旧疾新挑战：百日咳再度抬头

Caitlin Naureckas Li, MD, MHQS,[1] Kathryn M. Edwards, MD,[2] Sheldon L. Kaplan, MD,[3] Gary S. Marshall, MD,[4] Sarah Parker, MD,[5] C. Mary Healy, MD[3]

[1]Division of Infectious Diseases, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois; [2]Division of Infectious Diseases, Department of Pediatrics, School of Medicine, Vanderbilt University, Nashville, Tennessee; [3]Division of Infectious Diseases, Department of Pediatrics, Baylor College of Medicine, Houston, Texas; [4]Division of Pediatric Infectious Diseases, Norton Children's and the University of Louisville School of Medicine, Louisville, Kentucky; and [5]Division of Pediatric Infectious Diseases, Children's Hospital Colorado, Aurora, Colorado

Address correspondence to: Caitlin Naureckas Li, MD, MHQS, Division of Infectious Diseases, Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine, 225 E Chicago Ave, Chicago, IL 60611. cli@luriechildrens.org

尽管已有疫苗可用，百日咳仍是一种极难控制的疾病。由于分子诊断技术的进步、疫苗组分的变更以及疫苗接种时机的错失，导致百日咳发病率持续上升。婴幼儿是发生严重并发症和死亡的最高风险人群，但在孕期母亲接种疫苗可为其提供保护。婴儿百日咳的临床表现与成人典型的卡他期、痉咳期和恢复期分期存在一定差异。通过掌握各年龄段人群百日咳的临床表现，医护人员可更快速地开展针对性抗生素治疗及暴露后预防。同时，医护人员也是孕妇和家庭进行循证疫苗接种咨询的重要信息来源，而充分认识该疾病的并发症对于进行这些困难但至关重要的沟通具有重大意义。

引　　言

“目睹百日咳患儿呼吸艰难却束手无策，实为最令人痛心的场景之一。”—— Kathryn Edwards。

近年来，美国[1]和全球范围内[2]的疫苗覆盖率持续下降，导致多种疫苗可预防的疾病重新抬头[3-5]。其中，由百日咳鲍特菌引起的百日咳是防控难度最高的疾病之一。与过去相比，当前医护人员接触百日咳患者的概率显著增加。通过深入了解该疾病，医护人员能够更从容地照护感染者，并就孕产妇与儿童疫苗接种的重要性向患者及其家庭提供专业指导。

微生物学与免疫学

鲍特菌属是革兰阴性球杆菌；其中 4 种（百日咳鲍特菌、副百日咳鲍特菌、支气管败血鲍特菌和霍氏鲍特菌）可引起人类呼吸道疾病[6-10]。仅百日咳鲍特菌能够产生百日咳毒素 (PT)，该毒素通过使 G 蛋白失活，降低黏附分子表达，抑制血管外渗，并促进细胞从脾脏等滞留组织迁出，从而引发严重淋巴细胞增多症[11]。这些淋巴细胞可继发性聚集，导致肺动脉高压甚至死亡[12-14]。鲍特菌属还可产生其他毒力因子，如丝状血凝素 (FHA)、百日咳杆菌黏附素 (PRN) 和菌毛 (FIM)，使其能够黏附于呼吸道上皮[15,16]。此外，FHA 可促进红细胞凝集，PRN 则保护细菌免受中性粒细胞清除[17-19]。

无论是既往感染过百日咳还是疫苗接种，均不能提供完全或终身的免疫力，并且目前尚未建立明确的实验室保护相关性。母源免疫在婴儿基础免疫前阶段所展现的保护成效，明确证实了抗体对百日咳疾病的预防作用。然而，近期研究亦揭示了细胞免疫应答在疾病预防中的重要性[20-23]。自然感染百日咳及全细胞百日咳 (wP) 疫苗 —— 其成分包含经灭

