三軍總醫院 實證醫學應用

骨科部

腸病毒71型疫苗 進人體試驗三期

2016-12-13 19:28台灣醒報 記者林亭妤／台北報導

易造成兒童併發重症而死亡的腸病毒71型病毒，其疫苗已問世在即！國衛院研發團隊博士劉家齊13日指出，疫苗研發的相關成果已技轉給國內廠商，目前進入第三期人體臨床試驗中，問世時間得看廠商何時完成試驗。

劉家齊強調，目前「腸病毒71型疫苗」的研發，全球只有我國和對岸在競爭，且我國的臨床試驗較中國還要來得嚴格。

腸病毒71型病毒（EV71），常會造成兒童身體不適，嚴重時會導致神經受損而致死。國衛院「去活化腸病毒71型疫苗研發團隊」成功開發出「去活化腸病毒71型疫苗」，榮獲「衛福部．經濟部藥物科技研究發展獎」藥品類銀質獎，13日在頒獎典禮上接受表揚。

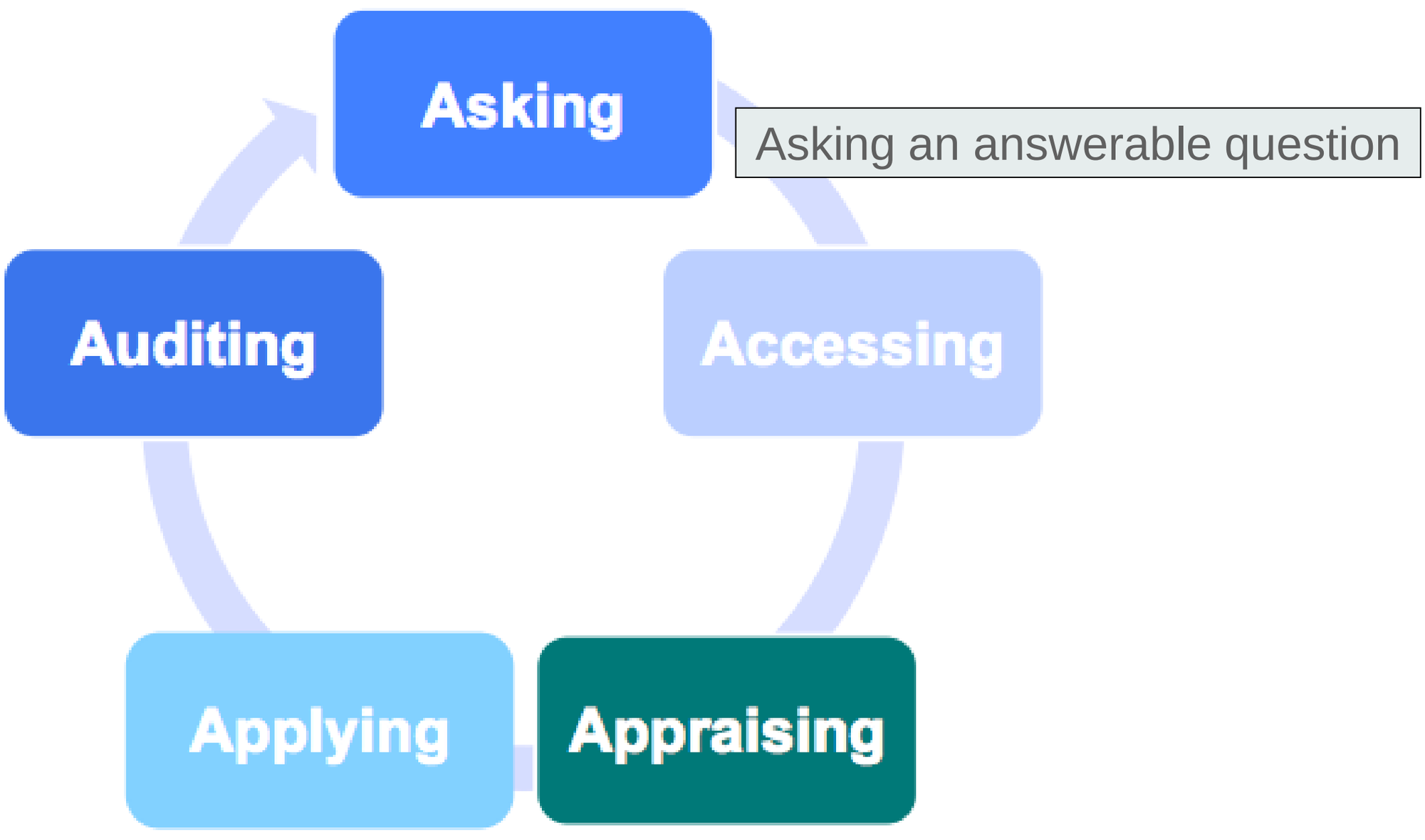
研發團隊受獎人、國衛院感染症與疫苗研究所博士劉家齊接受訪問時指出，腸病毒71型疫苗是最原型的疫苗、也是未來所有新型腸病毒疫苗研發的最基礎技術，目前全球只有2個國家正在研發，即台灣及中國大陸。

「我國現在正準備進入第三期人體試驗，而中國大陸雖然已完成第三期人體試驗，但他們並沒有遵照國際標準。」劉家齊指出，大陸的疫苗試驗比我們快一步，但品質是否有保障乃一大疑慮，因大陸的試驗法規全是自己制定的，不像我國遵循嚴格的國際標準在走，且我國產品有取得中華民國專利與美國專利。

Scenario

- 一名學齡前男童將赴大陸旅遊，但正值腸病毒71型大流行，父親考慮是否至大陸當地醫院施打疫苗，但對疫苗相關保護效果有疑慮……

5-Step Evidence-Based Medicine Process (5A)



5A step 1 - ASK:

PICO

-**P**atient, **I**ntervention, **C**omparison, **O**utcome

以病人為中心提出問題

- 施打腸病毒71型疫苗是否有保護效果?。

臨床問題

Key Word		Synonym 1
P	Children	Healthy children
I	**EV71 vaccine**	**inactivated enterovirus 71 vaccine**
C	Placebo	Placebo
O	Prevention of **enterovirus 71 infection**	Decrease the incidence of **enterovirus 71 infection**

這是一個 治療型/預防型　診斷型　預後型　傷害型問題

Background Knowledge

衛生福利部疾病管制署 專業版
Centers for Disease Control, R.O.C.(Taiwan)

- 腸病毒屬於小RNA病毒科（Picornaviridae），分為人類腸病毒A、B、C、D（Human enterovirus A、B、C、D）型，其中**腸病毒71型被歸類於人類腸病毒A型**。所有腸病毒中，除了小兒麻痺病毒之外，以腸病毒71型（Enterovirus Type 71）最容易引起**神經系統的併發症**

- 腸病毒適合在**濕、熱**的環境下生存與傳播，**人類**是腸病毒唯一的傳染來源，主要經由**腸胃道**（糞-口、水或食物污染）或**呼吸道**（飛沫、咳嗽或打噴嚏）傳染

