

国内外儿童用联合疫苗免疫原性、安全性和社会价值

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【摘要】 联合疫苗含有两种或多种抗原, 研究认为接种联合疫苗后能预防多种疾病, 同时可减少接种次数。本文对国内外儿童用联合疫苗, 如无细胞百白破疫苗(DTaP)、麻疹-风疹-腮腺炎疫苗(MMR)等免疫原性和安全性进行综述, 并从儿童家长、预防接种工作者和卫生服务方面进行社会价值探究, 为我国推动联合疫苗研发和使用提供决策证据。研究发现, 联合疫苗对儿童、家长、预防接种工作者和卫生服务方面均产生较好的收益, 能够保证其良好的免疫原性和安全性, 增强家长的接种便利和经济性, 提高预防接种工作者的工作效率, 同时能弥补新发疫情对免疫服务造成的影响, 提高接种覆盖率和及时率, 增加社会收益。目前我国联合疫苗的推广受到技术瓶颈多, 人群接种认知水平低等限制。建议加强联合疫苗安全性、有效性和卫生经济学等方面研究, 科学评估联合疫苗的价值; 增强公众对联合疫苗的认知和信任度; 促进多联多价疫苗研发应用; 政府应完善法规协助联合疫苗发展。

【关键词】 联合疫苗; 儿童; 免疫原性; 安全性; 价值

Review on immunogenicity, safety and social value of combined vaccines for children used both at home and abroad

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【Abstract】 Combined vaccines contain two or more antigens. Research suggested that combined vaccines could prevent multi diseases and reduce the frequency of vaccination. This article focus on combined vaccines for children used both at home and abroad, such as diphtheria-pertussis-tetanus vaccine (DTaP), measles-rubella-mumps vaccine (MMR), etc. and summarizes their immunogenicity, safety and social values, including benefits to families, vaccination workers and health services, to provide evidence for promoting the research, development and use of combined vaccines in China. We found that combined vaccines can not only ensure the immunogenicity and safety, but also give convenient and lower cost vaccination to families, and using combined vaccines can improve the work efficiency of vaccination workers, reduce the impact of the epidemic on immunization services and improve vaccination coverage and timeliness. At present, the promotion of combined vaccines in China is restricted by many technical bottlenecks, high prices, and low awareness among people. It is recommended that research on the safety, effectiveness and health economics of combined vaccines should be strengthened, and the value of combined vaccines should be scientifically evaluated; the public's awareness and trust in combined vaccines should be enhanced, as well as the development and application of multi-linked multivalent vaccines should be promoted. The government should improve regulations to assist the development and application of combined vaccines.

【Key words】 Combined vaccines; Children; Immunogenicity; Safety; Value

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联合疫苗指含有两种或多种活的、灭活的微生物或者提纯的抗原,可以在减少接种次数的同时预防更多种类的疾病,能解决就诊和接种次数增加的问题^[1]。联合疫苗包括多疾病联合疫苗和单疾病多型别联合疫苗。多疾病联合疫苗是联合多个不同疾病种类疫苗,预防多种疾病,如麻疹-风疹-腮腺炎疫苗(MMR);而单疾病多型别联合疫苗一般包括同一种细菌或病毒的不同亚型或血清型,如肺炎球菌多价疫苗^[2]。

联合疫苗的研发和应用已有数十年的历史。1948年,由白喉、破伤风与灭活全细胞百日咳疫苗组成的全细胞百日破联合疫苗(DTwP)在美国获批上市。1981年无细胞百日破疫苗(DTaP)研制成功,1991年在美国被批准使用^[3]。90年代以来,又陆续出现了百日破-灭活脊髓灰质炎联合疫苗(DTaP-IPV),无细胞百日破-b型流感嗜血杆菌联合疫苗(DTaP/Hib)等多联形式的疫苗^[4],联合疫苗的种类不断丰富。

