



# The Effect of Combination Vaccines on the Vaccine Schedule

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# Objectives

At the conclusion of this session, participants will be able to:

- Identify recent combination vaccines that have been made available to the clinical setting
- Recognize advantages and challenges of combination vaccines to make informed decisions when selecting vaccines for clinic practice
- Describe issues clinicians must consider related to the use of combination vaccines
- Summarize the role combination vaccines can make in reducing pain and vaccine hesitancy

# Disclosure

- As a recent voting member and current liaison of the Advisory Committee on Immunization Practices, personal honoraria are not accepted for this or any talk
- Current board member of NFID
- Speaking honoraria for this talk donated to NFID
- Brand names may be used for reasons of clarification not as a product endorsement

# Definition of Combination Vaccine

- An FDA licensed product whose components can be equally divided into independently available routine vaccines that prevent multiple diseases or multiple strains of the same disease
- End-users should NOT combine separate vaccines into the same syringe to administer together. Safety, immunogenicity, and effectiveness of such unlicensed combinations are unknown

# FDA Licensed Combination Vaccines

- Hib-Hep B Comvax<sup>®</sup> 1997
- DTaP/Hib TriHIBit<sup>®</sup> 1996
- HepA-HepB Twinrix<sup>®</sup> 2001
- DTaP-HepB-IPV Pediarix<sup>®</sup> 2002
- MMRV ProQuad<sup>®</sup> 2005
- DTaP-IPV Kinrix<sup>®</sup> 2008
- DTaP-IPV/Hib Pentacel<sup>®</sup> 2008
- Hib-MenCY MenHibrix 2012

# CDC Parent Education

## INFORMATION FOR PARENTS

### Combination Vaccines

Last updated April 2014

**Combination vaccines reduce the number of shots your child needs while protecting against several serious diseases.**

#### Fewer Shots—Same Protection

Combination vaccines take two or more vaccines that could be given individually and put them into one shot. Children get the same protection as they do from

The measles, mumps, and rubella vaccine (MMR) and diphtheria, tetanus, and pertussis vaccine (DTaP) each protect your child against three diseases. However, these two vaccines are not considered true combination vaccines because in the United States, you cannot get separate vaccines for all of the diseases that MMR and DTaP protect against.

#### Some examples of common combination vaccines for children are:

- Comvax, which combines Hib and Hep B
- Twinrix, which combines Hep A and Hep B

# Current Considerations

- The current immunization schedule could create a clinic visit where a child may receive 7 separate injections
- Example @ 15 months:  
MMR + DTAP + PCV + Hib + varicella + Hep A + influenza
- Combination vaccines are seen as a method of reducing the number of injections while providing protection against vaccine-preventable diseases and promoting return to clinic visits



# Do We Explain the Immune System Well Enough?



# “Too Many, Too Soon, Too Weak”

*Deadly Choices. How the Anti-Vaccine Movement Threatens Us All*” by Paul A. Offit, MD,  
Basic Books, 2011, p 173

- Teach parents early about the power of the human immune system
- While the number and combination of vaccines has gone up, the unique immunological challenges has gone down
- Smallpox alone had 200 viral proteins
- 14 vaccines used today have 160 viral and bacterial proteins and carbohydrates that stimulate the immune system
- Newborns manage 100 trillion bacteria in their nose, intestine, and skin with huge quantities of antibodies made daily for protection

# Challenges to Combination Vaccines will be Discussed

- Vaccine safety and determining which antigen may be causing a reaction
- Practical issues of interchangeability exist with patients moving to different practices
- Supply changes forcing revised product recommendations
- Staff education
- Documentation
- Errors

# Combination Vaccines Statements

## General Recommendations on Immunization

- **Original** 1999 statement: *The use of combination vaccine is preferred over separate injections of their equivalent component vaccines...*  
MMWR Vol 48/No RR-5, May 14, 1999
- **Current** 2011 statement:  
*The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Considerations should include provider assessment\*, patient preference, and the potential for adverse events.*
- *\*Provider assessment should include the number of injections, vaccine availability, likelihood of improved coverage, likelihood of patient return, and storage and cost consideration.*

MMWR, January 28, 2011; 60(RR02):1-60

# Combination Vaccines for Childhood Immunization: The following major statements were reviewed by ACIP Combination Workgroup

- Combination vaccines should be used to minimize the number of injections children receive
  - Practical for starting immunization series for children behind schedule
- Extra doses of vaccine antigens are justified when:
  - Products that contain only the needed antigens are not readily available or would result in extra injection
  - Potential benefits to the child outweigh the risk of adverse events associated with the extra antigen