- 病後**一週內傳染力最強**；而患者可持續經由腸道釋出病毒，時間長達8到12週之久

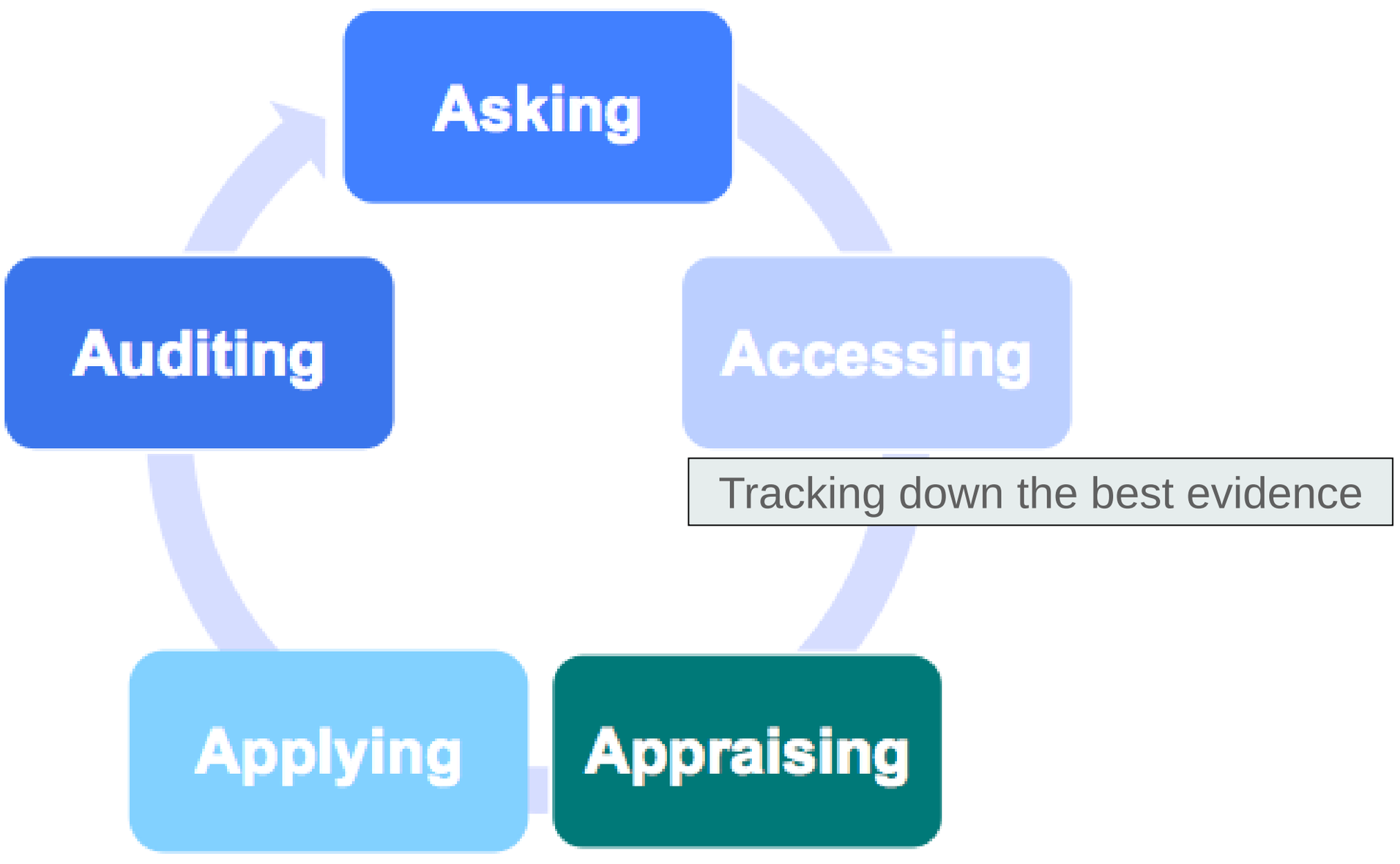
-

- 腸病毒可以引發多種疾病，其中很多是沒有症狀的感染，或只出現類似一般感冒的輕微症狀

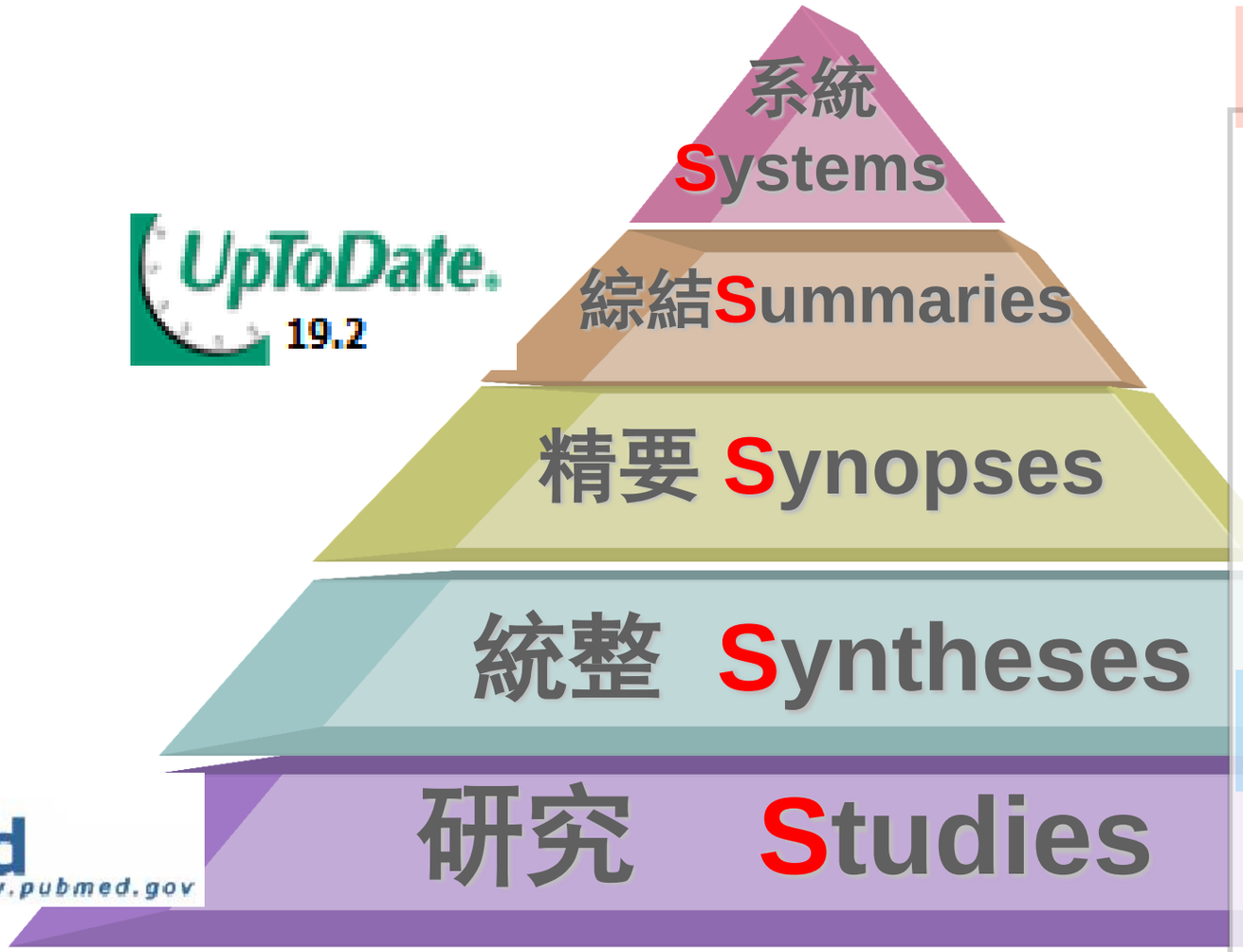
- 一般腸病毒感染主要常見症狀為手足口病或泡疹性咽峽炎，以年齡層分析，患者以**5歲以下幼童居多，約佔所有重症病例90%；在死亡病例方面，以5歲以下幼童最多**

- **手足口病**：主要由A族克沙奇病毒及腸病毒71型引起，特徵為發燒及身體出現小水泡，主要分布於口腔黏膜及舌頭，其次為軟顎、牙齦和嘴唇，四肢則是手掌及腳掌、手指及腳趾。常因口腔潰瘍而無法進食，病程為7-10天

5-Step Evidence-Based Medicine Process (5A)



檢索策略



The "5S" levels of organisation of evidence from healthcare research

Brian Haynes, R Evid Based Med 2006;11:162-164

Secondary database

Step1. Background review from textbook

Step 2. Background review from evidence base journal

Step 3. Systemic review articles and meta-analysis

Primary database

Step 4. Original articles with critical appraisal

Step 5. Conclusion

資料庫搜尋

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A novel inactivated enterovirus 71 vaccine can elicit cross-protective immunity against coxsackievirus A16 in mice Original Research Article
Vaccine, *Volume 34, Issue 48, 21 November 2016, Pages 5938-5945*
Lisheng Yang, Yajing Liu, Shuxuan Li, Huan Zhao, Qiaona Lin, Hai Yu, Xiumin Huang, Qingbing Zheng, Tong Cheng, Ningshao Xia
Abstract | Research highlights | PDF (3280 K)

Status of research and development of vaccines for enterovirus 71 Original Research Article — Open Access
Vaccine, *Volume 34, Issue 26, 3 June 2016, Pages 2967-2970*
Zarifah Reed, Mary Jane Cardosa
Abstract | Research highlights | PDF (378 K)

Similar protective immunity induced by an inactivated enterovirus 71 (EV71) vaccine in neonatal rhesus macaques and children Original Research Article
Vaccine, *Volume 33, Issue 46, 17 November 2015, Pages 6290-6297*
Ying Zhang, Lichun Wang, Yun Liao, Longding Liu, Kaili Ma, Erxia Yang, Jingjing Wang, Yanchun Che, Li Jiang, Jing Pu, Lei Guo, Min Feng, Yan Liang, Wei Cui, Huai Yang, Qihan Li
Abstract | Research highlights | PDF (1439 K) | Supplementary content

A bivalent virus-like particle based vaccine induces a balanced antibody response against both enterovirus 71 and norovirus in mice Original Research Article
Vaccine, *Volume 33, Issue 43, 26 October 2015, Pages 5779-5785*
Xiaoli Wang, Zhiqiang Ku, Wenlong Dai, Tan Chen, Xiaohua Ye, Chao Zhang, Yingyi Zhang, Qingwei Liu, Xia Jin, Zhong Huang
Abstract | Research highlights | PDF (1688 K)

