Review of the evidence: vaccine safety and co-administration

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Outline

- Safety profiles and key data*
  - Inactivated Vero cell vaccines (IXIARO)
  - Live attenuated vaccines (CD.JEVAX)
  - Chimeric vaccine (IMOJEV)
  - Summary
- Co-administration with measles containing vaccines

*Focus on children and serious AEs

IXIARO

INACTIVATED VERO CELL VACCINES

Inactivated Vero cell vaccine - IXIARO

Safety: 14 publications including 1 regulatory report

Primary and booster immunisation

- Adults in 7 RCT / Pooled safety analysis from 3558 IXIARO vaccinees compared to control groups (Dubischar-Kastner et al 2010; EPAR 2012)
- Adults in 10 RCT / Pooled safety analysis of 4043 vaccinees and 1 year post-marketing surveillance data (Schuller et al 2011)

Primary immunisation in children in 2 RCT (Kaltenboeck et al 2010; EPAR 2013)

data in children

Open-label, randomized, active-controlled Phase III study in the Philippines

Rates of SAEs or medically attended AEs up to day 56 (stratified by dose and age)

Age group	IXIARO 0.25 mL	IXIARO 0.5 mL	Prevnar	HAVRIX 720
≥ 2 months to < 1 year	(N=131) 38.2%	-	(N=64) 42.2%	-
≥ 1 year to < 3 years	(N=640) 26.7%	-	-	(N=213) 22.1%
≥ 3 years to < 12 years	(N=100) 7.0%	(N=301) 8.0%	-	(N=100) 5.9%
≥ 12 years to < 18 years	-	(N=240) 1.7%	-	(N=80) 3.8%.

- Between Day 56 and Month 7, 1 fatal SAE of disseminated intravascular coagulation was reported for a 12-year-old subject (IXIARO 0.5ml); the event was considered not related to study vaccine by the investigator.

EPAR, 2013

safety

12 months post-marketing data (2009-2010)

on 246,687 doses distributed in Europe, USA and Australia:
25 adverse drug reactions (ADR) reported; Overall reporting

Most frequently affected system organ class (SOC)	
skin and subcutaneous tissue disorders *mainly rash*	24%
general disorders and administration site conditions *mainly fever*	20%
nervous system disorders *mainly headache*	20%
gastrointestinal disorders	10%

doses
JE-VAX: 8.4/100,000 doses

-

Adverse events of special interest (AESI):

- 10 cases considered possible hypersensitivity reactions including rash (4 cases)

Schuller et al. 2011

Summary Safety

In children and adolescents from 2 months to <18 years:

- profile comparable with licensed vaccines (pneumococcal and Hep A vaccines)
  as regards frequency and severity of local and systemic AE.
  - below 1 year: fever was the most common reaction
    Systemic AE were mostly mild or moderate, they occurred more frequently in children
- No vaccine related SAE or death reported in RCTs up to 7 months

Adults:

- Comparable tolerability and reactogenicity with placebo (adjuvant alone) and MBDV JE vaccine except for local reactions. Significantly lower frequency of severe local reactions reported for IXIARO than MBDV vaccine.

No vaccine related SAE or death reported in RCTs up to 7 months

Potential risk of rare AE including hypersensitivity/allergic reactions

: Very limited information, but pregnancy is not a contraindication

CD.JEVAX

Live attenuated vaccine CD.JEVAX

Safety: 18 publications including 1 poster presentation

Safety

- Primary vaccination: 18 publications including 1 poster presentation
  - Primary

(Feroldi et al. 2014, Kim et al. 2014 (poster), Lu et al. (1997) et al. 2013)

- Booster vaccination
- Co-administration
- Post marketing surveillance (Lu et al. 2014) (Gatchalian et al. 2008)
- Case reports (Jia et al 2011)

Live attenuated

Comparison of IMOJEV and CD.JEVAX in 2

observer

-blind RCTs

Children aged 9-18 months or 12-23 months

Approximately 280 children randomized per vaccine group

- **2 cases of pyrexia** reported in the CD.JEVAX group as **SAE** were judged vaccine related

- Frequency of common injection site and systemic vaccine reactions were slightly higher in the CD.JEVAX group compared to IMOJEV; mostly mild to

