

# Summary of Evidence on the Administration of Multiple Injectable Vaccines in Infants during a Single Visit: Safety, Immunogenicity, and Vaccine Administration Practices

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# Background

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- Guidance on administration of multiple injectable vaccines **in a single visit**
  - Evidence on immunogenicity
  - Evidence on safety
  - Administration practices
  - Programmatic issues

# Systematic Review for Evidence: DTwP-HepB-Hib, PCV, IPV

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## 1. Immunogenicity:

- Non-inferiority of giving two or more injections in the same limb compared to administration in different limbs.

## 2. Safety:

- Adverse events from multiple injections in a single visit.

## 3. Administration:

- Recommendation of giving two injections 2.5 cm apart.
- Deltoid use for intramuscular (IM) injections in infants.
- IM versus the subcutaneous (SC) routes of administration.

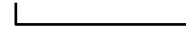
## 4. Programmatic:

- Preparation of multiple injections for a single visit.

# Methods

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- Peer literature search
  - Medline and Embase
- Grey literature
  - Country guidelines
  - WHO position papers
- Comments from immunology experts
- Inclusion criteria:
  - Primary study or literature review
  - Multiple injections
  - Infant vaccination visit
  - IM or SC administration routes
  - Vaccines: PCV, IPV, DTwP-HepB-Hib



# Summary of Evidence

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# Study Settings

WHO Region	Number of Studies (%)
AMR	49 (47%)
EUR	19 (18%)
WPR	12 (11%)
AFR	6 (6%)
SEAR	3 (3%)
EMR	1 (1%)
Multiple	3 (3%)
Literature/Systematic Reviews	12 (11%)

\*Publication dates ranged from 1985 to 2014.

# Immunogenicity of Multiple Injections:

## 1. Non-inferiority comparisons

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- Focus vaccines are known to be highly immunogenic when given in same visit -- many immunogenicity studies
  - PCV licensure studies had pentavalent co-administration
  - IPV immunogenicity studies with DTaP, Hib, or HepB
- Specific comparisons for this review:
  - Vaccines administered in separate visits versus same visit
  - Vaccines administered in same limb versus different limbs
- Findings:
  - No articles identified
  - No additional evidence from immunology experts

# Safety:

## 2. Adverse events and multiple injections

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45 articles reviewed

Vaccine type	Number
DTP-containing*	17
PCV-containing	15
DTP-HBV-Hib	6
IPV	5
Other	2

- Findings

- Simultaneous administration with other vaccines well-tolerated in infants (PCV, IPV, DTwP/pentavalent)
- Variety of adverse events following administration of different combinations of vaccines when co-administered in one visit
  - No patterns identified for vaccines relevant to review

*\*excludes DTP-HBV-Hib (pentavalent) vaccine*



# Administration Practices:

## 3. Recommendation for 2.5 cm spacing

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- Official guidance reviewed
  - USA, Canada, Australia
  - WHO
- Country guidance findings:
  - Separate injections by at least 2.5 cm
  - No studies cited for recommendation
  - Rationale for recommendation
    - Distance allows for local reactions to be differentiated by vaccine
- No additional guidance from immunology experts

# Administration Practices:

## 4. Use of deltoid for i.m. injections

- Findings

- Deltoid not well-developed in infants for i.m. injection
- Variable guidance on suitable age to use deltoid muscle
- Vastus lateralis (thigh) and ventrogluteal (hip) site recommended for infant i.m. injection – with thigh most commonly used
- Thigh or hip site: equal/more tolerability and equal immunogenicity as deltoid

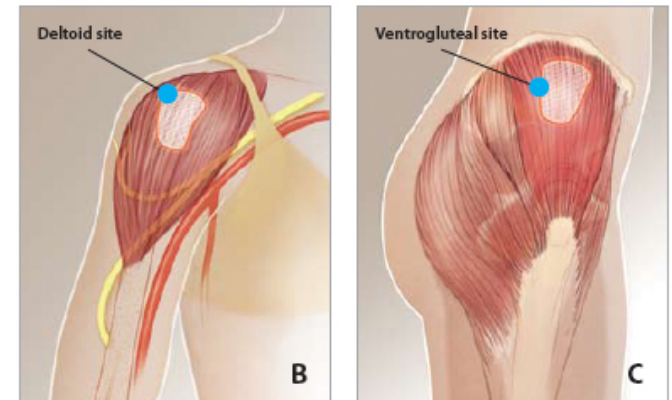
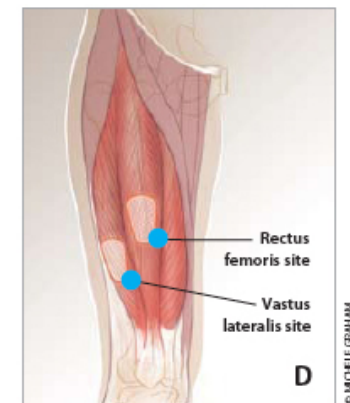