Immunogenicity and performance of an enterovirus 71 virus-like-particle vaccine in nonhuman primates Original Research Article
Vaccine, *Volume 33, Issue 44, 4 November 2015, Pages 6017-6024*
Pei-Yin Lim, Andrew C. Hickey, Mohamad F. Jamiluddin, Sharifah Hamid, Joshua Kramer, Rosemary Sant
Bossart, M. Jane Cardosa
Abstract | Research highlights | PDF (1326 K) | Supplementary content

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Primary database - Pubmed

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PubMed | children AND Enterovirus 71 vaccine AND placebo AND prevention

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Hum Vaccin Immunother. 2015;11(11):2723-33. doi: 10.1080/21645515.2015.1011975.
PMID: 25715318 Free PMC Article
Similar articles

5. Clinical evaluation for batch consistency of an inactivated **enterovirus 71 vaccine** in a large-scale phase 3 clinical trial.
Chen YJ, Meng FY, Mao Q, Li JX, Wang H, Liang ZL, Zhang YT, Gao F, Chen QH, Hu Y, Ge ZJ, Yao X, Guo HJ, Zhu FC, Li XL.
Hum Vaccin Immunother. 2014;10(5):1366-72. doi: 10.4161/hv.28397.
PMID: 24633366 Free PMC Article
Similar articles

6. A booster dose of an inactivated **enterovirus 71 vaccine** in chinese young **children**: a randomized, double-blind, **placebo**-controlled clinical trial.
Shenyu W, Jingxin L, Zhenglun L, Xiuling L, Qunying M, Fanyue M, Hua W, Yuntao Z, Fan G, Qinghua C, Yuemei H, Xin Y, Huijie G, Fengcai Z.
J Infect Dis. 2014 Oct 1;210(7):1073-82. doi: 10.1093/infdis/jiu113.
PMID: 24625805 Free Article
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7. An inactivated **enterovirus 71 vaccine** in healthy **children**.
Li R, Liu L, Mo Z, Wang X, Xia J, Liang Z, Zhang Y, Li Y, Mao Q, Wang J, Jiang L, Dong C, Che Y, Huang T, Jiang Z, Xie Z, Wang L, Liao Y, Liang Y, Nong Y, Liu J, Zhao H, Na R, Guo L, Pu J, Yang E Sun L, Cui P, Shi H, Wang J, Li Q.
N Engl J Med. 2014 Feb 27;370(9):829-37. doi: 10.1056/NEJMoa1303224.
PMID: 24571755 Free Article
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8. Efficacy, safety, and immunogenicity of an **enterovirus 71 vaccine** in China.
Zhu F, Xu W, Xia J, Liang Z, Liu Y, Zhang X, Tan X, Wang L, Mao Q, Wu J, Hu Y, Ji T, Song L, Liang Q, Zhang B, Gao Q, Li J, Wang S, Hu Y, Gu S, Zhang J, Yao G, Gu J, Wang X, Zhou Y, Chen C, Zhang M, Cao M, Wang J, Wang H, Wang N.
N Engl J Med. 2014 Feb 27;370(9):818-28. doi: 10.1056/NEJMoa1304923.
PMID: 24571754 Free Article
Similar articles

9. Chinese **children** aged 6 to 59 months.
Hu YM, Wang X, Wang JZ, Wang L, Zhang YJ, Chang L, Liang ZL, Xia JL, Dai
Zhu FC, Song YF, Gao F, Chen JT.

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查詢 (腸病毒71型疫苗) = 所有欄位

篇名.關鍵字.摘要 | 作者 | 刊名 | 起始年 — 結束年 | 檢索結果再查詢

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共 61 筆，1 - 10 筆

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中国药事 (3)
微生物与感染 (3)
感染控制雜誌 (3)
中华实验和临床病毒学杂志 (2)

1 **腸病毒71型疫苗的回顧**
感染控制雜誌 25卷2期 (2015/04) , 99-104
加入追蹤 全文下載

2 **腸病毒71型病毒疫苗之研發**
劉家齊 ；
感染控制雜誌 23卷3期 (2013/06) , 160-165
加入追蹤 全文下載

3 **腸病毒71型感染**
陳國東(Kow-Tong Chen) ； 蘇世斌(Shih-Bin Su) ；
台灣家庭醫學雜誌 25卷2期 (2015/06) , 120-128
腸病毒71型 ； 手足口症 ； 咽峽炎 ； 腦炎 ； 疫苗 ； Enterovirus 71 ； hand-foot-and-mouth disease ； herpangina ； encephalitis ； vaccine
10.3966/168232812015062502002
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airiti Library 華藝線上圖書館	3	1

Flowchart for selection of articles

Search for potential relevant articles (n=90)

Studies excluded (n=76)

Not fitting with our PICO

Articles retrieved for further evaluation (n=14)

Studies excluded (n=11)

- Not systematic review or RCT
- Repeated article

Article selected for inclusion (n=3)

THE LANCET

Volume 381, Issue 9882, 8–14 June 2013, Pages 2024–2032

Articles

Efficacy, safety, and immunology of an inactivated alum-adjuvant enterovirus 71 vaccine in children in China: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Feng-Cai Zhu, MSc[a, b], , , Fan-Yue Meng, MSc[a], Jing-Xin Li, MSc[a, b], Xiu-Ling Li, MSc[c], Qun-Ying Mao, PhD[d], Hong Tao, BS[a], Yun-Tao Zhang, PhD[c], Xin Yao, PhD[d], Kai Chu, MSc[a], Qing-Hua Chen, MSc[c], Yue-Mei Hu, BS[a], Xing Wu, MSc[d], Pei Liu, PhD[e], Lin-Yang Zhu, BS[f], Fan Gao, MSc[d], Hui Jin, PhD[e], Yi-Juan Chen, MSc[e], Yu-Ying Dong, MSc[e], Yong-Chun Liang, BS[g], Nian-Min Shi, MSc[h], Heng-Ming Ge, BS[i], Lin Liu, BS[j], Sheng-Gen Chen, BS[g], Xing Ai, MSc[h], Zhen-Yu Zhang, BS[i], Yu-Guo Ji, BS[g],

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2015	195,553	44.002	42.579	46.119	13.210	309	9.0	4.7	0.40717	19.136	91.91	46.4...	99.032
2014	185,361	45.217	43.967	42.724	12.967	271	9.2	4.7	0.39555	17.592	91.14	44.3...	99.026
2013	176,528	39.207	37.887	39.315	12.649	276	9.0	4.5	0.38061	15.986	90.58	41.9...	99.038
2012	166,922	39.060	37.888	36.427	9.556	313	9.1	4.8	0.36172	14.575	91.69	Not A...	99.032
2011	158,906	38.278	37.025	33.797	10.576	276	8.9	4.3	0.36095	13.611	94.57	Not A...	99.032
2010	155,736	33.633	32.520	32.498	10.852	271	8.7	4.2	0.37864	12.715	90.04	Not A...	99.020
2009	152,843	30.758	29.740	29.443	10.211	280	8.5	4.7	0.37928	10.906	77.14	Not A...	98.872
2008	148,106	28.409	27.293	27.264	8.505	289	8.1	4.7	0.41177	9.946	94.46	Not A...	97.664
2007	135,949	28.638	27.612	24.201	8.636	305	7.7	4.4	0.45171	9.318	80.33	Not A...	98.500
2006	133,932	25.800	24.899	Not A...	7.419	301	7.4	4.5	Not A...	Not A...	72.09	Not A...	98.544
2005	131,616	23.878	23.168	Not A...	7.347	360	7.1	4.6	Not A...	Not A...	78.89	Not A...	98.571
2004	126,002	21.713	21.097	Not A...	5.827	415	6.8	4.7	Not A...	Not A...	72.77	Not A...	97.573
2003	123,292	18.316	17.653	Not A...	5.826	553	6.8	4.4	Not A...	Not A...	78.66	Not A...	97.549
2002	118,123	15.397	14.714	Not A...	5.299	522	6.9	4.2	Not A...	Not A...	88.51	Not A...	97.664
2001	117,415	13.251	12.664	Not A...	4.251	569	7.0	4.0	Not A...	Not A...	91.74	Not A...	97.768

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy, Safety, and Immunogenicity of an Enterovirus 71 Vaccine in China

Fengcai Zhu, M.D., Wenbo Xu, M.D., Jielai Xia, Ph.D., Zhenglun Liang, Ph.D., Yan Liu, M.P.H., Xuefeng Zhang, M.D., Xiaojuan Tan, Ph.D., Ling Wang, Ph.D., Qunying Mao, M.Sc., Junyu Wu, Ph.D., Yuemei Hu, M.D., Tianjiao Ji, M.P.H., Lifei Song, M.Sc., Qi Liang, M.P.H., Baomin Zhang, M.P.H., Qiang Gao, M.Sc., Jingxin Li, M.Sc., Shenyu Wang, M.Sc., Yuansheng Hu, M.P.H., Shanru Gu, M.D., Jianhua Zhang, M.D., Genhong Yao, M.D., Jianxiang Gu, M.D., Xushan Wang, M.D., Yuchun Zhou, M.D., Changbiao Chen, M.D., Minglei Zhang, M.D., Minquan Cao, M.D., Junzhi Wang, Ph.D., Hua Wang, M.D., and Nan Wang, M.Sc.