RCT in 26,239 children in 180 health

reported

rate in one year olds

- 59.1% of 44.4%
  vaccine alone
- Concomitant administration in 41.3% subjects: thereof 47.9% with Measles Rubella, 13% with -

	AE reported	
AE	1426	61.24
SAEs	36	1.55
(≥38.6°C)	521	22.37
	570	24.48
	31	1.33

Liu et al 2014

Summary Safety

Children from 9 months to 6 years:

- Moderately higher frequency of：
  CD.JEVAX than local and systemic AEs after
  vaccine-related SAE reported in 1 recent RCT (pyrexia
- Huge)
  post marketing experience, however underreporting is to
  be expected
- Potential risk
  hypersensitivity/allergic and neurologic reactions
  of rare adverse reactions including
- No published information

IMOJEV

CHIMERIC VACCINE

Chimeric vaccine - IMOJEV

and 1 poster

Primary and booster immunisation in children

- Unvaccinated children in 3 RCTs (Feroldi et al 2012, 2014; Kim et al 2013/Poster)
- Unvaccinated and MBDV-primed children in 1 RCT (Chokephaibulkit et al 2010)
- IMOJEV-primed children in 1 RCT (Feroldi et al 2013)

Primary and booster immunisation in adults

- Adults in 3 RCTs (Nasfeld et al 2010, Torresi et al 2010)

IMOJEV – safety data in children

HepA vaccine in 2 RCTs (Thailand, Philippines)

VZV vaccine in 1 RCT (Philippines)

Children aged between 9-24 months

Approximately 1600 children vaccinated with IMOJEV

- **No** vaccine-related SAE reported for IMOJEV
- Common vaccine reactions were comparable between IMOJEV and licensed Hep A and VZV vaccine groups and across studies, mostly mild to moderate

Summary Safety - IMOJEV

from 12 months

- No vaccine related SAE of death reported in RCTs (up to 7 months) as regards frequency and severity of local and systemic AE
- Comparable tolerability and reactogenicity with placebo and MBDV JE vaccines (Hep A and VZV vaccines)

Adults:

- Significantly lower of local with placebo except for local reactions reactions reported for IMOJEV reported in RCTs (up to 7 than months)

Potential risk of neurologic in pregnant women and immunocompromised

Not data

Acceptable safety profile

Potential: contraindicated pregnant women and immunocompromised contraindicated

Acceptable safety profile

Potential risk of neurologic events

- Neurologic events including cases of encephalitis with temporal

  assessment not

  illness that occurs in temporal association with JE vaccination to rule out this possibility. Coincidental cases of encephalitis should be expected (and have

  investigation will help maintain confidence in the vaccination program.

	Inactivated JE-VAX	adsorbed IXIARO	CD.JEVAX Attenuated CD.JEVAX	IMOJEV Chimeric IMOJEV
Substrate	Mouse brain	Vero cells	Primary hamster kidney cells	Vero cells
Excipients/ residuals with known effects	, residual mouse brain protein	Protamine sulphate as residual	Gelatine	Glutamic acids (?) Antibiotics (?)
urticaria, angio-oedema or urticaria, angio-oedema or respiratory distress	6.3-8.4/100,000 (US, mostly adults) 6.3-8.4/100,000 (US, mostly adults)	adults)	2.8/100,000 (mostly children)	?
encephalitis, encephalopathy, convulsions myelitis	children) 0.0 (US, mostly adults)	meningism, headache (2x), migrane, migrane, of serious)considered serious)	1.3/1,000,000	? No postmarketing data yet