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活与脱毒处理的全菌体百日咳鲍特菌 —— 能够激发 Th1/Th17 CD4+ T 淋巴细胞介导的细胞免疫应答。相比之下，无细胞百日咳 (aP) 疫苗则主要诱导更为显著的 Th2 型应答 [20-23]。由于 aP 疫苗所含抗原种类较 wP 疫苗更为有限，其激发的免疫应答亦较为局限。与全细胞制剂相比，aP 疫苗接种后免疫保护的衰退速度更快 [24]。

在美国获批上市的百日咳 - 白喉 - 破伤风联合疫苗 (DTaP 与 Tdap 分别适用于儿童期及青少年或成人期）含有不同浓度的 PT、FHA 和 PRN，部分疫苗还包含 FIM。基础免疫程序完成后，DTaP 疫苗的即时保护效力为 75% 至 90%[25-26]。针对美国加利福尼亚州百日咳爆发疫情开展的模型研究显示，Tdap 疫苗接种 4 年后其保护效力降至约 9%[27]。

历史背景与流行病学

早在 16 世纪，百日咳已被明确认识。世界各地社群依据其独特的咳嗽症状为该病命名：意大利语称其为“tosse canina”，意为“犬吠样咳嗽”；法语中使用“coqueluche”一词，意为“鸡鸣样咳嗽”；而汉语则称之为“百日咳”，指其病程可持续百日之久 [17]。

在美国，百日咳的公共卫生负担与疫苗政策密切相关。在 20 世纪 40 年代末期，白喉、破伤风类毒素与全细胞百日咳联合疫苗 (DTwP) 获批上市之前，美国每年约有 10 万 ～ 20 万例百日咳病例。随着 5 剂次 DTwP 疫苗接种程序的推行，年发病率在 1976 年降至最低点，仅为 1 010 例 [17,28]。然而，自 20 世纪 80 年代中期起，由于公众对疫苗反应原性及接种后可能引发严重不良事件的担忧，疫苗接种率出现下降，百日咳病例数开始回升 [28-29]。日本 2 例婴儿接种 DTwP 疫苗后死亡（尽管未证实存在因果关系），瑞典使用的某批次 DTwP 疫苗被证实无效，以及英国对疫苗相关脑病的担忧，导致多国完全中止或显著减少该疫苗接种，继而引发多起百日咳暴发疫情，并造成大量婴儿死亡 [30-34]。

对 DTwP 接种后不良反应的担忧，推动了旨在开发低反应原性疫苗的深入研究，其主要策略是分离百日咳杆菌的免疫原性组分，并将其用于疫苗抗原。这一努力催生了 aP，该疫苗与白喉及破伤风组分结合，于 20 世纪 90 年代获批成为 DTaP 疫苗。在亚洲、欧洲和非洲开展的大量研究，采用不同配方的 DTaP 疫苗进行验证 [25,35-39]，结果表明在预防婴儿经实验室确诊的百日咳方面，DTaP 疫苗的反应原性低于 DTwP 疫苗，且效力相当。基于这些数据，美国于 1992 年将 DTaP 疫苗引入儿童免疫程序的第 4 和第 5 剂次，并于 1997 年将其用于整个接种程序 [17]。随后的数年中，百日咳似乎得到了有效控制，但 21 世纪初的多起疫情暴发凸显了 DTaP 疫苗诱导的免疫力会随时间减弱 [28,40-41]。因此，研究人员开发了加强疫苗 (Tdap)，其所含抗原与 DTaP 疫苗相同，但部分组分的含量有所降低 [42]。Tdap 加强针于 2005 年被纳入美国儿童免疫计划，用于 11 ～ 12 岁儿童，并纳入现行的入学接种要求中 [43-44]。