*General Recommendations on Immunization*  
Source: MMWR, January 28, 2011; 60(RR02):1-60

# Combination Vaccines for Childhood Immunization: The following major statements were reviewed by ACIP Combination Workgroup

- The benefits and risks of administering the combination vaccine with an unneeded antigen should be compared
- The reactogenicity of the inactivated vaccine must be considered in balancing the benefits and risks of extra doses (risk of hypersensitivity reactions after diphtheria and tetanus-toxoid containing vaccines such as DTaP-Hib, DT)
- Conjugate vaccine carrier proteins: “administering large amounts of tetanus toxoid carrier protein simultaneously with PRPT- conjugate vaccine has been associated with a reduction in the response to PRP”

General Recommendations on Immunization  
Source: MMWR, January 28, 2011; 60(RR02):1-60

# Additional Topics Identified by the Working Group

- Impact of using combination vaccines on immunization schedule
- Programmatic, administrative, and financial “burden” on private providers in the current vaccine market
- Expressing the level of preference of combination vaccines vs. single-antigen ones
- Identify circumstances, if any, when single-antigen vaccines should be strongly considered, considered, or preferred

# Disadvantages of Combination Vaccines

- Adverse events may occur more frequently compared to separate antigens at same visit
  - CDC. Recommendations from the Advisory Committee on Immunization Practices (ACIP) Regarding Administration of Combination MMRV Vaccine. MMWR 2008; 57: 258-260.
- Multiple providers with various products causes confusion when patient changes clinics
- Reduced immunogenicity of one or more components
- Shortened shelf life
- Complicated manufacturing processes
- Cost issues vary due to direct, indirect costs, delayed vs. missed vaccinations

# Advantages of Combination Vaccines

- Improved coverage rates
  - Happe LE, Lunacsek OI, Kruzikas DT, et al. Impact of a Pentavalent Combination Vaccine on Immunization Timeliness in a State Medicaid Population. *Pediatric Infect Dis J.* 2009; 28:98-101
- Parents and providers are uncomfortable with multiple injections at a single visit
  - Kuppermann M, Nease RF, Ackerson LM, et al. Parents' preferences for outcomes associated with childhood vaccinations. *Pediatric Infect Dis J.* 2000;19:129-133.
- Improving timely coverage for those delayed
- Reducing shipping cost
- Reducing stocking space
- Reducing cost for extra visits due to deferral
- Facilitating addition of new vaccines into the already crowded immunization schedule

# The Role Pain Plays



- Confidence in the necessity of vaccinations is high among most parents
- But concerns about safety (short and long term) is high too
- Number one concern is PAIN!
- Increased number of injections = increased stress = perceived as a higher level risk
  - Kennedy, A. et al Vaccine Attitudes, Concerns, and Information Sources Reported by Parents of Young Children: Results From the 2009 HealthStyles Survey *Pediatrics* Vol 127, Supplement 1, May, 2011

# Reducing the Pain of Childhood Vaccination: An Evidence-Based Clinical Practice Guideline

- Vaccines: Most common source of iatrogenic pain
- Pain is a source of distress for child, parent, vaccinator
- If unaddressed, leads to pre-procedure anxiety, needle phobia, lack of adherence to the vaccine schedule, avoidance of seeking healthcare
- Positive vaccine experiences promote trust in HCPs
- Simple, cost-effective, evidence-based strategies are available to reduce pain
- Combining the 3 P's provides best result (physical, psychological, and pharmacological)

CMAJ December 14, 2010 vol. 182 no. 18 First published  
November 22, 2010, doi: 10.1503/cmaj.101720

# Address Pain Management

## Reducing Vaccine Injection Pain in Children A Guide for Health Care Providers

### Preparation:

- Review this evidence-based guide
- Provide parent/caregiver with information and tools
- Discuss pain management strategies

### Procedure:

Combine strategies to improve pain relief



**HELP**  
Eliminate Pain  
**inKids**

Taddio et al Reducing the pain of childhood vaccination: an evidence based clinical guideline CMAJ 2010.