考虑到联合疫苗在提升疫苗覆盖率和卫生服务管理效率等方面的优势,全球范围内的大多数发达国家都制定了联合疫苗的使用推荐意见。美国CDC的免疫实施咨询委员会指出,为了尽量减少儿童接种次数,应使用联合疫苗,而不是其等效单剂疫苗^[1]。全球疫苗免疫联盟(GAVI)也充分认可联合疫苗在节省包括设备、运输、废料处理等方面成本中带来的社会经济价值,最近20年以来,GAVI协助全球73个国家使用全细胞百日破-灭活脊髓灰质炎-b型流感嗜血杆菌联合疫苗,大幅提升当地接种率,保护了超过4亿儿童^[5]。目前,联合疫苗在各国已得到广泛使用,无细胞百日破-乙型肝炎-灭活脊髓灰质炎-b型流感嗜血杆菌联合疫苗(DTaP-HBV-IPV/Hib)已在110多个国家获批,并有30多个国家将其纳入了国家免疫规划。

1. 联合疫苗的免疫原性和安全性:

(1)DTaP-X联合疫苗:

①DTaP/Hib、DTaP-IPV 四联疫苗:Li等^[6]在2010年选取中国720名3月龄婴儿,随机分配到DTaP/Hib(国产)组和DTaP+Hib组进行接种,结果显示,两组的不良反应发生率均较低,每种抗体血清转化率均超过90%,联合疫苗在免疫原性和安全性方面均不低于分开单独接种。这一结果与Nilsson等^[7]、李艳萍等^[8]研究相似。Aristegui等^[9]通过西班牙216名婴幼儿随机对照试验表明,与分开单独接种疫苗组相比,DTaP/Hib组具有更好的免疫原性和安全性。Black等^[10]在美国招募了4209名4~6岁儿童,随机接种DTaP-IPV和DTaP+IPV的结果显示,该四联疫苗比分开接种具有非劣效的免疫原性,且安全性良好,该结果与韩国Lee等^[11]、Kim等^[12]研究相似。

②无细胞百日破-灭活脊髓灰质炎-b型流感嗜血杆菌联合疫苗(DTaP-IPV/Hib)、无细胞百日破-乙型肝炎-b型流感嗜血杆菌联合疫苗(DTaP-HBV/Hib)五联疫苗:我国1809名婴幼儿的随机对照试验表明,与DTaP/Hib+IPV分开接种相比,DTaP-IPV/Hib通常具有良好的耐受性,并能对

健康婴儿的5种疫苗抗原产生稳定的抗体反应^[13]。该结果与韩国^[14-15]、英国^[16]等国的研究相似。同样,与DTaP-IPV+Hib^[17]、DTaP+IPV+Hib^[18]相比,联合疫苗的免疫原性和安全性良好。但是,Yüksel等^[19]通过449名12月龄婴儿的随机对照试验得出,单独接种组比DTaP-IPV/Hib组的免疫原性更好。从整体看,DTaP-IPV/Hib的免疫原性和安全性均不劣于单独接种单价的疫苗。Gabutti等^[20]通过360名婴幼儿的随机对照试验比较了DTaP-HBV/Hib五联疫苗和DTaP-HBV+Hib疫苗接种反应,结果显示该联合疫苗具备较好的安全性、免疫原性和耐受性,能简化儿童的免疫接种程序。

③DTaP-HBV-IPV/Hib六联疫苗:2004年,德国一项2883名3~5月龄婴儿的随机对照试验表明,DTaP-HBV-IPV/Hib组和DTaP-IPV/Hib+HBV分开接种组的免疫原性和安全性相似^[21]。该结论得到了同类型研究的证明^[22-26]。Aristegui等^[27]通过多中心试验,比较了分别接受DTaP-HBV-IPV/Hib和DTaP-HBV+Hib接种的两组婴儿情况,得出联合疫苗组发热的不良反应率略高,其余安全性评价结果相似,且联合疫苗和单独接种疫苗对百日咳抗原的应答率分别超过97.0%和90.0%,免疫原性均较好。