在 COVID-19 大流行期间，社交隔离措施导致百日咳病例显著减少；但随着防控措施放松，病例数量急剧上升，甚至超过大流行前水平。2024 年，美国共报告 35 435 例百日咳病例，其中包括 6 例婴儿死亡（图 1）。美国阿拉斯加、爱达荷和威斯康星州的发病率最高，每 10 万人中分别报告 81 例、54 例和 45 例 [45]。最新数据显示，尽管老年患者中存在漏诊现象，近半数报告病例发生于 11 ～ 19 岁人群，17% 发生于 20 岁以上人群 [45]。一项研究估计，青少年和成人中每出现 1 例临床百日咳病例，就存在 5 例无症状感染者，这一事实无疑加剧了社区传播 [46]。大流行后全球百日咳发病率亦呈上升趋势，多个大陆报告了疫情暴发 [47]。中低收入国家在 COVID-19 大流行前的常规监测数据可能不完整 [48-49]，但广泛的疫苗接种已促使病例数和死亡率下降 [50]。全球范围

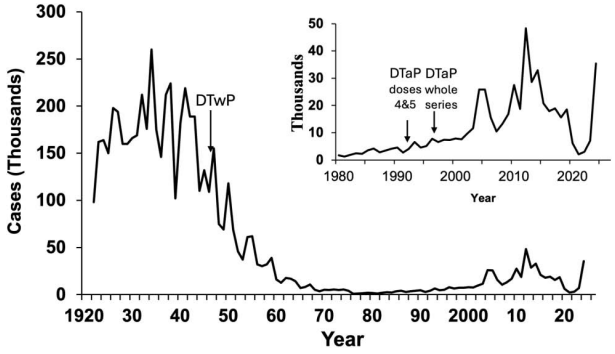


图 1　美国报告的百日咳病例数 (1922—2024 年)

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DTaP：白喉、破伤风、无细胞百日咳联合疫苗；
DTwP：白喉、破伤风、全细胞百日咳联合疫苗。

内，在疫苗接种与检测可及性、因对典型与非典型临床表现认知不足导致的漏诊以及报告完整度方面均存在显著差异[51-52]。

临床表现与诊断

在年龄较大的儿童和成人中，百日咳的临床表现通常分为 3 个阶段。卡他期以咳嗽和流涕为主要症状，通常与病毒性上呼吸道感染难以区分，且常不伴有发热。咳嗽症状在 1 ～ 2 周内逐渐加重，随后患者进入痉咳期。此阶段持续数周，患者出现阵发性快速咳嗽，继之以试图通过部分关闭的声门吸气而产生的“鸡鸣样”回声。患者常伴有咳嗽后呕吐，并可导致体重下降[17,52-53]。进入恢复期后，咳嗽发作的严重程度和频率逐渐减轻，但咳嗽症状可持续数月，并在病毒感染后复发，即使是在看似完全康复的患者中也是如此[13,54]。百日咳的疾病谱广泛，无症状和轻症感染已被充分记录，尤其在青少年和成人群体中较为常见[55-58]。值得注意的是，副百日咳鲍特菌感染虽临床表现相似，但通常病程较短且症状较轻[9]。

百日咳在婴儿中表现更为严重且复杂。在疾病初期，患儿可呈现相对良好的状态，症状与病毒性上呼吸道感染相似。典型的阵发性咳嗽与“鸡鸣样回声”可能不明显，但呼吸暂停现象较为常见。白细胞计数可升高至 100 000 个 /mm^3，且淋巴细胞增多程度与不良预后呈正相关[13,14,17,53,59]。婴幼儿出现极度淋巴细胞增多时，应高度警惕百日咳。