N Engl J Med 2014; 370:818-828 | February 27, 2014 | DOI: 10.1056/NEJMoa1304923

Enterovirus 71 (EV71), an enterovirus that is not associated with poliomyelitis, was one of the major causative agents of outbreaks of hand, foot, and mouth disease or herpangina in Europe,[1-3] Australia,[4,5] and Japan[6,7] between 1972 and 1988, and it has been implicated in a series of outbreaks across the Asia–Pacific region since the 1990s.[8-11] The largest Asia–Pacific epidemic occurred in China in 2008, when approximately 490,000 infections and 126 deaths in infants and young children were reported.[12] The vast majority of severe cases and fatal cases occurred in children younger than 3 years of age. EV71 infection can cause a wide spectrum of disease, including hand, foot, and mouth disease, herpangina, aseptic meningitis, and nonspecific illnesses such as febrile illness, viral exanthema, and airway infection.[13-15] There are currently no approved vaccines against EV71, but by analogy with poliomyelitis, vaccination may offer the best option for disease control.

The Vero cell–based EV71 inactivated vaccine with aluminum hydroxide has consistently been shown to induce immune responses to EV71 in infants and young children, 6 to 35 months of age, in phase 1 and 2 trials,[16,17] and no safety concerns have been identified in these trials. Here, we report the results of a phase 3 trial.

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2015	283,525	59.558	58.912	56.170	20.012	342	8.3	5.0	0.68235	25.710	87.43	77.7...	99.677
2014	268,652	55.873	55.192	54.390	13.844	353	8.4	5.1	0.67634	24.284	86.69	75.7...	99.675
2013	257,469	54.420	53.682	52.426	14.747	348	8.2	4.7	0.65797	22.412	89.37	72.5...	99.679
2012	245,605	51.658	50.955	50.807	12.667	360	8.0	5.0	0.65957	21.642	88.89	Not A...	99.677
2011	232,068	53.298	52.414	50.075	11.484	349	7.8	4.8	0.66383	21.304	88.83	Not A...	99.677
2010	227,679	53.486	52.774	52.363	10.675	345	7.5	4.7	0.68835	21.349	89.86	Not A...	99.673
2009	216,752	47.050	46.403	51.410	14.557	352	7.5	4.5	0.67236	19.868	90.91	Not A...	99.624
2008	205,750	50.017	49.212	49.911	12.225	356	7.3	4.4	0.68029	18.763	88.76	Not A...	99.533
2007	186,402	52.589	51.667	45.941	11.962	343	7.0	4.6	0.69405	17.864	90.38	Not A...	99.500
2006	177,505	51.296	50.448	Not A...	12.743	303	6.9	4.7	Not A...	Not A...	85.81	Not A...	99.515
2005	167,894	44.016	43.131	Not A...	13.422	308	6.9	4.5	Not A...	Not A...	84.74	Not A...	99.524
2004	159,498	38.570	37.841	Not A...	10.478	316	6.9	4.6	Not A...	Not A...	81.65	Not A...	99.515
2003	152,715	34.833	34.083	Not A...	11.719	366	7.1	4.9	Not A...	Not A...	83.88	Not A...	99.510
2002	143,124	31.736	31.013	Not A...	8.138	378	7.2	4.9	Not A...	Not A...	88.10	Not A...	99.533
2001	139,337	29.065	28.408	Not A...	7.571	375	7.2	5.0	Not A...	Not A...	82.13	Not A...	99.554

嚴格評讀 *Critical Appraisal*

The NEW ENGLAND JOURNAL of MEDICINE

HOME | ARTICLES & MULTIMEDIA | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS

ORIGINAL ARTICLE

An Inactivated Enterovirus 71 Vaccine in Healthy Children

Rongcheng Li, B.S., Longding Liu, Ph.D., Zhaojun Mo, M.Sc., Xuanyi Wang, M.D., Ph.D., Jielai Xia, Ph.D., Zhenglun Liang, M.D., Ph.D., Ying Zhang, Ph.D., Yanping Li, B.S., Qunying Mao, M.Sc., Jingjing Wang, M.Sc., Li Jiang, B.S., Chenghong Dong, B.S., Yanchun Che, M.Sc., Teng Huang, M.Sc., Zhiwei Jiang, Ph.D., Zhongping Xie, B.S., Lichun Wang, B.S., Yun Liao, B.S., Yan Liang, Ph.D., Yi Nong, B.S., Jiansheng Liu, M.Sc., Hongling Zhao, B.S., Ruixiong Na, B.S., Lei Guo, Ph.D., Jing Pu, B.S., Erxia Yang, B.S., Le Sun, M.Sc., Pingfang Cui, B.S., Haijing Shi, M.Sc., Junzhi Wang, Ph.D., and Qihan Li, M.D., Ph.D.

N Engl J Med 2014; 370:829-837 | February 27, 2014 | DOI: 10.1056/NEJMoa1303224

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Abstract | Article | References | Citing Articles (77) | Metrics

Epidemics of hand, foot, and mouth disease in children have emerged recently in Asia and have been caused primarily by enterovirus 71 (EV71) and coxsackievirus A16,[1] which typically show two peak epidemic incidences each year, in May and October.[2-5] An important clinical concern regarding hand, foot, and mouth disease is central nervous system injury, which occurs during the disease course in some severe cases and may result in a poor outcome.[6-11] Infection with the EV71 C4 genotype accounts for 40.1 to 55.4% of cases of hand, foot, and mouth disease, with considerable associated mortality, including thousands of deaths in China.[3,9,12,13] To reduce morbidity, an EV71 vaccine is needed.[2-5]

A human diploid-cell–based inactivated EV71 C4 genotype vaccine is being developed and has shown evidence of safety and immunogenicity in phase 1 and 2 studies.[14] We conducted a double-blind, randomized, placebo-controlled, phase 3 clinical trial to evaluate the protection induced by this vaccine against EV71-associated hand, foot, and mouth disease in children 6 to 71 months of age.

這篇文獻「納入理由」

- ✓ 符合臨床問題
- ✓ 發表年份較新
- ✓ 較佳的研究設計
- ✓ 有全文可供評讀

確定問題類型

—找尋不同的研究設計

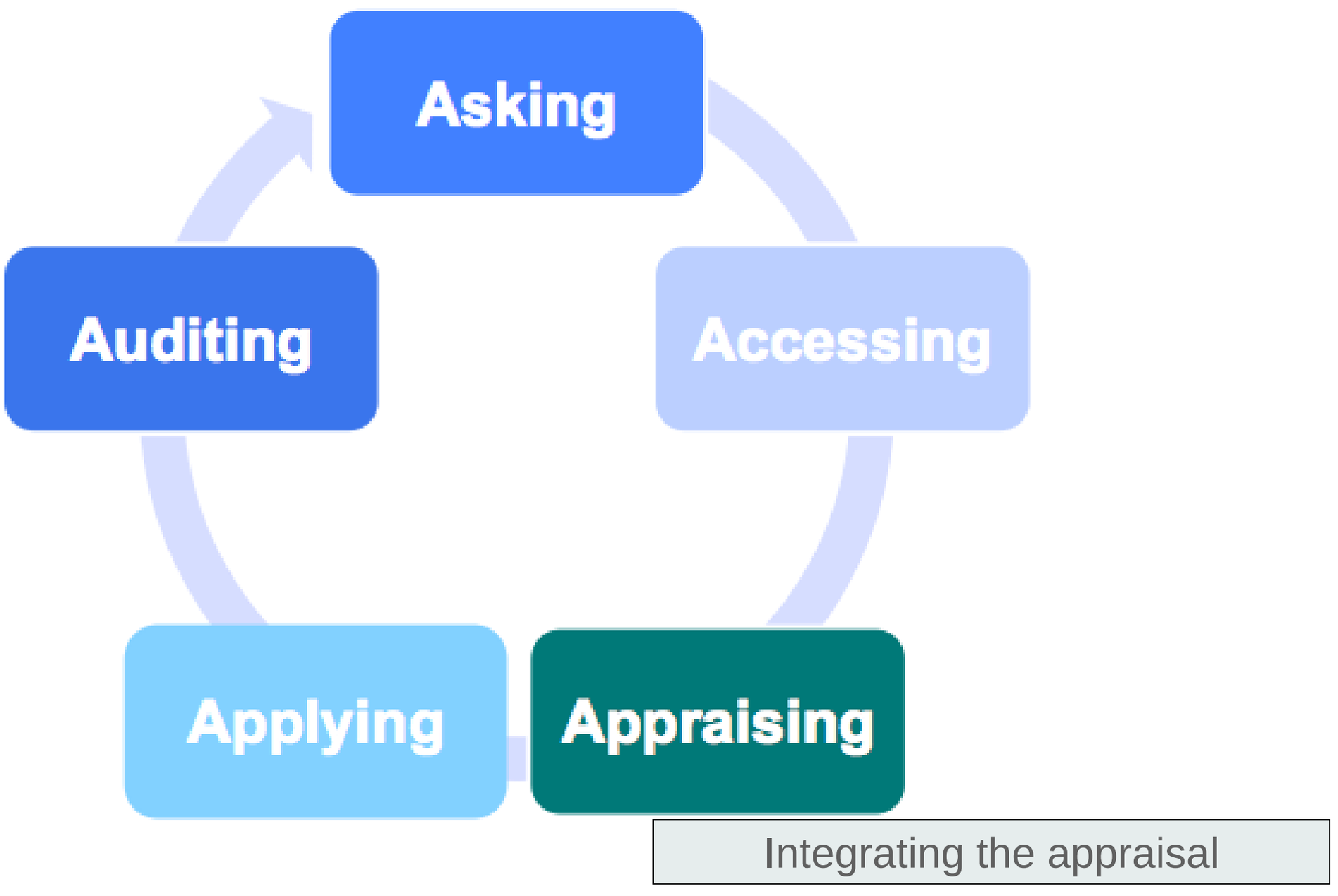
臨床問題	最適當的研究設計	
治療型	□隨機對照臨床試驗 □世代研究 □病歷對照研究	RCT＞cohort study ＞ case control ＞ case series
診斷型	□系統性回顧研究 □隨機對照臨床試驗	Prospective , blind comparison to gold standard
傷害型	□隨機對照臨床試驗 □世代研究 □病歷對照研究	RCT＞cohort study ＞ case control ＞ case series
預防型	□隨機對照臨床試驗 □世代研究 □病歷對照研究	RCT＞cohort study ＞ case control ＞ case series