(2)MMR-X联合疫苗:吴媛和黎丽^[28]在2016年对国产MMR进行了相关研究发现,300名8~12月龄儿童分为MMR组、麻疹疫苗组、腮腺炎疫苗组和风疹疫苗组4个接种组的总不良反应发生率分别为9.3%、8.0%、8.0%和10.7%,即MMR与传统的接种单一疫苗比较,没有增加不良反应的发生率。且接种MMR组婴儿的麻疹、腮腺炎和风疹抗体转阳率较好(分别为100.0%、92.0%和100.0%),但其风疹几何平均滴度明显上升,为1:320。该结果与于丹和汪静^[29]、胡丽娜^[30]的研究相似。刘卫民等^[31]发现国产MMR与风疹疫苗的免疫原性两组之间无明显差异,国产MMR具有良好的免疫原性。

此外,麻疹-腮腺炎-风疹-水痘联合疫苗(MMRV)效果也受到了研究者的广泛关注。欧洲的德国、奥地利、法国和意大利^[32-35],亚洲的中国、印度等^[28,36-38]国家,MMRV与单独接种相比,具有相似或非劣的免疫原性和安全性。但也有研究发现,MMRV在初期接种时可能增加发热、惊厥、疼痛的发生率^[34,39-48]。

2. 联合疫苗的社会价值:

(1)联合疫苗对儿童家长的价值:Dodd^[49]认为,联合疫苗可减少婴儿疼痛感的次数从而减少了父母的焦虑情绪。Meyerhoff等^[50]对294名父母进行为减轻或避免儿童接种疼痛和情绪困扰的支付意愿的问卷调查,结果显示,父母愿意为此付出更多经济成本,以避免儿童接种疫苗引起的疼痛和情绪的困扰,经计算愿意避免的单独接种平均成本为30.3美元,中位数为8.1美元。

Shono和Kondo^[51]对母亲选择联合疫苗的偏好的相关研究发现,日本1243名2~3岁儿童母亲的网络调查问卷结果显示,母亲表现出对联合疫苗能预防多种疾病的偏好,并

认为联合疫苗能减少就诊和接种次数,降低平均价格和不良事件的风险。值得肯定的是,联合疫苗的使用不仅减少了儿童错过疫苗接种时间的可能性^[52-53],提高了父母陪同儿童接种疫苗的便利性,还减少了交通、误工的费用,特别是对于高收入人群^[49,54-55]。

(2)联合疫苗对接种工作者的价值:使用联合疫苗减少了接种的次数,简化了接种医生的工作流程^[56],降低了疫苗的整体管理费用,降低了接种服务方的总成本^[52,57]。Pellissier 等^[58]发现,使用联合疫苗后,接种门诊总护理时长有明显减少,能提高接种医生和疫苗管理人员的工作效率。Dodd^[49]认为联合疫苗的使用有助于降低存储成本,并且由于减少了注射器的使用而减少了医生工作失误、针刺受伤的风险。

(3)联合疫苗对卫生服务的价值:

①经济学价值:刘卫民等^[59]对深圳市≤14岁儿童接种MMR进行成本-效益分析的研究发现,2007年深圳市≤14岁儿童麻疹、腮腺炎及风疹的发病人数分别为3 795、1 413和48例,平均每例麻疹、风疹、腮腺炎造成的总经济负担分别为1 063.9、935.5、759.1元,这3种传染病给国家和家庭造成的总经济损失为5 395 949.4元。若给这些儿童接种1剂次MMR,则成本-效益比为11.4:1;接种2剂次MMR,则成本-效益比为5.7:1,MMR可产生巨大的经济效益和社会效益。

国外研究中,Hammerschmidt等^[60]对德国采用MMRV预防水痘的经济成本进行分析,对比12~15岁青少年接种单价水痘疫苗和11~23月龄儿童接种两剂MMRV后在2~17岁接种单价水痘疫苗两种策略,发现使用MMRV可以节省卫生体系和社会两个层面成本。Zhou等^[61]对2009年美国4 261 494名婴儿的出生队列进行全生命周期的随访调查,分析儿童常规免疫接种DTaP和MMR等9种疫苗发现,接种疫苗可减少或预防4.2万例过早死亡和2 000万例疾病,可节省135亿美元的直接成本和688亿美元的总社会成本,儿童常规接种这9种疫苗的直接和社会效益-成本比分别为3.0和10.1。Rivière等^[62]对加拿大儿童接种MMR的潜在经济利益进行分析,发现在18月龄时接种第二剂MMR可预防9 200例麻疹、6 120例腮腺炎和1 960例风疹,每花费1美元用于接种从卫生体系的角度可节省6.3美元,从全社会角度可节省3.3美元,第二剂MMR的常规免疫将产生成本节约。