百日咳最敏感、最快速的检测方法是聚合酶链式反应 (PCR)，可作为独立检测项目，也可作为多重呼吸道病原诊断组合的一部分。PCR 在咳嗽发作后的最初 3 ～ 4 周呈阳性，但敏感性在第 4 周后逐渐下降[60-61]。历史上，细菌培养因其优异的特异性及在流行病学研究中的实用性，曾被视为咳嗽前 2 周内诊断百日咳的金标准[60,62]。然而，该方法通常不易获取，从样本收集到获得结果的周转时间较长，且其敏感性存在波动，尤其在疾病后期更为明显，这限制了其常规应用[60,63-64]。血清 PT 抗体滴度升高在疾病病程后期可支持百日咳的诊断，特别是在临床表现可能不典型的青少年和成人群体中。尽管目前尚未完全确立统一的诊断界值，但对于近期未接种疫苗且具备相应临床与流行病学背景的个体，抗 PT 免疫球蛋白 G 水平升高至 100 IU / mL 或以上 (采用经标准参考血清校准的检测方法) 高度提示近期感染[65]；但需注意，市售检测试剂的性能特征可能存在较大差异，在条件允许时，分子诊断方法仍为首选[60,66]。

并 发 症

尽管在年长儿童和成人中严重并发症并不常见，但仍可能出现呕吐及大小便失禁等令人痛苦的症状[17，53]。少数患者可能发生继发性细菌性肺炎、中耳炎、晕厥及肋骨骨折等并发症[52，67-69]，亦有气胸、颈动脉夹层、癫痫发作与脑病的相关报道[52，68-73]。纵观疾病全病程，百日咳会带来显著的经济负担，包括缺课和缺勤[74]。

严重并发症在婴儿中更为常见，美国大多数 2

月龄以下的百日咳患儿需住院治疗[75]。约 2 / 3 的幼婴因喉痉挛或咳嗽引发的迷走神经刺激而出现呼吸暂停[17,76]。严重肺动脉高压被认为是由极度白细胞增多及呼吸道黏膜脱落导致的肺血管阻塞所引起，可导致死亡[59,77]。惊厥发作可因呼吸暂停期间出现的低氧血症引起，亦可由抗利尿激素分泌异常综合征引发的低钠血症所致[71,78-80]。百日咳相关死亡（包括美国近期报告的病例[81]）几乎全部发生于 3 月龄以下婴儿，并且百日咳与被称为不明原因婴儿猝死的事件有关[82,83]。现代研究显示，美国的百日咳病例病死率超过 1%[14]。

治 疗 管 理

对于所有确诊或疑似百日咳的患者，建议尽快开始抗生素治疗。若在阵发性咳嗽阶段前早期用药，该治疗可改善临床症状。尽管晚期治疗不太可能改变疾病进程，但仍能降低传播风险。大环内酯类药物（如阿奇霉素）被视为一线治疗方案，但对于月龄超过 2 个月且无法使用阿奇霉素的患者，可选用甲氧苄啶 - 磺胺甲噁唑作为替代药物。虽然阿奇霉素与极低月龄婴儿的幽门狭窄存在关联，但考虑到该人群常出现严重的百日咳并发症，目前认为其治疗获益远高于潜在风险[17,65,84]。

除抗生素治疗以外，支持治疗亦很重要。对于婴幼儿，若出现肺动脉高压、心源性休克或极度白细胞增多等情况，可考虑进行换血治疗；该操作在发生多器官功能障碍前实施效果更佳[14,17,53,85-88]。对于机械通气治疗后病情持续恶化的低龄婴幼儿，应考虑采用体外膜肺氧合；但需注意，回顾性数据表明，进展至需要此级别支持的患儿死亡率较高[14,87]。不推荐使用类固醇药物，回顾性研究与动物模型均显示会增加死亡风险[14,86,89]。同样，虽然一氧化氮可用于其他类型的肺动脉高压，但并未改善重症百日咳患儿的临床结局[86-87]。虽有病例系列报道提及羟基脲的应用，但目前尚无确凿的临床试验支持该疗法[90-91]。

感 染 控 制

百日咳通过呼吸道飞沫传播。患者在卡他期和痉咳期初期的传染性最强，但婴幼儿排出细菌的时间通常较年长儿童更长。既往感染、疫苗接种史以及抗生素治疗可缩短传染期。住院患者应采取飞沫预防措施。门诊患者在接受有效治疗满 5 d 后方可返岗、返校或返回托幼机构；未治疗患者需隔离 21 d[65,92]。