Validity (Reliability)-RAM bo

RAM-bo

- 研究樣本是否具有代表性(Representative)？隨機分派、隱匿？兩組在治療開始時的基準是否相似？
- 是否追蹤夠久和完整(Accounted/follow-up)？(追蹤率＞80%)？是否是治療意向分析(Intention-to-treat, ITT)？
- 結果的測量(Measurement)是否公正？恰當？治療方法對病患、醫療相關人員、研究者是否盲化(blinded)？或客觀的(objective)估計，除了研究治療項目以外，其他的治療在各組間是否相同？

5-Step Evidence-Based Medicine Process (5A)



Critical appraisal

CASP CHECKLISTS

This set of eight critical appraisal tools are designed to be used when reading research, these include tools for Systematic Reviews, Randomised Controlled Trials, Cohort Studies, Case Control Studies, Economic Evaluations, Diagnostic Studies, Qualitative studies and Clinical Prediction Rule.

These are free to download and can be used by anyone under the Creative Commons License.

CASP Checklists (click to download)

CASP Systematic Review Checklist	CASP Qualitative Checklist
CASP Randomised Controlled Trial Checklist	CASP Case Control Checklist
CASP Diagnostic Checklist	CASP Cohort Study Checklist
CASP Economic Evaluation Checklist	CASP Clinical Prediction Rule Checklist

Ref : http://www.casp-uk.net/

Did the trial address a clearly focused issue?
此研究是否問了一個清楚明確的問題?

With considerable associated mortality, including thousands of deaths in China, To reduce morbidity, an EV71 vaccine is needed.
A human diploid-cell–based inactivated EV71 C4 genotype vaccine is being developed and has shown evidence of safety and immunogenicity in phase 1 and 2 studies. We conducted a double-blind, randomized, placebo-controlled, phase 3 clinical trial to evaluate the protection induced by this vaccine against EV71-associated hand, foot, and mouth disease in children 6 to 71 months of age.

This paper: Yes ■ No □ Unclear □

Was the assignment of patients to treatments randomised?
此研究是否適當的隨機分派病患?

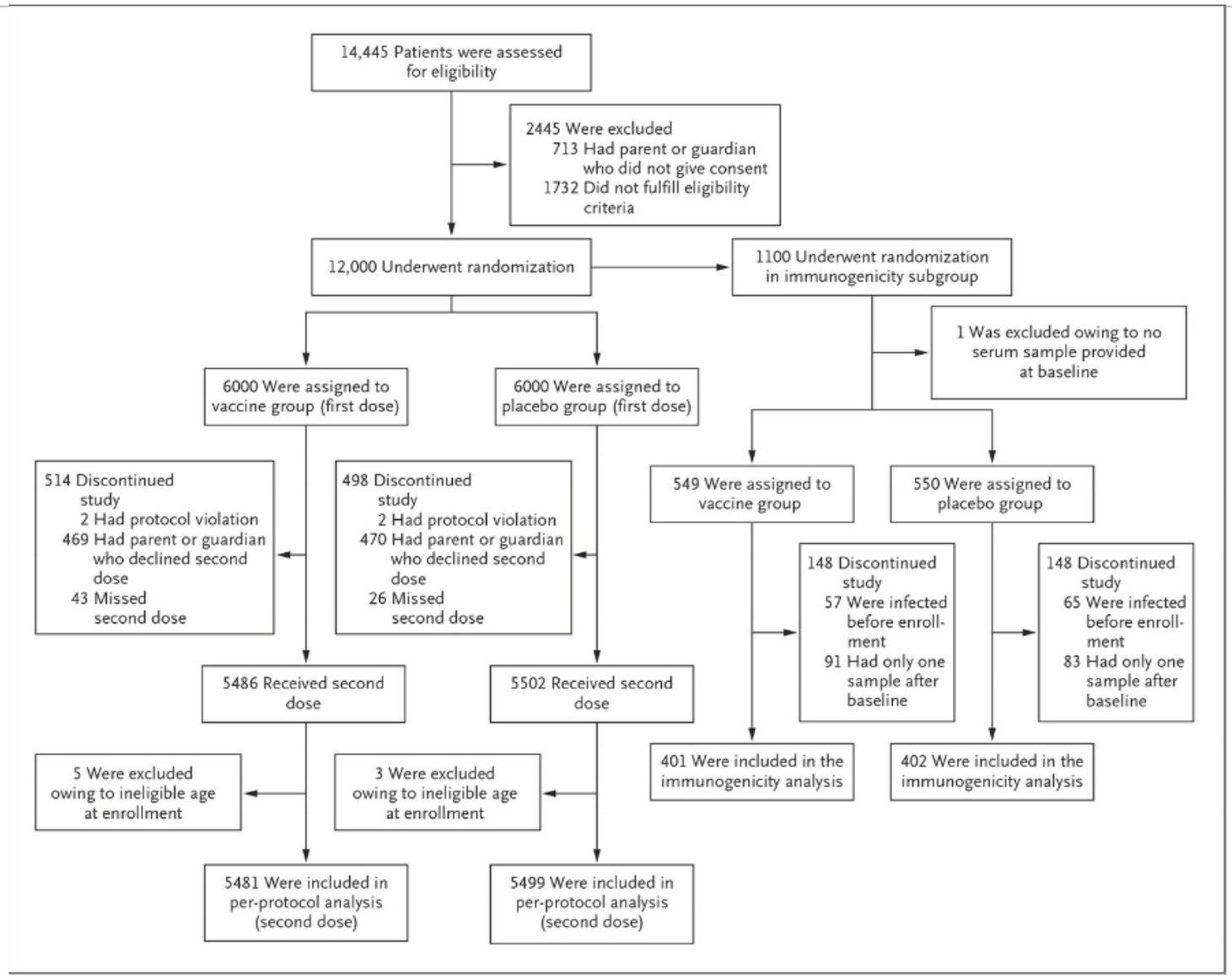
原文： We conducted a double-blind, randomized, placebo-controlled, phase 3 clinical trial to evaluate the protection induced by this vaccine against EV71-associated hand, foot, and mouth disease in children 6 to 71 months of age.

This paper: Yes ■ No □ Unclear □

Were all of the patients who entered the trial properly accounted for at its conclusion?

是否所有的病患被適當納入結果中去分析？

原文：



This paper: Yes ■ No □ Unclear □

4. Were patients, health workers and study personnel 'blind' to treatment?

病患、(給藥、測量結果的)醫療照護者、分析數據人員是否都是「盲性的」?