Ipp and Taddio. Paediatr Child Health 2011;16:541-543

Brighton Collaboration. Immunization site Pain... Vaccine 2012;30:4558-77

**Children's**  
Hospitals and Clinics  
of Minnesota

**National  
Foundation for  
Infectious  
Diseases**

# Pharmacologic Considerations

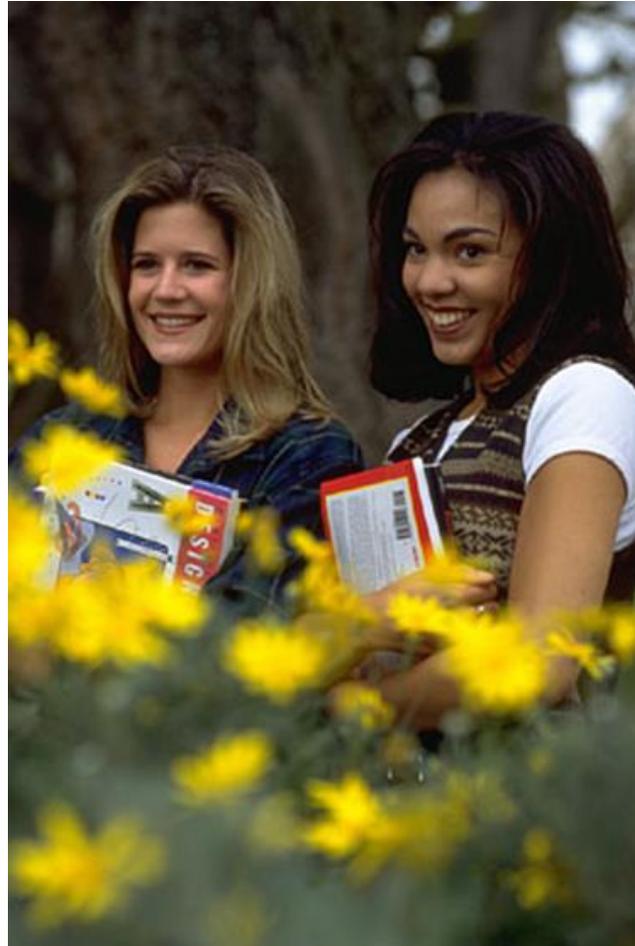
## Canadian Institutes of Health Study on Vaccine Pain

CMAJ December 14, 2010 vol. 182 no. 18 First published November 22, 2010, doi: 10.1503/cmaj.101720

- Topical anesthetics are shown to reduce pain from vaccines (e.g., EMLA or Ela-max)
- Topical anesthetics do not reduce immunogenicity in MMR, DTaP, polio, Hib, and Hepatitis B
- Further studies are needed on the immunogenicity effect from EMLA on other childhood vaccines
- Oral analgesics at the time of vaccination did reduce fever, did not significantly reduce pain, and may interrupt immunogenicity of common childhood vaccines. More study needed.

Lancet. 2009 Oct 17;374(9698):1339-50. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials., [Prymula R](#) et al.

# Breaking Down the Issues



# Issue of Safety

## Emphasize Ongoing Monitoring

Many ways that vaccines are monitored on an ongoing basis:

- Vaccine Safety Datalink (large HMO data analysis)
- VAERS (Vaccine Adverse Event Reporting System through the CDC & FDA, relies on providers)
- CISA centers (6 centers for Clinical Immunization Safety Assessments)
- Ongoing post-marketing surveillance by manufacturers

# MMRV and Febrile Seizures

- Presented at Feb '09 ACIP, two separate studies (VSD and Merck post-licensure studies) confirm association between first dose of MMRV and increased risk for febrile seizures
- 1 in every 2,600 children 12-23 months within 1<sup>st</sup> 2 weeks after vaccination
- 4-5 cases of febrile seizures per 10,000 doses compared to MMR first dose
- Preference for combination vaccines removed from general recommendations
- Practices should weigh the benefits of fewer injections against the uncommon risk for febrile seizures

Pediatrics. Published online June 28, 2010

# Revised MMRV Recommendations

## Recommendations for use of MMRV vaccine are as follows:

- Routinely recommended ages for measles, mumps, rubella, and varicella vaccination continue to be age 12 through 15 months for the first dose and age 4 through 6 years for the second dose.
- For the first dose of measles, mumps, rubella, and varicella vaccines at age 12 through 47 months, providers may use either measles, mumps, and rubella (MMR) vaccine and varicella vaccine or MMRV vaccine. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers.
- Unless the parent or caregiver expresses a preference for MMRV vaccine, CDC recommends that providers administer MMR vaccine and varicella vaccine for the first dose in this age group.
- For the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months through 12 years) and for the first dose at age 48 months and older, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and varicella vaccine).
- A personal or family (i.e., sibling or parent) history of seizures of any etiology (i.e., cause) is a precaution for MMRV vaccination, and such children generally should be vaccinated with MMR vaccine and varicella vaccine.