②接种覆盖率和及时性价值:Happe等^[63]对无细胞白破-乙型肝炎-脊髓灰质炎(DTaP-HBV-IPV)五联疫苗的接种覆盖率和及时性进行了研究。出生队列中,是否接种过DTaP-HBV-IPV五联疫苗的1 730名儿童采用1:1配对纳入并随访2年,结果显示,接种过该联合疫苗的儿童中该年龄所有推荐疫苗接种完成率和及时率分别为86.9%和45.2%,均高于对照组74.1%和37.5%。一项美国部分地区的回顾性免疫覆盖率调查发现,单次访问接种门诊但未能获得多种推荐疫苗的接种是导致疫苗覆盖率降低的原因之

一^[64]。联合疫苗能改善或解决该问题,帮助简化当前的免疫规划程序,解决不同疫苗错开接种时间有限的问题,增加接种及时性和接种覆盖率,对总体预防接种有益^[49,53,56,65-66]。

③疫情影响下的应急价值:2019年12月以来,全球各国开始暴发新型冠状病毒肺炎(新冠肺炎)疫情^[67-68],据WHO调查,2020年3~6月,几乎所有国家的卫生服务都受到干扰,其中推广常规免疫(70%)和由医疗机构提供的常规免疫接种(61%)服务中断明显^[69]。新型冠状病毒存在人传人机制^[70],为降低人群聚集风险,避免疫情进一步扩散,我国各地陆续暂停或调整了当地预防接种工作安排,强调科学统筹新冠肺炎疫情防控和预防接种工作^[71]。WHO认为,由儿童错过常规免疫接种而造成的可避免的痛苦和死亡可能远远超过新冠肺炎疫情本身,号召各国保证疫苗的覆盖率^[72-73]。在疾病大流行的情况下,联合疫苗作为国家免疫规划疫苗的有益补充,可以发挥减少接种针次、接种单位访问次数从而降低感染相关疾病风险的优势^[74];同时增加了疫苗的覆盖率,为防控其他传染性疾病预防提供保障。

3. 联合疫苗在我国的发展:

(1)发展现状:随着国家扩大免疫规划的推进,免疫规划疫苗种类增加至14种,可预防传染病15种,接种剂次增加至22~25剂/人^[75]。《中华人民共和国疫苗管理法》提出“国家根据疾病流行情况、人群免疫状况等因素,制定相关研制规划,安排必要资金,支持多联多价等新型疫苗的研制”^[76]。相关领域专家对今后联合疫苗的研发上市及未来应用策略持积极态度^[74]。

我国联合疫苗研发与使用起步较晚,品种较少^[77]。根据国家药品监督管理局数据,我国联合产品以吸附白喉破伤风联合疫苗等低联疫苗居多^[78]。目前常用联合疫苗有DTaP、MMR和A群C群流脑多糖疫苗,尽管近年来23价肺炎多糖疫苗、DTaP/Hib四联疫苗、AC群脑膜炎球菌(结合)b型流感嗜血杆菌三联疫苗、四价流感病毒裂解疫苗、人乳头瘤病毒疫苗等联合疫苗陆续上市,但是仍有较多联合疫苗,如13价肺炎多糖结合疫苗和DTaP-IPV/Hib五联疫苗依赖进口,需求量较大^[79]。

(2)联合疫苗应用:尽管联合疫苗是今后发展的趋势,但其推广使用仍有很多限制。在供给市场方面,联合疫苗的研发和初始阶段成本较高,因受各种因素制约,联合疫苗接种率偏低。当下社会对新疫苗研发、引入和联合的需求不断,这可能导致原有联合疫苗潜在市场缩短^[80]。此外,我国联合疫苗行业还存在瓶颈较多,如DTaP共纯化工艺生产含有的硫柳汞会破坏IPV抗原的免疫原性^[79]、研究阶段的疫苗联合程度较低、联合疫苗和单一疫苗接种程序不一致、法规制度下企业合作受限^[81]等问题。

