guidance on Japanese encephalitis vaccines.

ATAGI has reviewed the evidence on the intradermal (ID) administration of Japanese encephalitis (JE) vaccines and considered the potential use of Imojev as a dose-sparing mechanism, in the context of the risk of future outbreaks, expanded eligibility in risk areas, and ongoing supply considerations.

### Recommendations

- ATAGI re-emphasises that use of either Imojev (0.5mL) delivered via the subcutaneous (SC) route, or JEspect delivered by the intramuscular (IM) route is optimal and preferred.
- Imojev (single dose) is preferred for non-pregnant healthy adults and children  $\geq 9$  months of age.
- JEspect (two-dose schedule) is the only vaccine suitable for pregnant women, children 2 months to  $< 9$  months of age, and people with immunocompromise.
- JEspect is acceptable if Imojev is not available.
- Intradermal administration of Imojev live Japanese encephalitis vaccine may be used as a dose-sparing strategy in settings where public health benefit outweighs potential risks, for example in outbreak risk populations where vaccine supply would otherwise be insufficient, as determined by State/Territory public health authorities (see [Table 1](#)). This recommendation is made based on limited available evidence.
- Currently, there are insufficient data to recommend routine ID use of Imojev over conventional SC use.
- Intradermal Imojev use as a dose-sparing strategy is **not** recommended for children  $\geq 9$  months to 18 years of age, due to the lack of safety and effectiveness data in this group.
- ATAGI's deliberations highlighted that comparative data on immunogenicity and vaccine effectiveness (including duration of immune response) are needed for ID versus SC administration.
- If public health authorities determine that ID use is indicated, ATAGI recommends jurisdictions use ID Imojev with reference to the following considerations:
  - Use 0.1mL single dose ID
  - Use only in non-pregnant, non-breastfeeding adults without immunocompromise
  - Use in settings where there is appropriate training and logistics for ID administration (see [Appendix A](#) for suggested training resources on ID administration, and [Appendix B](#) for multi-dose vial guidance)
  - Use where there is scope to follow up all vaccinated individuals clinically, in case emerging evidence indicates a booster dose is required for optimal protection following ID administration

- Follow-up studies are strongly encouraged, to address uncertainties around comparative vaccine effectiveness
- Provide patient information materials and seek informed consent, including advice to patients about the limited data on protection (including duration of protection), compared with use of SC route.
- Recommendations for the standard SC (Imojev) or intramuscular (JEspect/Ixiaro) use of JE vaccines have not changed: refer to [ATAGI clinical guidance](#).

**Table 1: Individuals who may be considered for intradermal Imojev as part of a dose-sparing strategy where public health benefit outweighs risk**

**\*Subcutaneous use of Imojev remains optimal and preferred.**

Population group	Consider intradermal Imojev?	Rationale
Healthy adults	Y	As part of a dose-sparing strategy where public health benefit outweighs risk, and vaccine supply would otherwise be insufficient (as determined by State/Territory authorities)
Pregnant women	N	Imojev contraindicated in pregnancy
Breastfeeding women	N	No available data on safety and vaccine effectiveness of ID use in this group
People with immunocompromise	N	Imojev contraindicated in immunocompromised people
Children aged < 2 months	N	Imojev not suitable for children <9 months
Children aged 2 months to <9 months	N	Imojev not suitable for children <9 months
Children aged ≥9 months to 18 years	N	No available data on safety and vaccine effectiveness of ID use in this group, recommend subcutaneous route

## Background

Since the start of the current Australian JE outbreak in 2021, there have been 42 human cases reported and seven resulting deaths<sup>1</sup>. It is anticipated that there may be further cases of JE in the coming 2022-2023 summer season given a range of environmental factors, including forecasting of above average rainfall<sup>2</sup>. Vaccination against JE has been a cornerstone of the public health response in affected states and

territories, and given the predictions for increased mosquito-borne risks, a number of jurisdictions have expanded eligibility to a range of risk groups within specified geographical areas<sup>3-6</sup>.

Expanded eligibility and subsequent demand are likely to contribute to existing supply pressures<sup>7</sup> for Imojev and JEspect (also known as Ixiaro), the two JE vaccines registered in Australia. In this context, ATAGI has reviewed the evidence for fractional dosing via the intradermal route as a dose-sparing strategy.

