表4 推奨される百日咳の年齢別治療および曝露後予防薬 (CDC)

	標準的抗菌薬			代替抗菌薬
年 齢	AZM	EM	CAM	TMP-ST*
1カ月未満	10mg/kg 1日1回が推奨されるが安全性のデータが限られている	肥厚性幽門狭窄症との関連ため，推奨されない。AZMが使用できないとき，40～50mg/kg/日分4で14日間	安全性のデータがなく推奨しない	禁忌
1～6カ月未満	10mg/kg 1日1回 5日間	40～50mg/kg/日分4で14日間	15mg/kg/日分2で7日間	2カ月以上ではTMP 8 mg/kg/日，SMZ 40mg/kg/日分2で14日間
6カ月の小児	10mg/kg 初日1回，以後5mg/kg/日（最大500mg）4日間	40～50mg/kg/日（最大2g/日）分4で14日間	15mg/kg/日（最大1g/日）分2で7日間	TMP 8 mg/kg/日，SMZ 40mg/kg/日分2で14日間
成人	500mg 初日1回，以後250mg/日を4日間	2g/日を分4で14日間	1g/日を分2で7日間	TMP 320mg/日，SMZ 1,600mg/日分2で14日間

*TMP-ST：生後2カ月以上でマクロライド薬にアレルギー，経口摂取できない，あるいは極めてまれであるがマクロライド耐性百日咳菌に対して使用することができる。

CDC：米国疾病対策センター，AZM：アジスロマイシン，EM：エリスロマイシン，CAM：クラリスロマイシン，TMP-ST：トリメトプリム，SMZ：スルファメタジン

(文献10より引用)

V 感染管理

米国小児科学会では，①患者との接触者でDTPワクチン1～2回接種者は追加接種，②家族内や保育施設内の濃厚接触者はEM 14日間内服，③医療従事者も接触後21日間は咳に注意し，咳が出始めたら培養検体採取後，抗菌薬内服を推奨している[11]。「濃厚接触者」とは有症状患者と3フィート（約0.9 m）以内での対面や1時間以上狭い室内での同室などの状況を挙げている。

VI 予防接種

わが国は世界に先駆け，発熱など副反応の強かった全菌体百日咳ワクチンを改良し，有効成分のみを単離し，副反応は少なく効果も同等な無細胞百日咳ワクチンを開発した。ジフテリア・破傷風トキソイドと混合し，DTaP (a：acellular) として1981年秋から開始し，25年以上が経過した。接種率の向上とともに，百日咳患者は著明に減少し，優れた効果を示してきたが，相対的に10歳以上の患者数が増加している。

欧米では，思春期・成人百日咳対策として新しくジフテリア・百日咳の抗原量を減らした三種混合ワクチン (Tdap) を導入して推奨している[12]。日本でも，増加してきた思春期・成人の百日咳対策が必要な時期となっている。現行2期接種 (11～12歳) のDTワクチンに替わり，百日咳ワクチンを加えたDTaPが有益と考えられ，DTaPとDTとの比較試験で有効性と安全性の検討を開始した。