# MMRV Use

Vaccine, Ackerson, BK. Et al. Feb 7, 2014 Association of the Use of MMRV in infants by pediatric infectious disease specialists with that of other affiliated specialists

- Kaiser Permanente Research
- 30,017 children - May, 2010-April, 2011
- What parent, provider, or facility characteristics impact the use of MMRV?
- 10.2% received MMRV at dose 1
- 89.8% received MMR + Var dose 1
- More likely to use MMRV
  - if non-compliant with vaccines at age 1
  - if Peds ID gave MMRV other providers did too
  - Most providers followed ACIP recommendations



# Issues of Interchangeability



- FDA generally licenses a combination vaccine based on safety and efficacy that are “non-inferior”/comparable with or equal to single antigen products previously licensed
- Products from same manufacturer may be used interchangeably to continue vaccine series
- Similar vaccines made by different manufacturers have been considered interchangeable by most experts, although data on effects are limited
  - *Red Book 28<sup>th</sup> Edition, 2009, p. 32*
- ACIP or AAP interchangeability from different manufacturers include dip, tet toxoids, hep A, Hep B for infants, and rabies
- Not interchangeable is the 2<sup>nd</sup> dose Hep B for teens (if teen started on 3-dose or 2-dose Hep B should finish and vice versa)
  - *Red Book 28<sup>th</sup> Edition, 2009, p. 33*

# Issues of Extra Doses

- Administering extra antigens in a combination vaccine is often permissible if it keeps the child on schedule and reduces the number of injections
- May be justified when products are not readily available (extra Hep B dose to catch up Hib)
- Consider potential benefits over risk
- Minimum intervals of individual antigens should be followed to reduce risk of adverse event
  - MMWR 2006;55(RR-3): 1-41
- Giving an extra live vaccine to an immunocompetent person has not shown increased adverse events
- Extra inactivated vaccines can cause increased local reactogenicity; can increase risk of hypersensitivity reactions
  - MMWR 2006;55(RR-3): 1-41

# Issues of Vaccine Supply

- Providers should stock sufficient quantities of combination and monovalent vaccines to keep kids on schedule
- Stocking all products is not necessary
- Stocking a consistent, limited supply of products has the advantages of
  - Reduced staff confusion
  - Decreased patient safety accidents
  - Minimal waste due to expiration
  - Decreased storage capacity needs
  - Decreased administrative overhead in accounting, purchasing, and handling

# Issues of Reimbursement

- Some Medicaid plans are equalizing administration fees for combination and single vaccines attempting to remove financial disincentives *TX, MO, MS Medicaid programs 2/11/08*
- Combination vaccines have the potential for increased and decreased costs
- Considerations include:
  - Cost of the vaccine(s)
  - Direct and indirect costs of extra injections
  - Delayed or missed vaccination
  - Additional handling
  - Additional storage

# Issues of Reimbursement

- Impact on reimbursement policies:

“Administering extra antigens contained in a combination vaccine, when justified..., is acceptable practice and should be reimbursed on the patient’s behalf by the indemnity health insurance and managed-care systems. Otherwise... it might be discouraged...”



# Issues of Changing Providers

- 25% of children vaccinated by more than one provider in the first 2 years of life *NHIS Survey 1994*
- Eligibility for Medicaid is sporadic and averages 9 months duration (in and out of VFC program)
- Not all providers participate in electronic Immunization Information Systems
- Extra doses may be unnecessarily administered when records are incomplete
- Providers may carry different products causing complexities in determining doses needed

# Common Questions

[www.immunize.org/askexperts/experts\\_combo.asp](http://www.immunize.org/askexperts/experts_combo.asp)

Question:

Can you use combination vaccines if someone is following a delayed schedule?



# Common Questions

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## Question:

Can you use combination vaccines if someone is following a delayed schedule?

## Answer:

**Yes**, if you always follow the minimum interval rule: The minimum interval between doses is the greater interval between any 2 individual antigens.

Comvax<sup>®</sup>: Hib dose 2-3 interval is 4 weeks, Hep B dose 2-3 interval is 8 weeks therefore minimum interval for Comvax<sup>®</sup> is 8 weeks

# Common Questions

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Question:

Can we switch  
between single and  
combination vaccines?



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Question:

Can we switch  
between single and  
combination vaccines?

Answer:

**Yes**, as long as the  
minimum interval rule is  
followed.

# Common Questions

[www.immunize.org/askexperts/experts\\_combo.asp](http://www.immunize.org/askexperts/experts_combo.asp)

Question:

Twinrix<sup>®</sup> question  
(Hep A-Hep B combo).

Usual schedule is 0,1, and  
6 months.

Is there an alternative  
schedule that protects  
sooner?



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Question:

Twinrix<sup>®</sup> question  
(Hep A-Hep B combo).  
Usual schedule is 0, 1, and  
6 months.  
Is there an alternative  
schedule that protects  
sooner?