A range of other viral vaccines (including monkeypox and yellow fever) have been widely used intradermally as a dose-sparing strategy<sup>8-11</sup>, and evidence for fractional intradermal administration in these vaccines has demonstrated similar immune response compared to standard-dose SC administration<sup>12-14</sup>.

## Vaccine effectiveness

### Immunogenicity

A recent single-arm clinical study was conducted in 51 healthy adults to investigate the ID use of a single fractional dose of 0.1mL (1/5 of standard dose) JE live attenuated chimeric vaccine (Imojev)<sup>15</sup>. All participants seroconverted at day 28 and remained seropositive at day 56. At day 28, five participants (10%) presented neutralising antibody titre levels >40, 24 (48%) titre levels >160, and 21 (42%) titre levels >640. Between days 28 and 56, antibody levels declined in 22 participants (44%), remained stable in 26 (52%), and increased in two (4%).

Immunogenicity data comparing single or multiple fractional ID doses of inactivated mouse-brain derived Nakayama strain JE vaccine (JE-VAX) to standard SC administration using 0.5mL are available from two randomised controlled trials<sup>16,17</sup>. A 1993 study in Thailand of 224 participants administering JE-VAX reported no difference in seroconversion between standard SC (1.0mL) and dual/triple site (two-site, total dose 0.2mL and three-site, total dose 0.3mL) ID vaccination methods. However, single (one site, 0.1mL) ID vaccination was less effective in stimulating seroconversion, though authors note the study was underpowered to achieve statistical significance at the 95% confidence level<sup>16</sup>.

An Australian study of 408 military personnel compared the immunogenicity of JE-VAX between single-site (0.1mL) and dual-site (total dose 0.2mL) fractional ID administration and standard SC administration<sup>17</sup>. It reported that seroconversion rates and levels of neutralising antibody titres were similar in the dual-site ID group compared to the SC injection group, but significantly lower in the single ID group. One year post-vaccination, 51% remained seropositive in the SC group, compared to 49% in the dual ID group.

Imojev JE vaccine is based on a yellow fever vaccine virus backbone (strain 17D-204), developed by replacing the genes coding two structural proteins of yellow fever 17D virus with that of a JE SA14-14-2 strain. Intradermal administration of a live attenuated 17D yellow fever vaccine (Stamaril) was investigated in a study comparing fractional ID dose (1/5th; 0.1mL) to the standard SC dose in 175 adults<sup>12</sup>. With the fractional ID dose, seroprotection (defined as 80% virus neutralisation) was achieved in all study participants; this was no different to the standard SC dose. YF-17D and chimeric JEV share similarities in terms of antigenic determinants (i.e. non-structural coding sequences), and ID use of YF vaccines may provide insights for JE in the absence of ample direct evidence.

One animal study from 2005 comparing SC and ID administration of Chimerivax JE vaccine in monkeys reported a greater GMT in the ID group than the SC group at days 31 and 61, contrary to the findings in humans<sup>18</sup>. No safety issues were identified.

## Duration of protection

The duration of protection from ID use of existing JE vaccines is currently unknown. A possible decreased duration of protection was shown in one study following the ID injection of Imojev, where neutralisation titres declined in 44% of the participants after 56 days post-vaccination<sup>15</sup>. Another study showed a trend of decreased neutralisation titres 90 days post-vaccination of JE-VAX compared to 30 days, but the differences were minor and not statistically significant<sup>16</sup>.

Duration of protection has been examined for fractional ID dosing of the live attenuated 17D yellow fever vaccine (Stamaril), with one year the longest follow-up. At 52 weeks post vaccination, the neutralising antibody titres were statistically no different between the intradermal and subcutaneous vaccination groups<sup>12</sup>.

## Use in key risk groups

There are no available immunogenicity or safety data for ID use of JE vaccines in key risk groups including children, pregnant women, and people with immunocompromise. Further studies are required to characterise the risks and benefits of ID use in special risk groups.

## Safety

There are limited studies directly examining safety or immunogenicity of intradermal use of JE vaccines in healthy adults, and none in immunocompromised people, children or pregnant women (noting that live JE vaccines are contraindicated altogether in pregnant women and immunocompromised people and for children <9-months of age).