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小児科疾患アルゴリズム

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小児科疾患
アルゴリズム

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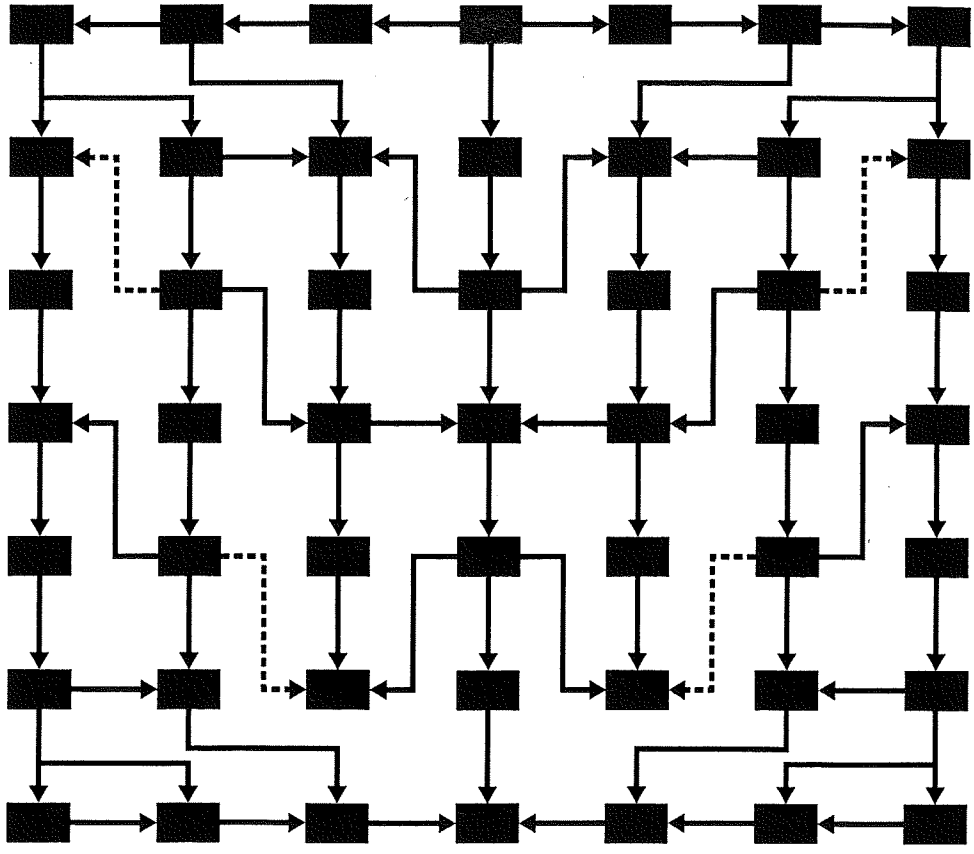

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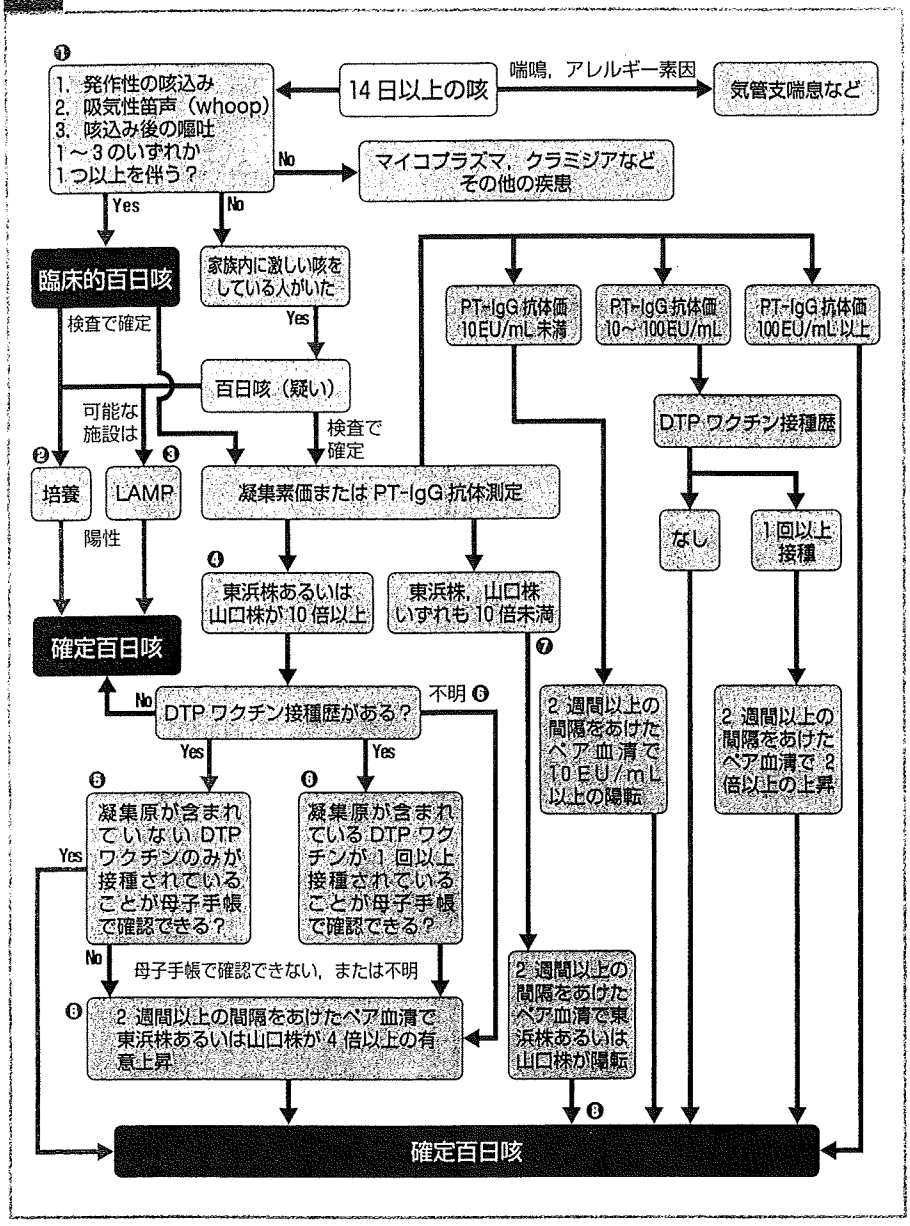
7 百日咳