家庭接触者及其他密切接触者（例如同一托育机构内的人员）应接受暴露后预防 (PEP)。尽管学校范围内的接触者通常不建议常规进行 PEP，但对于罹患重症百日咳风险较高、或可能接触婴幼儿及其他高风险人群的接触者，应考虑实施 PEP。在医疗环境中，所有可能接触新生儿、孕妇等高危患者的医护人员 (HCP) 若存在暴露风险，均应接受 PEP。目前，关于医疗环境中构成暴露的接触时长与类型尚无明确定义，但美国疾病预防控制中心 (CDC) 将未佩戴口罩的近距离面对面接触（例如体格检查期间发生的接触）视为职业暴露[93,94]。PEP 方案与治疗方案相同（表 1）。既往接种疫苗史不改变对 PEP 的需求，但免疫接种不全者，除抗生素预防外，还应额外接种 1 剂含百日咳成分的疫苗以完成补种[65,95]。

预　　防

现行疫苗策略

CDC 当前推荐的 DTaP 疫苗接种方案：2 月龄、4 月龄、6 月龄、15 ～ 18 月龄、4 ～ 6 岁，分别接种 1 剂。建议 11 ～ 12 岁时接种 1 剂 Tdap 加强疫苗，未按时接种者可补种至 18 岁[96-97]。尽管接种 aP 组分疫苗后仍可能出现局部反应和发热，但其局部及全身不良反应的发生率远低于 wP 组分疫苗。约 2% 的受种者在接种第 4 剂或第 5 剂 DTaP 疫苗后会出现整

表 1　推荐的百日咳暴露后预防与治疗方案

抗生素种类	年龄组		
	＜ 1 月龄	1 ～ 5 月龄	≥ 6 月龄
首选药物			
阿奇霉素	10 mg / kg，1 次 / d，连用 5 d	10 mg / kg，1 次 / d，连用 5 d	第 1 天：10 mg / kg (最大 500 mg)，1 次 / d；第 2 ～ 5 天：5 mg / kg (最大 250 mg)，1 次 / d
克拉霉素	不推荐	15 mg / kg / d，分 2 次服用，连用 7 d	15 mg / kg / d (最大 1 g / d)，分 2 次服用，连用 7 d
红霉素	不推荐	40 ～ 50 mg / kg / d，分 4 次服用，连用 14 d	40 ～ 50 mg / kg / d (最大 2 g / d)，分 4 次服用，连用 14 d
替代药物			
TMP-SMX (复方新诺明)	禁忌	对于＜ 2 月龄者禁忌，对于≥ 2 月龄者：TMP 8 mg / kg / d + SMX 40 mg / kg / d，分 2 次服用，连用 14 d	TMP 8 mg / kg / d + SMX 40 mg / kg / d (TMP 最大 320 mg /d)，分 2 次服用，连用 14 d

TMP-SMX：甲氧苄啶 - 磺胺甲噁唑。

本表基于 Tiwari T, Murphy TV, Moran J; National Immunization Program; CDC. Recommended antimicrobial agents for treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines. MMWR Recomm Rep. 2005;54(RR-14):1–16.

个大腿或上臂肿胀。若临床医生不熟悉这一现象，可能将其误诊为蜂窝织炎或肌炎。出现此类反应的个体，无需终止后续疫苗接种。DTaP 疫苗接种后不会增加癫痫发作风险，且该疫苗配方引起低张力 - 低反应性发作的情况极为罕见 [100-103]。DTaP 与 Tdap 疫苗的唯一禁忌证：(1) 既往接种疫苗或疫苗成分后出现严重过敏反应 (如过敏性休克)；(2) 既往接种 DTwP、DTaP 或 Tdap 疫苗后 7 d 内出现无法以其他原因解释的脑病。