Protocol:

声明：本伦理委员会组成和工作程序符合 GCP 原则和国家相关法律法规

批准证明书

GXIRB
广西伦理审查委员会
IRB00001594　FWA00001359
广西疾病预防控制中心
IORG0001186
中国广西南宁市金洲路 18 号，530028

以下内容已经批准：

广西现场负责人：　莫兆军　电话：0771—2518724

申办者：中国医学科学院医学生物学研究所

题　目：在 6 月龄－71 月龄健康婴幼儿及儿童中进行的肠道病毒 71 型灭活疫苗（人二倍体细胞）的多中心、随机、双盲、安慰剂对照的Ⅲ期临床研究

批准项目包括：

临床研究方案、知情同意书、日记卡、受试者联系卡、原始记录表

审阅内容包括：

1. 中国医学科学院医学生物学研究所委托函
2. SFDA 药物临床研究批件　批件号：2010L05009
2. 中国药品生物制品检定所检验报告　报告编号：SH201200066
3. 研究者手册　版本号：3.0 版本日期：2011 年 7 月 9 日
4. 肠道病毒 71 型灭活疫苗方案（Ⅲ期）　版本号：4.0 版本日期：2012 年 2 月 9 日
5. 接种知情同意书（Ⅲ期）　版本号：2.0 版本日期：2012 年 2 月 9 日
6. 疫苗接种日记卡（Ⅲ期）　版本号：1.0 版本日期：2012 年 2 月 7 日
7. 受试者联系卡（Ⅲ期）　版本号：1.0 版本日期：2012 年 2 月 7 日
8. 原始记录表（Ⅲ期）　版本号：1.0 版本日期：2012 年 2 月 5 日
9. 主要研究者简历　日期：2012 年 2 月 8 日

2012 年 2 月 9 日广西伦理审查委员会召开会议，在本次会议上对上述所列项目内容进行了有关伦理方面的审查，通过审查，认为上述文件符合中国的伦理，可以用于中国医学科学院医学生物学研究所的"肠道病毒 71 型灭活疫苗Ⅲ期"项目，会议对上述文件的审查进行了投票决定，参加会议的委员一致通过，并批准上述方案在广西进行研究。

谢水洪，主席　2012 年 2 月 9 日（日　期）

本临床研究中，受种者随机入组，接种设盲疫苗。疫苗设盲由统计分析负责人完成，应用 SAS 统计软件按照事先设定的区组长度产生随机编码，按随机编码对疫苗进行随机和设盲，所有临床研究疫苗和安慰剂将重新粘贴设盲标签。

标签样式如下所示。6--11 月龄婴幼儿接种疫苗编号原则为：06 + 4 位流水号，顺序为 060001 至 063500；12--23 月龄婴幼儿接种疫苗编号原则为：12 + 4 位流水号，顺序为 120001 至 123500；24 月龄—35 月龄健康儿童接种疫苗编号原则为：24 + 4 位流水号，顺序为 240001 至 243000；36-71 月龄健康儿童接种疫苗编号原则为：36+4 位流水号，顺序为 360001 至 362000。盲底一式两份，完成编盲后封存，由申办者和研究者各自保存一份。

疫苗包装大盒（内装 5 支疫苗）的标签如下：

EV71 灭活疫苗 III 期临床试验 **研究号：060001-060005　第一剂** **2-8℃保存** **（仅用于临床试验，批件号 2010L05009）**	**EV71 灭活疫苗 III 期临床试验** **研究号：060001-060005　第一剂** **2-8℃保存** **（仅用于临床试验，批件号 2010L05009）** **备用**
EV71 灭活疫苗 III 期临床试验 **研究号：060001-060005　第二剂** **2-8℃保存** **（仅用于临床试验，批件号 2010L05009）**	**EV71 灭活疫苗 III 期临床试验** **研究号：060001-060005　第二剂** **2-8℃保存** **（仅用于临床试验，批件号 2010L05009）** **备用**

单支疫苗包装盒的标签如下：

疫苗编号：_____

单支疫苗标签如下

疫苗编号：060001
受种者姓名缩写：_____

受种者入组后均分配一个随机编号，接种与其随机编号一致的设盲疫苗。

每个编号均设有一支备用疫苗，如受试疫苗在临床研究过程中发现破损或沉淀，则相应编号临床研究疫苗废除，同时使用对应编号的备用疫苗。

This paper: Yes ■　No □　Unclear □

5. Were the groups similar at the start of the trial?

隨機分派後的兩組病患是否具有可比性？

Table 1. Demographic Characteristics of the Participants Included in the Intention-to-Treat Analysis.*

Characteristic	Efficacy Cohort		Immunogenicity Subgroup	
	Vaccine Group (N=6000)	Placebo Group (N=6000)	Vaccine Group (N=549)	Placebo Group (N=550)
Sex — no. (%)				
Male	3151 (52.5)	3099 (51.6)	279 (50.8)	296 (53.8)
Female	2849 (47.5)	2901 (48.4)	270 (49.2)	254 (46.2)
Age at entry — mo				
Mean	23.7±15.2	23.7±15.2	21.2±12.9	21.3±12.8
Range	6.0–71.9	6.1–71.9	6.1–71.3	6.1–69.1
Weight at entry — kg				
Mean	11.9±3.1	11.9±3.1	11.3±2.7	11.4±2.8
Range	4.2–33.6	4.5–30.0	5.0–22.0	5.0–23.0
Ethnic group — no (%)†				
Han	5278 (88.0)	5201 (86.7)	494 (90.0)	477 (86.7)
Zhuang	434 (7.2)	485 (8.1)	28 (5.1)	38 (6.9)
Yao	207 (3.4)	227 (3.8)	22 (4.0)	27 (4.9)
Miao	27 (0.4)	31 (0.5)	1 (0.2)	5 (0.9)
Other	54 (0.9)	56 (0.9)	4 (0.7)	3 (0.5)

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline. The intention-to-treat analysis included data from all participants who received at least one dose of vaccine or placebo.
† Ethnic group was reported by a parent or guardian and verified by a study investigator.

This paper: Yes ■ No □ Unclear □

6.Aside from the experimental intervention, were the groups treated equally?
除了研究介入（intervention)的差别，兩組間其他的治療是否相等？

17.5. 合并用药

允许用药：在临床研究期间，受种者如出现不良事件，应允许必要的药物治疗。

允许用疫苗：本临床研究期间内不允许进行其它疫苗临床研究或接种其它非常规免疫接种疫苗，除非需要医疗而应急接种疫苗，如狂犬病或破伤风等。婴幼儿遇常规免疫接种时，合并使用的疫苗可按产品说明书的规定进行，并与接种研究疫苗间隔 7 日之后在不同部位注射。

用药记录：为了解临床研究期间使用药物对疫苗安全性和免疫原性的影响，以及无遗漏地收集可能与疫苗接种相关的不良事件，研究者需有措施收集观察期间受种者用药情况，指导受种者监护人尽可能地将就诊和用药情况记录到日记卡中，需要将药物按照下列类别转录到病例报告表：