在市场需求方面:①联合疫苗主要为自费疫苗:除DTaP、MMR外,现有联合疫苗均属于非免疫规划类疫苗,均由接种者自愿自费接种^[82]。目前我国非免疫规划类疫苗接种与收入水平相关^[83],且研究表明价格是影响非免疫规划类疫苗接种的重要因素之一^[84-85]。②公众对非免疫规划类

表 1 联合疫苗社会价值研究维度和主要结果发现

| 研究维度 | 临床价值 | 人文价值 | 经济价值 | 需要研究的问题 |
|---------|---|--|---|------------------------|
| 儿童 | 安全性良好;较分开接种具有非劣效性 免疫原性(DTaP-X ^[6-27] 和MMR-X ^[28-48] 等) | 减少疼痛的次数 ^[49-50] | - | - |
| 家长 | - | 降低情绪焦虑 ^[49-50] ; 提高便利性 ^[51-53] | 减少接种次数的交通、误工费用 ^[49,54] | 疫苗犹豫及其影响 |
| 预防接种工作者 | 降低针次受伤、感染的风险 ^[49] | 简化工作流程 ^[56] ; 提高工作效率 ^[52,56-58] | 降低疫苗管理和存储费用 ^[49] | - |
| 卫生服务体系 | 简化接种程序 ^[53,56] ; 解决错分接种时间有限问题 ^[66] ; 提高接种的覆盖率和及时率 ^[49,63-65] | - | 降低疫苗接种成本 ^[60,62] ; 降低疾病治疗负担 ^[60,62] ; 疫情期间的应急使用更有优势 ^[74] | 成本效果; 成本效益; 成本效用 |

注:- 无结果

疫苗的认知程度普遍不高,接种率较低:一项延边朝鲜族自治州儿童家长对非免疫规划类疫苗的调查发现,家长对非免疫规划类疫苗认知及格率仅为 15.7%,接种过至少一种非免疫规划类疫苗仅占 74.5%^[86]。③接种工作者推荐意愿偏低:据调查,某地区预防接种门诊医护人员对DTaP/Hib、DTaP-IPV/Hib的知识知晓率均为 71.7%,推荐意愿分别为 60.2%和 42.2%^[87]。

4. 小结:

联合疫苗的使用对儿童、家长、预防接种医生和卫生服务方面均有较好的效益,能够在保证免疫原性和安全性的前提下,减少就诊次数,提高家长的便利性和经济性,提高接种工作者的工作效率,快速弥补疫情对免疫服务的影响,增加接种覆盖率和及时性,提高社会收益(表 1)。

但国内目前关于联合疫苗价值研究相对较少,联合疫苗的应用价值并没有得到充分的认识。目前对联合疫苗的卫生经济学评价主要为以疾病负担为主的成本分析或成本-效益分析,缺少以单一疫苗为对照的成本-效果或成本-效用分析,应当考虑疫苗接种对儿童生活质量的影响,以及全面纳入各项相关的成本包括非医疗成本和间接成本进行测算。应正确认识联合疫苗的应用价值,通过科学、可靠的评价方法对联合疫苗的安全性、免疫原性、卫生经济学及公共卫生价值进行评价,科学开展多联多价等新型疫苗的研发和使用。

同时应提高公众对联合疫苗的认同度。只有对联合疫苗的价值得到认可,才能促进接种率的提高,确保联合疫苗的持续发展。疫苗研究、生产单位应当不断更新技术,加强创新,促进多联、多价疫苗的开发利用。政府应鼓励联合疫苗研发创新,加强审评部门与免疫策略制定部门之间的沟通,制定多元化的疫苗使用策略,允许联合疫苗接种程序在早期阶段有一定的灵活性,以推动人群整体免疫接种率的提高。

利益冲突 所有作者均声明不存在利益冲突

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