既往未接种过 Tdap 的 19 岁及以上人群应接种 1 剂。2019 年，Tdap 的接种方案在以下情况中允许调整：作为 10 年期破伤风和白喉联合疫苗 (Td) 加强剂接种，用于曾接种过 Tdap 者的伤口破伤风预防，以及作为 7 岁及以上百日咳疫苗接种史不全者的补种程序中的多剂量方案 [104]。鉴于保护持续时间有限、流行病学影响不明确以及成本因素，目前尚未形成明确建议，不推荐对普通公众或非妊娠期 HCP 常规进行重复 Tdap 接种 [104-105]。

预防婴儿百日咳

对孕妇进行免疫接种可预防百日咳，并降低幼婴的死亡率和发病率。该策略能够增强母体的百日咳抗体水平 —— 这些抗体在妊娠晚期最易通过胎盘传输，从而为婴儿提供保护，直至其开始接种疫苗系列。关于这一方法的首次“概念验证”研究可追溯至 20 世纪 30 ～ 40 年代，当时有少量孕妇在妊娠晚期接种了 wP 疫苗 [106-107]。研究证实，该策略安全性良好，且接种疫苗的母亲所产婴儿未感染百日咳。至 21 世纪初，由于未达到基础免疫接种月龄的婴儿死亡病例持续增加，而“茧式免疫策略 (通过为母亲及婴儿照护者接种产后 Tdap 间接保护婴儿)”被证实成本高昂、实施困难且未能显著降低婴儿患病率 [97,108-109]，该疫苗接种方案被再次提出。

基于所有这些原因，CDC 于 2012 年建议在每次妊娠期间普遍接种 Tdap，最佳时间在妊娠 27 ～ 36 周。之所以建议在每次妊娠期间都进行免疫接种，是基于观察到 Tdap 诱导的百日咳抗体衰退很快，并且在第 1 次妊娠期间接种疫苗预计无法保护后续妊娠所生的婴儿 [97,110]。许多 (但非所有) 高收入国家推荐孕妇接种疫苗 [111]。对孕妇免疫接种预防婴儿百日咳的效果评估显示，可使婴儿住院率降低 90% 以上，死亡率降低 95%[75,97,112-116]。然而，其效力在 7 ～ 8 月龄婴儿中下降至 43%，且在 8 月龄后无显著影响 [117]。虽然在妊娠期间接种 Tdap 的孕妇所生婴儿，

其对基础免疫系列的抗体应答会有所减弱，但其对后续剂次的应答反应依然强劲，且百日咳发病率并未升高[118-119]。就妊娠结局和婴儿健康而言，妊娠期接种 Tdap 是安全的[113,118,120-123]。需要持续警惕和监测该策略的有效性，尤其是对于那些仅接种过 aP 的孕妇所生的婴儿，因为有研究表明，与接种 wP 的孕妇相比，这些孕妇对 Tdap 的抗体应答略低[123]。尽管如此，孕产妇免疫接种目前仍是预防极低月龄婴儿百日咳相关发病和死亡的最佳策略。

新型疫苗方法

理想的百日咳疫苗应具备以下特征：对预防感染和疾病具有高度的临床效力，能够阻断百日咳鲍特菌 (B. pertussis) 的传播，提供持久的保护作用，并具备可靠的安全性。由于现有疫苗尚无法全面满足这些要求，目前已有多种创新疫苗策略正在研发中，其中之一为减毒活疫苗 (BPZE1 减毒活疫苗，ILiAD Biotechnologies 公司)。该疫苗删除了多个毒力基因，并通过鼻内接种途径给药，旨在同时诱导黏膜免疫和全身免疫。研究显示，该疫苗在人体中安全性良好，具有免疫原性，可激发体液抗体和黏膜抗体反应[124-126]。针对青少年和成人的III期临床试验即将启动。此外，一种通过基因灭活而非化学灭活的百日咳毒素 (PT) 疫苗也正在评估之中，该疫苗可诱导更强的百日咳毒素免疫应答[127-128]。目前，研究人员还在现有百日咳疫苗中添加多种外膜蛋白、其他百日咳抗原、佐剂及免疫刺激剂，相关研究正在进行之中；同时，针对信使 RNA (mRNA) 疫苗的动物实验也在推进之中[129-133]。