A 退热/镇痛药/非甾体抗炎药(阿司匹林、布洛芬、芬必得等)；

B 抗生素；

C 激素/类固醇药物(地塞米松等)；

D 抗过敏药物(扑尔敏等)；

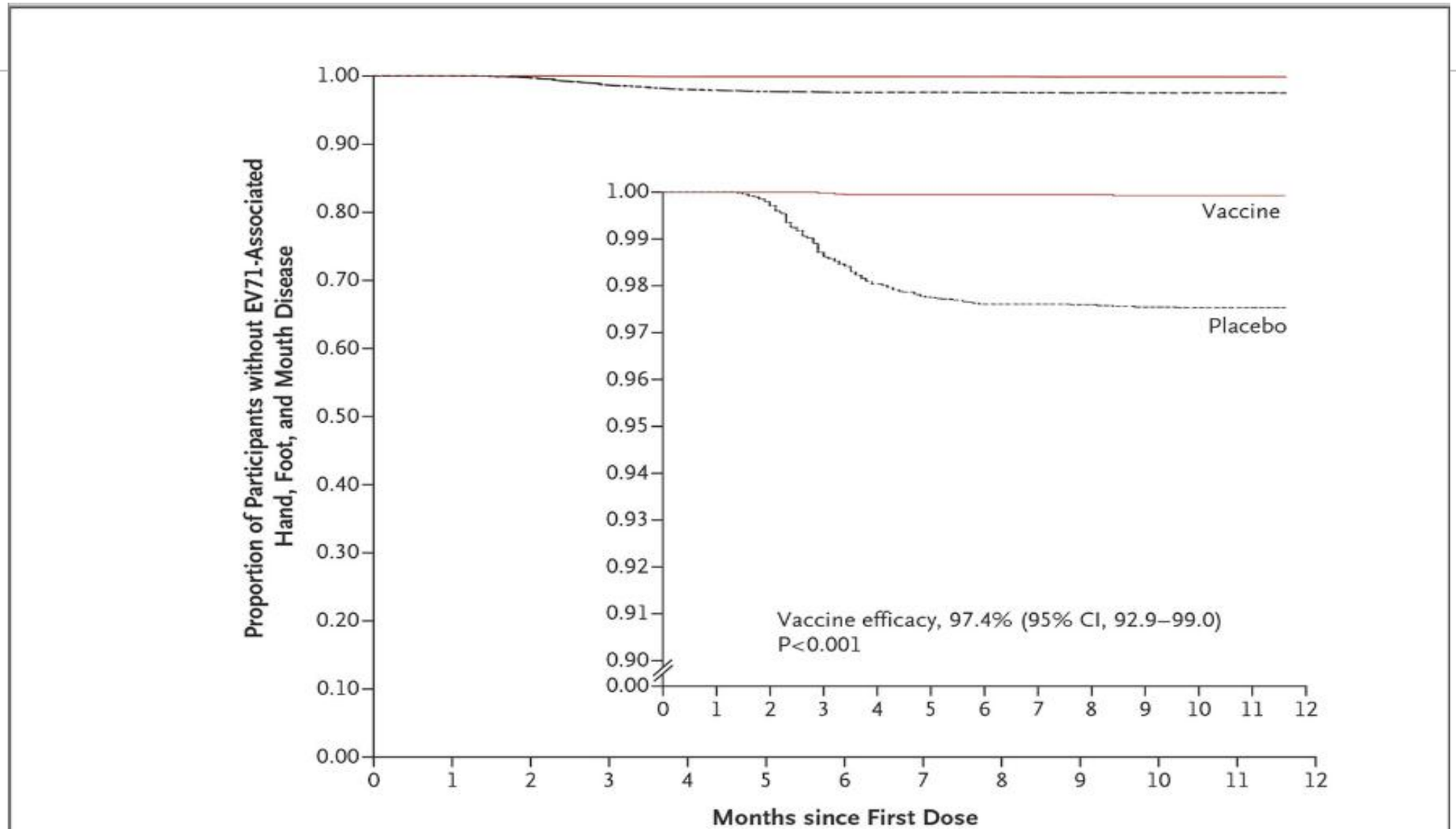
E 疫苗；

F 免疫球蛋白；

G 其他(如预防性用药、中药、保健药品等)。

This paper: Yes ■ No □ Unclear □

7. How large was the treatment effect?
介入的治療效果有多大？



No. at Risk

Vaccine	6000	6000	6000	5999	5997	5997	5997	5997	5997	5996	5996	5996
Placebo	6000	6000	5980	5914	5880	5862	5854	5854	5853	5850	5849	5849

No. of Events

Vaccine	0	0	1	2	0	0	0	0	1	0	0
Placebo	0	20	66	34	18	8	0	1	3	1	0

Table 2. Efficacy of the Enterovirus 71 (EV71) Vaccine against Overall Hand, Foot, and Mouth Disease and EV71-Associated Hand, Foot, and Mouth Disease over an 11-Month Period, According to the Intention-to-Treat Analysis.

Cases of Hand, Foot, and Mouth Disease	Vaccine Group (N=6000)		Placebo Group (N=6000)		Vaccine Efficacy*	P Value
	Participants	Incidence	Participants	Incidence		
		no. of cases/ 1000 participants/yr		*no. of cases/ 1000 participants/yr*	*% (95% CI)*	
Clinically diagnosed and pathogenically confirmed cases						
Caused by EV71 — no.	4	0.7	151	25.2	97.4 (92.9 to 99.0)	<0.001
Age 6–23 mo — no./total no.	2/3500	0.6	94/3500	26.9	97.9 (91.4 to 99.5)	<0.001
Age 24–72 mo — no./total no.	2/2500	0.8	57/2500	22.8	96.5 (85.6 to 99.1)	<0.001
Caused by coxsackievirus A16 — no.	48	8.0	54	9.0	11.1 (–30.8 to 39.6)	0.55
Caused by other enterovirus — no.	106	17.7	128	21.3	17.2 (–6.0 to 35.8)	0.15
Clinically diagnosed cases — no.	202	33.7	392	65.3	48.5 (39.2 to 56.3)	<0.001

* The calculation of overall vaccine efficacy was adjusted for study center.

如果 paper有給我們兩組病患事件的發生率：實驗組事件發生率 (EER, experimental event rate)、對照組事件發生率 (CER, control event rate)，我們可以進一步計算：

(4 cases in the vaccine group and 151 in the placebo group)

EER:2/3500=0.00057

CER: 94/3500=0.02685

ARR or ARI = | EER – CER | =0.00057-0.02685=0.02628

NNT=1/0.02628=38

This paper: Yes ■ No □ Unclear □

8. Can the results be applied in your context? 此研究是否可應用到你的病患？

Table 1. Demographic Characteristics of the Participants Included in the Intention-to-Treat Analysis.*

Characteristic	Efficacy Cohort		Immunogenicity Subgroup	
	Vaccine Group (N=6000)	Placebo Group (N=6000)	Vaccine Group (N=549)	Placebo Group (N=550)
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Ethnic group — no (%)†				
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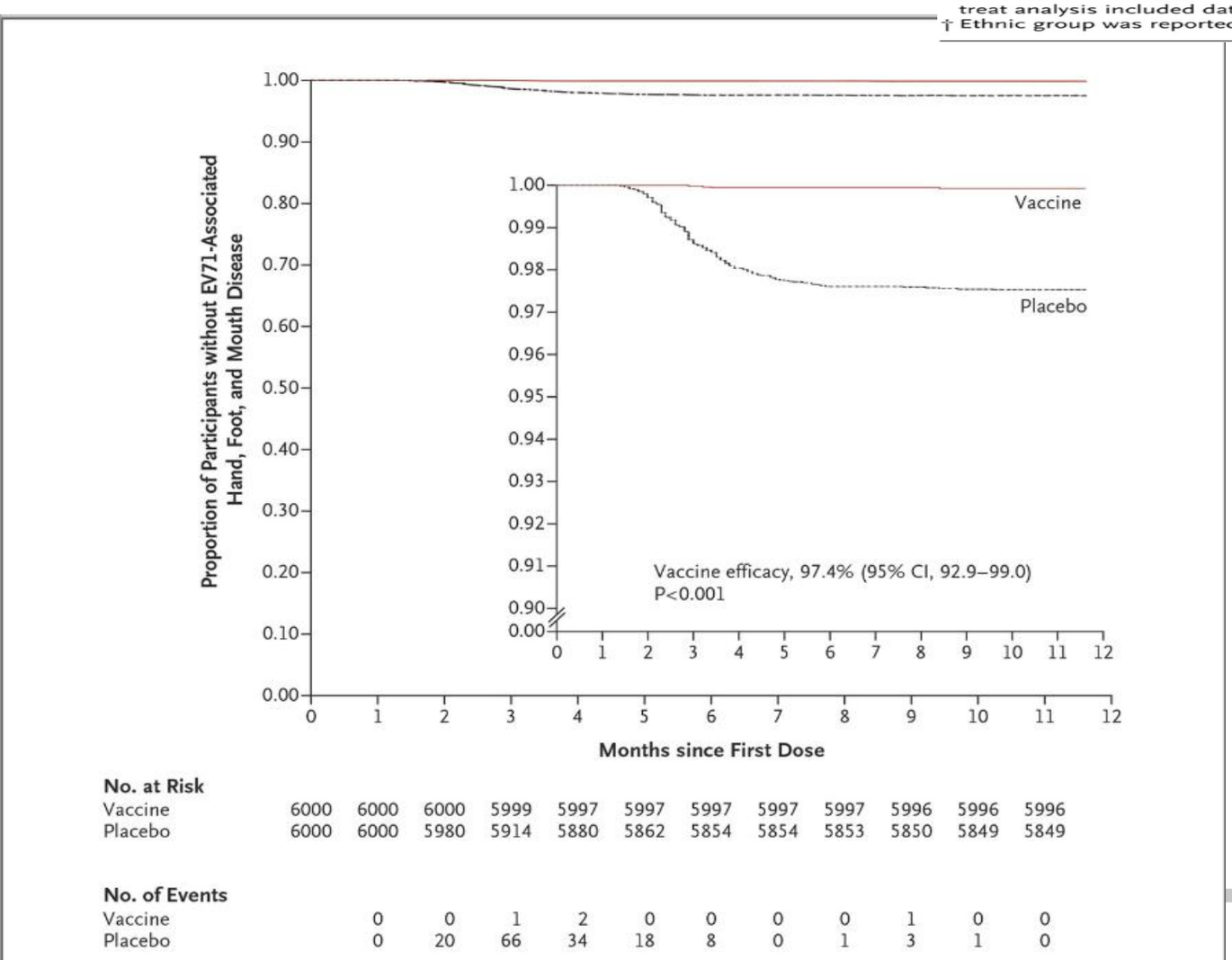
Zhuang	434 (7.2)	485 (8.1)	28 (5.1)	38 (6.9)
Yao	207 (3.4)	227 (3.8)	22 (4.0)	27 (4.9)
Miao	27 (0.4)	31 (0.5)	1 (0.2)	5 (0.9)
Other	54 (0.9)	56 (0.9)	4 (0.7)	3 (0.5)

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline. The intention-to-treat analysis included data from all participants who received at least one dose of vaccine or placebo.
† Ethnic group was reported by a parent or guardian and verified by a study investigator.