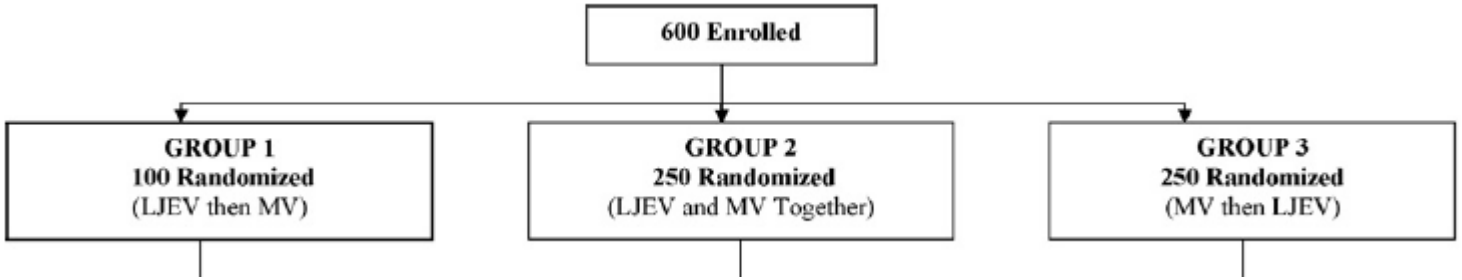
Co-Administration

– MMR

*Data on co-administration with available travellers vaccines

MEASLES VACCINE

Concomitant use of CD.JEVAX with measles vaccine in children 8-10 months



Safety:

- No vaccine related SAEs observed (Follow-Up 4 weeks)
- Co-administration with MV raised no specific safety concerns

Safety

- No vaccine related SAEs observed (Follow-Up 4 weeks)

Limitations of the study

Vaccine-related systemic reactions expected 7 days for systemic reactions to peak between 5-14 days

Follow

as

Immunogenicity

- Co-administration CD.JEVAX vaccines in children 8-10 months CD.JEVAX age

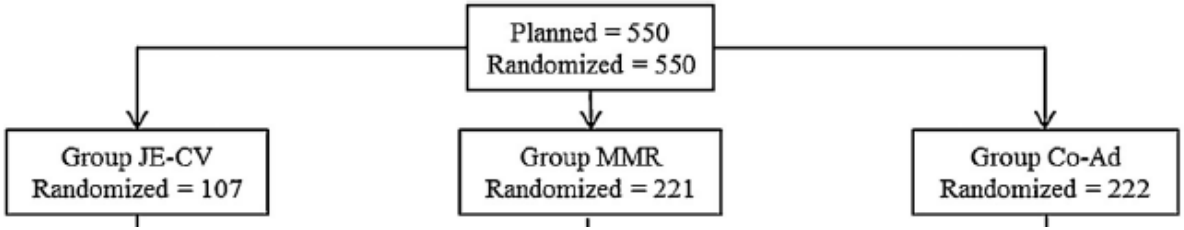
acceptable SP rates and GMTs

Gatchalian Victor et al 2014 2008

CHIMERIC VACCINE AND MMR

IMOJEV – co-administration with MMR

RCT in children aged 12-18 months in Taiwan; *(Huang et al 2014)*



Safety:

- No vaccine-related SAEs, no immediate AEs or AEs leading to withdrawal
- In general, the frequency of systemic reactions was comparable in the coadministration group and the group receiving MMR alone.
- Rash was reported more frequently in the co-administration group

Safety: Co-administration with MMR vaccine in children raised no safety concern

Immunogenicity

- coadministration group and the group receiving MMR alone.
- **Co-administration with MMR vaccine in children raised no safety**
- Persistence demonstrated for SP rates and GMT/GMC against JEV observed after 1 year:
  - **Lower seroprotection rates**

Conclusions

- Given current scope of use, schedules, and primary concerns of live vaccines co-administered together, of most relevance is co-administration CD.JEVAX and IMOJEV with live measles-containing vaccines
- Further assessment, particularly with MR, is warranted
- Available data on CD.JEVAX/MV and IMOJEV/MMR suggest co-administration with these vaccines is acceptable.

Back-up slides

IMOJEV – safety data in children

- **No** vaccine related SAEs reported for IMOJEV
- Common vaccine reactions were generally comparable between IMOJEV and HepA

Study 2: children aged 36-42 months

- **No** vaccine related SAEs reported for IMOJEV
- Common vaccine reactions were generally comparable between IMOJEV and VZV naïve vaccine groups.
- Fever rate in primed children was comparable with VZV immunized naïve children

(primed IMOJEV-N=345; naïve immunized with VZV-N=391)

and 1 was headache, all resolved with medication

- Common vaccine reactions were generally comparable between IMOJEV and VZV naïve vaccine groups.
- Fever occurred more frequently in IMOJEV primed children than in naïve children.
- Fever rate in primed children was comparable with VZV immunized naïve children
- Severe (Grade 3) reactions were reported for 8/391 children in the IMOJEV groups, 7 were fever and 1 was headache, all resolved with medication