疫苗接种率

疫苗接种仍是控制地方性流行和暴发性百日咳最为有效的方法。在美国，百日咳疫苗的覆盖率仍存在显著差距。CDC 最新数据显示，尽管存在入学接种规定且真正具有疫苗接种医学禁忌证的情况极少，2024—2025 学年幼儿园儿童的 DTaP 疫苗覆盖率仅为 92.1%。美国各州接种率差异悬殊，爱达荷州低至 78.3%，而康涅狄格州和弗吉尼亚州高达 98.2%[134]。疫苗接种率不完整的原因具有多因素性，但日益增多的州级宗教与哲学豁免、普遍存在的对疫苗接种的不信任，这些情况因关于疫苗风险与收益的错误信息而加剧，并因关于 COVID-19 疫苗的虚假信息而进一步恶化，所有这些因素均在其中扮演重要角色[134-136]。美国儿科学会已确定了循证策略，以帮助HCP与对疫苗接种价值存疑的家长进行沟通[137]。这些技巧侧重于积极倾听，并认识到家长经常接触不准确信息。其中一个关键信息是，家长与医疗卫生服务提供者站在同一立场，均致力于为儿童做出正确选择。同样值得注意的是，绝大多数家长会为其子女接种百日咳疫苗，医护人员必须避免将选择不接种疫苗正常化[138]。

预防百日咳相关死亡的主要手段是妊娠期疫苗接种。尽管已有令人安心的疫苗安全性数据，并证实该干预措施效果显著[75,97,112-115,118,120-122]，美国妊娠期 Tdap 三联疫苗的接种率仍仅为 50% 左右。虽然 COVID-19 大流行后孕妇对接种 Tdap 疫苗的犹豫情绪有所增加[139]，但妊娠期 Tdap 接种率较疫情前基线水平仍有所上升[140]。研究表明，与儿童疫苗接种类似，妊娠期疫苗接种的主要推动因素是获得 HCP 的强烈推荐[141-143]。具体到 Tdap 疫苗，当医疗保健提供者通过强烈推荐并结合现场接种或转介至接种点的方式推动免疫时，妊娠期接种率可达 71%；反之，若医疗保健提供者未作推荐，孕妇接种率仅为 1%[115,143]。最后，当临床医生能够分享自身及其家人、同事均已接种疫苗的事实时，所有来自提供者的疫苗推荐效果都会增强，因此需要正视并解决医疗工作者单剂次 Tdap 接种覆盖率欠佳的现实问题。

结　论

百日咳仍然构成切实的威胁。对年长青少年和成人而言，百日咳至少是一种令人不适且干扰日常生活的疾病；而对婴幼儿来说，百日咳更是导致发病和死亡的重要原因。通过深入了解这一疾病，医

护人员可成为关键的防御力量 —— 通过早期识别，实施恰当的感染控制措施，以及（或许最为重要的）推广疫苗接种，作为控制这种重疾重现的最佳手段。

缩略语

aP：无细胞百日咳疫苗

CDC：美国疾病控制与预防中心

DTaP：白喉、破伤风、无细胞百日咳疫苗

DTwP：白喉、破伤风、全细胞百日咳疫苗

FHA：丝状血凝素

FIM：菌毛

HCP：医护人员

PCR：聚合酶链式反应

PEP：暴露后预防

PRN：Pertactin

PT：百日咳毒素

URTI：上呼吸道感染

wP：全细胞百日咳疫苗

（卞元兮 译　陈庆会 校）

联系人：丁欣 etyxcbzx@suda.edu.cn

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