Answer:

**Yes.** If need protection  
sooner than 6 months,  
can give as 0, 7, and 21-  
30 days followed by a  
dose at 12 months

# Common Questions

[www.immunize.org/askexperts/experts\\_combo.asp](http://www.immunize.org/askexperts/experts_combo.asp)

Question:

The Pediarix<sup>®</sup>

schedule calls for 3 doses at 2, 4, and 6 months.

Can it be used in older patients for catch up?



# Common Questions

[www.immunize.org/askexperts/experts\\_combo.asp](http://www.immunize.org/askexperts/experts_combo.asp)

Question:

The Pediarix<sup>®</sup> schedule calls for 3 doses at 2, 4, and 6 months. Can it be used in older patients for catch up?

Answer:

**Yes**, as long as it is not used as a 4<sup>th</sup> dose (licensed for 3 doses only) and not used in patients < 6 weeks or > 7 years of age.

# Common Questions

[www.immunize.org/askexperts/experts\\_combo.asp](http://www.immunize.org/askexperts/experts_combo.asp)

Question:

How do we document combination vaccines?



# Common Questions

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## Question:

How do we document combination vaccines?

## Answer:

Don't use brand names  
Use generic abbreviation (DTaP, IPV, etc.) in each section of the record by each single antigen

# Common Questions

[www.immunize.org/askexperts/experts\\_combo.asp](http://www.immunize.org/askexperts/experts_combo.asp)

Question:

What's the difference between the – and the / in the product names?



# Common Questions

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## Question:

What's the difference between the – and the / in the product names?

## Answer:

– means the 2 products were premixed at the manufacturer

/ means the 2 products are reconstituted by the user

# Near Horizon!

## Hexavalent—6 in one

- FDA application accepted Oct.2014
- Merck and Sanofi Pasteur collaborating
- DTaP-IPV-Hib-HepB at 2, 4 and 6 months
- Phase III Trial of 1400 kids comparing to Pentacel + Recombivax
- Non-inferior results for 18 of 19 comparators (1 pertussis comparison)

# Hexavalent Adverse Events

- Irritability, crying, drowsiness main AE
- Similar to comparator vaccine
- Increased rates of mild-mod fever for fewer than 2 days
- Safety and immunogenicity reviewed in the trial looked favorable
- Doubt a preference would be recommended

# Hexavalent Next Steps

- Data was presented at ID Week meeting last fall
- FDA now reviewing the data
- License could be mid to late August 2015
- ACIP Combination workgroup now being activated to review due to the complexity of the vaccine
- Representatives from NAPNAP, AAP, AAFP and others

# Combination Vaccines on the Horizon?

- Hexavac<sup>®</sup>: combines DTaP, IPV, Hib, and hepatitis B (used in Europe, not FDA approved in US)
- Combination of combination..?
- Edible vaccines-combined with food like vitamins and minerals!
- New vaccine delivery modes such as micro needle patches



# Spreading out Vaccines in the News

- *Washington Post, Boston Globe, LA Times*
- Combination vaccines should help the 74% of physicians spending time on sometimes or always spreading out vaccines
  - Less pain and trips to the clinic
  - Less delay adding to the unimmunized herd



# When switching between single and combination vaccines, what rule applies:

1. Maximum interval rule
2. Age in months rule
3. Minimum interval rule
4. Just vaccinate.
5. There are no rules.

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THE GOOD THING  
ABOUT SCIENCE IS  
THAT IT'S TRUE  
WHETHER OR NOT  
YOU BELIEVE IN IT  
• NEIL DEGRASSE TYSON •



# References

- **General Recommendations on Immunization**  
**Source: MMWR, January 28, 2011; 60(RR02):1-60**
- Morbidity Mortality Weekly Review, Combination Vaccines for Review May 14, 1999, Vol. 48, No. RR-5. 1-15
- Red Book 2009 Report of the Committee on Infectious Diseases
- CDC. Preventing Tetanus, Diphtheria, and Pertussis Among Adolescents: Use of Tetanus Toxoid, reduced Diphtheria Toxoid and Acellular Pertussis Vaccines: Recommendations of the Advisory committee on Immunization Practices (ACIP). MMWR 2006;55(RR-3): 1-41
- ACIP meeting minutes Feb 2009 Febrile seizures following MMRV
- MMRV and Febrile Seizures. *Pediatrics* June 28, 2009
- Merck.Sanofi joint Hexavalent news release Oct 20,2014
- Kemp, O’Leary, Kennedy, et al. Physicians Response to Parental Requests to Spread Out the Recommended Vaccine Schedule; *Pediatrics*, March 2, 2015