Across two key studies that reported safety outcomes in ID use of live JE vaccines (Imojev and JE-VAX), a similar proportion of participants (around 15-20%) reported at least one adverse event following vaccination<sup>15,17</sup>. The most frequently reported adverse events were local reactions including redness, swelling and injection site pain. Systematic adverse events such as fatigue, headache and abdominal pain were also reported. None of the reported adverse events required medical attention. Only one study directly compared safety outcomes between SC and fractional ID use of the JE vaccine JE-VAX; safety profiles were largely comparable except for more arm pain in one of the ID-dose groups<sup>17</sup>.

During 2022, ID administration of JYNNEOS monkeypox (mpox) vaccine was deployed in Australia as a dose-sparing strategy. To date, safety surveillance data have reported no serious safety issues and only a minimal increase in local adverse events such as itching or swelling, compared to SC use<sup>19</sup>. As with any intradermally-administered vaccine, there is potential for inadvertent SC injection of Imojev, but Australian experience with JYNNEOS suggests this is an uncommon event.

## Key areas of uncertainty

ATAGI will continue to monitor the evidence on JE vaccines and will review the emerging epidemiology in Australia, including any future outbreaks during the 2022/3 and 2023/4 summer seasons. ATAGI may revise its recommendations as further evidence accumulates on the ID use of JE vaccines, including:

- Evidence on safety and effectiveness of intradermal Imojev vaccine use, especially in key risk groups such as children and adolescents aged > 9 months to ≤ 18 years of age.

- Note that pregnant women and people with immunocompromise are [recommended to receive the full-dose intramuscular \(IM\) inactivated \(JEspect\) vaccine](#).
- Optimal dose for fractional ID use in terms of immunogenicity.
- Duration of protection from fractional ID use (noting the potential need for revaccination if ID use is found to be inferior to SC use).

## Summary

In the limited available literature, the safety profile of fractional ID use of JE vaccines in adults appears comparable to that of conventional SC use. Immunogenicity data from several available studies demonstrated equivalent short-term seroconversion rates and levels of neutralising antibodies in ID administration, compared to full-dose SC administration. However, considerable uncertainty remains around immune response following ID administration of JE vaccines.

Based on available safety data, short-term immunogenicity data and precedent from other vaccines, there is evidence to suggest a potential role for the fractional ID use of Imojev in healthy adult populations, where public health benefit outweighs risk. In the context of supply constraints, relevant settings for using ID Imojev as a dose-sparing strategy could include significant JE outbreaks, as defined by State/Territory public health authorities. However, there are insufficient available data on vaccine effectiveness to currently recommend ID use of Imojev over conventional SC use in a non-outbreak risk setting.

There is an urgent need to build the evidence base on the fractional ID use of currently available JE vaccines, including studies directly comparing safety and immunogenicity of SC to ID Imojev use, studies examining duration of antibody response, and studies including children, pregnant women and people with immunocompromise. ATAGI is aware that there are planned studies on ID use of Imojev and expects further information to become available before the 2023/24 summer season.

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## Appendix A Training resources for intradermal vaccine administration

There are no existing training materials on the ID use of Imojev, but the following are resources for ID administration of JYNNEOS mpox (monkeypox) vaccine that feature relevant technical advice. Please note that they are suggested references, and not material formally endorsed by ATAGI.

- [Victorian monkeypox vaccination program](#) (See: Vaccinations procedures section – preparation for intradermal administration, considerations for multi-use vials, intradermal administration technique on pages 20-27, Intradermal injection skills and competencies checklist on pages 52-53)
- [Victorian Immunisation e-Learning \(Monkeypox vaccination course\)](#) – See: Intradermal administration of JYNNEOS vaccine section)
- Australian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) [MPX Vaccination Training Module](#) (See: Administering the vaccination section – Intradermal injections).

## Appendix B Guidance for use of subcutaneous-dose vaccine vials as multi-dose vials for intradermal administration.

Imojev vaccine is supplied as single subcutaneous-dose vials. With fractional (using a portion of a standard dose) intradermal dosing, this means that the original single-dose vials are being used for multiple doses.

Appendix Table 1 provides three options of procedures that can be followed to optimise safety for both the patient and the immunisation provider.

Due to the small volumes required for each intradermal dose, the use of low-deadspace syringes or low-deadspace needles is recommended to facilitate five 0.1mL doses to be withdrawn from each vial.