FIGURE 1B, C, D. Potential sites for intramuscular injection: Deltoid, ventrogluteal, rectus femoris, and vastus lateralis sites



Rectus femoris, and vastus lateralis sites

# Administration Practices:

## 5. Intramuscular versus subcutaneous routes

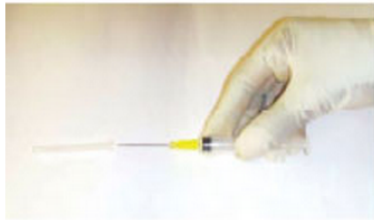
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- Findings:
  - Immunogenicity: SC is non-inferior to IM
  - Reactogenicity: SC > IM
  - Intramuscular route preferred
  - Subcutaneous route acceptable alternative

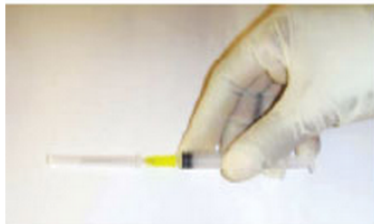
# Programmatic Issues:

## 6. Preparation of multiple vaccines

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**STEP 1**  
Place the cap on a flat surface, then remove your hand from the cap.



**STEP 2**  
With one hand, hold the syringe and use the needle to 'scoop up' the cap.



**STEP 3**  
When the cap covers the needle completely, use the other hand to secure the cap on the needle hub. Be careful to handle the cap at the bottom only.

- Reviewed country and medical organizations' documentation
- Findings
  - Inconsistent guidance on preparation techniques:
    - Prepare all vaccines for same child, then administer;
    - Prepare and administer each vaccine separately;
- Reviewed country and medical organizations' documentation
- Findings
  - Inconsistent guidance on preparation techniques:

# Existing WHO Recommendations:

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- All WHO Vaccine Position papers reviewed
- Findings:
  - Simultaneous administration with other vaccines recommended for Hib; whole-cell Pertussis/acellular Pertussis; PCV10/PCV13; IPV
- No guidance for tetanus or diphtheria vaccines
- No safety concerns listed for vaccines with available guidance

# Key Conclusions (1)

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- **Immunogenicity of multiple injections:**

- Co-administration not a concern
- Unknown preference for same or different limbs, by antigen
- Unknown impact on immunogenicity if separate visits

- **Safety of multiple injections:**

- Evidence supports minimal adverse events for reviewed vaccines
  - DTP-HepB-Hib vaccine can be given in one thigh and IPV, PCV in other thigh
- But lack of safety/immunogenicity data on:
  - Specific limbs of administration for DTP-HepB-Hib vaccine, IPV, and PCV in a single visit

# Key Conclusions (2)

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- **Distance between injections:**
  - Study-based evidence lacking on 2.5 cm guidance
  - 2.5 cm likely allows for distinguishing localized adverse events
- **Intramuscular versus subcutaneous routes:**
  - IPV: Safe and effective via IM or SC route
  - Intramuscular route less reactogenic for inactivated vaccines
- **Site of IM injections:**
  - Evidence lacking on risks/benefits of site selection
  - Vastus lateralis (thigh) is a viable site; ventrogluteal (hip) is acceptable alternative – thigh is most commonly used
  - Deltoid also a viable site; use will depend on muscle mass of individual

# Key Conclusions (3)

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- **Preparation for multiple injection visit:**
  - Little evidence on best approaches
  - Potential viable approach:
    - Draw up vaccines in clean, designated area
    - Cover clean needle with cap using 1-hand scoop technique
    - Administer vaccinations in quick succession
    - Do not recap syringe after use



# Considerations

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- **Systematic review revealed limitations of data and evidence on administration of multiple injections among infants**
  - No head to head trials (co-administration vs. separate visits, or same limb vs. different limbs) for:
    - immunogenicity or adverse events;
    - administration approaches;
    - programmatic best practices.

# Acknowledgements

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Thank you

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# Summary of Evidence:

Additional information on IPV administration:

- **From *Vaccines*:**

- IPV may be given SC or IM per manufacturer's information and there are no clinical trials on the relative immunogenicity of one versus the other
- IPV is more frequently administered in a combination vaccine, and this has led IPV to almost exclusively be administered via the IM route even when it is administered without other vaccines

IPV Manufacturer	Dose Volume	Site of administration for infants	Route of administration
Sanofi Pasteur (IPOL)	0.5 mL	Mid-lateral aspect of thigh	IM or SC
Bilthoven Biologicals	0.5 mL	NA	IM or SC
Serum Institute of India (Poliovac-PFS)	0.5 mL	Mid-lateral aspect of thigh	IM or SC
GSK (Poliorix)	0.5 mL	Anterolateral aspect of thigh	IM
Statens Serum Institut	0.5 mL	NA	IM or SC
Panacea Biotec	0.5 mL	Lateral aspect of mid-thigh	IM