This paper :

Yes ■

No □

Unclear □

9. Were all clinically important outcomes considered?
是否所有重要的臨床結果都被考量到？

Table 3. Adverse Events and Serious Adverse Events.

Event	All Adverse Events			Adverse Events of Grade 3 or Higher*		
	Vaccine Group (N=6000)	Placebo Group (N=6000)	P Value	Vaccine Group (N=6000)	Placebo Group (N=6000)	P Value
	no. of participants with event (%)			*no. of participants with event (%)*		
Adverse event ≤7 days after injection						
Systemic event	2916 (48.6)	2574 (42.9)	<0.001			
Fever	2498 (41.6)	2111 (35.2)	<0.001	147 (2.4)	149 (2.5)	0.95
Diarrhea	498 (8.3)	535 (8.9)	0.24	8 (0.1)	12 (0.2)	0.50
Nausea, vomiting, or anorexia	530 (8.8)	475 (7.9)	0.08	6 (0.1)	7 (0.1)	1.00
Irritability, drowsiness, or weakness	360 (6.0)	303 (5.0)	0.03	3 (<0.1)	7 (0.1)	0.34
Allergy	166 (2.8)	156 (2.6)	0.61	2 (<0.1)	0	0.50
Local event	356 (5.9)	138 (2.3)	<0.001			
Pain	211 (3.5)	80 (1.3)	<0.001	1 (<0.1)	0	1.00
Redness	130 (2.2)	34 (0.6)	<0.001	1 (<0.1)	0	1.00
Itching	59 (1.0)	31 (0.5)	0.004	0	0	—
Swelling	106 (1.8)	22 (0.4)	<0.001	0	0	—
Adverse event ≤28 days after injection	2841 (47.4)	2985 (49.8)	0.009	136 (2.3)	136 (2.3)	1.00
Serious adverse event	—	—	—	68 (1.1)	125 (2.1)	<0.001
Death†	—	—	—	1 (<0.1)	1 (<0.1)	1.00
Hospitalization‡	—	—	—	67 (1.1)	124 (2.1)	<0.001
Hand, foot, and mouth disease	—	—	—	41 (0.7)	88 (1.5)	<0.001
Injection-related cause§	—	—	—	2 (<0.1)	2 (<0.1)	1.0
Other cause¶	—	—	—	24 (0.4)	34 (0.6)	0.34

* Adverse events of grade 3 or higher were defined as those severe enough to prevent activity, according to the common terminology criteria of adverse events from the Ministry of Health in China (see the Supplementary Appendix). Participants could have had multiple events.
† Two participants died (one patient in the vaccine group, from a traffic accident; and one in the placebo group, from severe EV71-associated hand, foot, and mouth disease).
‡ All serious adverse events except for death were events that required hospitalization.
§ Events that were considered to be associated or most likely associated with injection included fever (in two participants in the vaccine group), vomiting (in one in the placebo group), and allergy (in one in the placebo group).
¶ Events that were considered not to be associated with injection (i.e., those that occurred >28 days after injection or for which there was strong evidence against the association) included cold or respiratory infection; inguinal hernia; convulsion; fever; diarrhea; nausea, vomiting, or anorexia; and irritability, drowsiness, or weakness.

This paper: Yes ■ No □ Unclear □

11. Are the benefits worth the harms and costs? 這些好處隨之而來的傷害和花費是否值得？

建議分級(GRADES OF RECOMMENDATION)

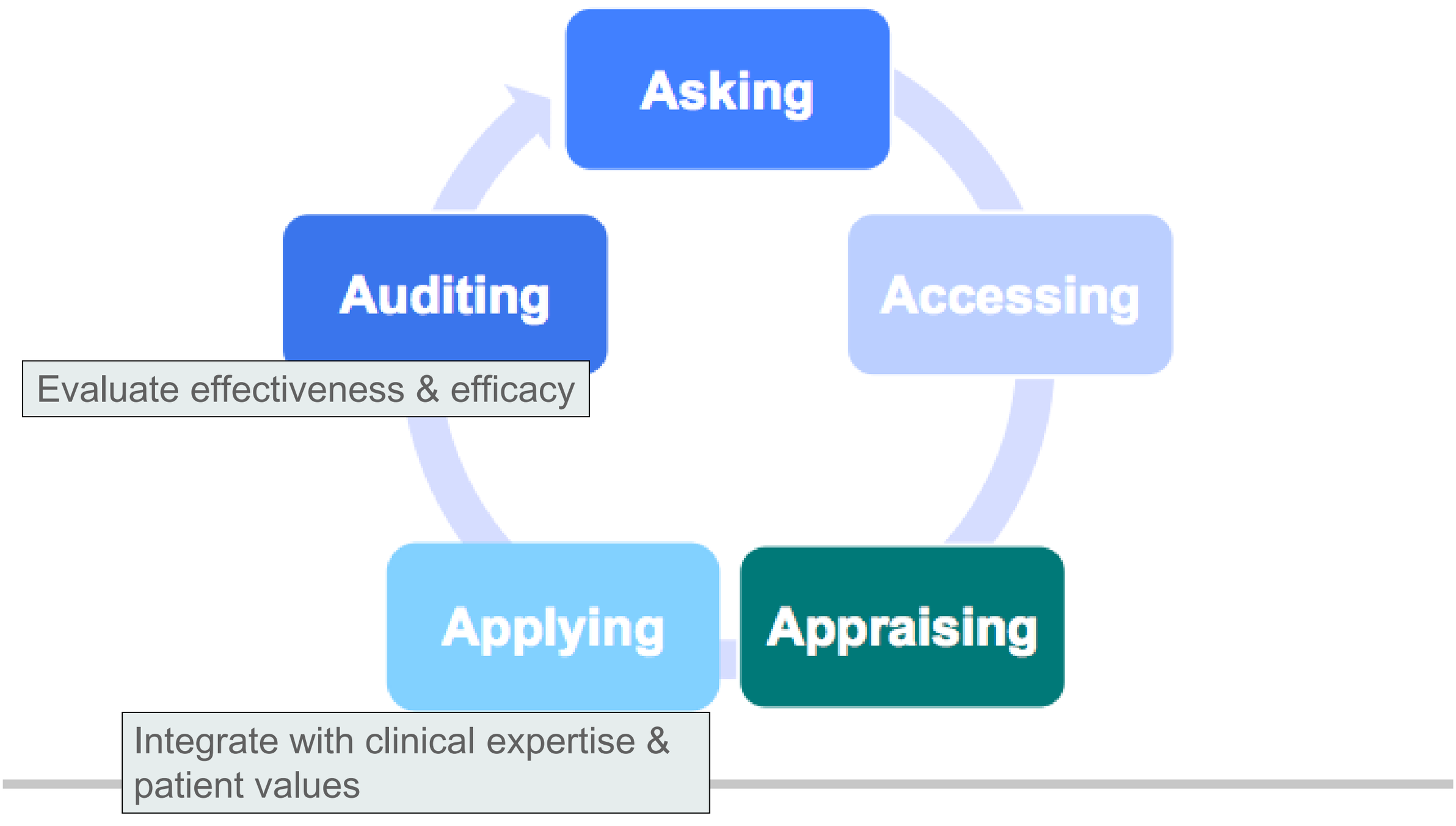
Grades of Recommendation	
A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

建議等級	說明
A	有好的證據支持此建議 (level 1研究有一致結論)
B	有相當的證據支持此建議 (level 2或3研究有一致結論，或根據level 1研究之推論)
C	沒有充分證據支持或反對此建議 (level 4研究，或根據level 2或3研究之推論)
D	有level 5的證據，或研究沒有一致結論

Conclusion

- Our systematic review results do not indicate any increased risk of **fetal death** or **preterm birth** associated with maternal influenza vaccination

5-Step Evidence-Based Medicine Process (5A)



臨床回覆

林爸爸你好，根據目前實證醫學證據顯示，學齡前孩童施打腸病毒71型疫苗可於人體產生經由人體試驗發現，可以誘 發對抗目前在亞洲流行的腸病毒71 型足量的中和抗體，並且證實相當安 全。在中國，由三個針對 6~60 個月 的小孩且已經進入第三期人體試驗的 研究指出，FI-EV71 疫苗所誘發的抗 體足以保護大於 90% 的小孩免於得 到腸病毒 71 型感染，大於 80% 的小 孩免於因腸病毒71 型感染後造成嚴重疾病，但目前台灣尚未進行第3期試驗，而大陸已有相關研究並已發表於新英格蘭期刊，建議可到大陸地區醫院進一步諮詢。

感謝聆聽

Thanks for your attention!!

“實證醫學 (evidence-based medicine; EBM) 是結合臨床問題、病患價值、研究證據 與 臨床經驗的學問...”

Brian Haynes MD, PhD