**Appendix Table 1 – Procedures for drawing up multiple intradermal doses from a standard vial**

Step	Method for extraction of a single dose at a time	Method for extraction of multiple doses using different needles for drawing up and administration	Method for extraction of multiple doses using the same needle for drawing up and administration
	<p>This method is recommended whenever one or more doses will be extracted from a vial and the remaining contents of the vial will be stored.</p> <p>Use an aseptic technique throughout this procedure.</p>	<p>This method is only appropriate where multiple doses from a vial are to be drawn up in immediate succession for administration within a single vaccination session.</p> <p>Use an aseptic technique throughout this procedure.</p> <p>Vials should never be stored with a drawing up needle attached.</p>	<p>This method uses the same needle to draw up and administer a vaccine dose.</p> <p>Use an aseptic technique throughout this procedure.</p>



Step	Method for extraction of a single dose at a time	Method for extraction of multiple doses using different needles for drawing up and administration	Method for extraction of multiple doses using the same needle for drawing up and administration
A	Attach a sterile 26-27 gauge drawing up needle to a sterile syringe, and insert the needle through the bung into the vial.	Attach a sterile 26-27 gauge drawing up needle to a sterile syringe, and insert the needle through the bung into the vial.	Attach a sterile 26-27 gauge injection needle to a sterile syringe, and insert the needle through the bung into the vial.
B	Draw up 0.1mL for a single dose. Do not touch the shaft of the needle and avoid moving the needle in and out of the vial.	Draw up 0.1mL for a single dose. Do not touch the shaft of the needle and avoid moving the needle in and out of the vial.	Draw up the required volume for a single dose. Do not touch the shaft of the needle and avoid moving the needle in and out of the vial.
C	Remove the filled syringe with the drawing up needle attached. Do not leave the drawing up needle in the vial. Avoid touching the top of the vial.	Remove the filled syringe from the drawing up needle, leaving the drawing up needle in the bung.	Remove the filled syringe with the needle attached. Avoid touching the top of the vial.
D	Detach the filled syringe and attach a new sterile 26-27 gauge injection needle.	Attach a new sterile 26-27 gauge injection needle to the filled syringe, ready for administration to the patient. Without delay or distraction, attach a new sterile syringe to the drawing up needle to draw up each dose.  Attach a new sterile 26-27 gauge injection needle to each filled syringe.	If doses are not going to be administered immediately, the needle must be resheathed (using safe aseptic technique).  Repeat the procedure for all required doses.
E	Administer the dose as soon as possible after drawing up.	The prepared dose can be administered immediately or must be used as soon as practical for the next recipient. Doses drawn up	The prepared dose can be administered immediately or must be used as soon as practical for the next recipient. Doses drawn up

Step	Method for extraction of a single dose at a time	Method for extraction of multiple doses using different needles for drawing up and administration	Method for extraction of multiple doses using the same needle for drawing up and administration
		<p>into a syringe must ideally be used within 1h if kept at room temperature, or 8h if stored at 2-8°C.</p> <p>Until ready to be administered, store any prepared syringes at the appropriate temperature as per product information. This includes storing in a suitably sized, clean container. Label the container clearly with the date and time doses were drawn, the name of the person who prepared the doses, vaccine name, age range, vial batch number, vial identifier (if available) and expiry time of drawn doses. Discard any filled syringe where there is suspicion that contamination or a sterility breach has occurred.</p> <p>Any unused doses that have been withdrawn into a syringe must be discarded after 8 hours, even if stored at 2-8°C, due to potential infection control concerns.</p>	<p>into a syringe must ideally be used within 1h if kept at room temperature, or 8h if stored at 2-8°C.</p> <p>Until ready to be administered, store any prepared syringes at the appropriate temperature as per product information. This includes storing in a suitably sized, clean container. Label the container clearly with the date and time doses were drawn, the name of the person who prepared the doses, vaccine name, age range, vial batch number, vial identifier (if available) and expiry time of drawn doses. Discard any filled syringe where there is suspicion that contamination or a sterility breach has occurred.</p> <p>Any unused doses that have been withdrawn into a syringe must be discarded after 8 hours, even if stored at 2-8°C, due to potential infection control concerns.</p>