岡田賢司（国立病院機構福岡病院小児科）



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疫学

◆1982年から4～5年ごとに小さな増減を繰り返しながら報告数は着実に減少してきたが，2005年から微増，2008年は過去10年にない多くの患者が報告された．

◆これまでは，乳児の割合が約半数を占めていたが，近年20歳以上の成人の増加が目立つ．2008年は20歳以上の割合が36.7%となった．

症状

◆DTPワクチン未接種児に認められる典型的な症状に変化はない．DTPワクチン接種児や思春期・成人では，14日以上の長引く咳に，①発作性の咳込み，②吸気性笛声(whoop)，③咳込み後の嘔吐の3症状のうち1つ以上伴えば，臨床的百日咳と診断できる（❶）．

◆家族内に長引く咳など同様な有症状者がいる場合は，百日咳の可能性もあり，確定のために検査を行う．

診察・検査所見

◆聴診所見は，通常異常がない．胸部X線所見も肺炎など合併症がなければ正常である．

◆ワクチン未接種児では，末梢血白血球15,000/μL以上，リンパ球70%以上を呈することが多いが，ワクチン接種児や成人ではこれらの所見は認められない．

◆小児科医が百日咳を疑った場合，半数以上から百日咳菌を分離できる．後鼻腔から軟らかい針金の付いたスワブで検体を採取し，選択培地に塗布する．分離率は，第3病週までが高い．選択培地のため，検査室に目的菌を事前に知らせておく必要がある（❷）．

◆核酸増幅法：LAMP(loop-mediated isothermal amplification) 法は培養より感度がよく，時間的にも早く，死菌でも検出できる．現時点では実施できる施設が限られているが，LAMP法は特別な機器が必要でないため，日常検査として実施できる可能性がある（❸）．

◆わが国では血清診断，とくに凝集素価が検査されることが多い．流行株（山口株）あるいはワクチン株（東浜株）のいずれか10倍以上の場合，DTPワクチン未接種児では，百日咳と確定できる（❹）．凝集原が含まれていないDTPワクチンのみが接種されていることが母子手帳で確認できた場合は，百日咳と確定できる（❺）．凝集原が含まれているDTPワクチンが1回以上接種されていることが母子手帳で確認された場合や接種歴不明の場合，単血清では評価できない．2週間以上の間隔をあけたペア血清での山口株，東浜株いずれか4倍以上の上昇を確認する必要がある（❻）．山口株あるいは東浜株のいずれも10倍未満の場合，抗体価が十分に上昇していない可能性も考慮して再検する（❼）．陽転すれば確定できる（❽）．

◆酵素免疫法 (EIA) でPT (百日咳毒素)-IgG抗体も測定できる．PTは現行DTPワクチンの主要抗原であり，接種により上昇するため，ワクチン接種歴を確認する必要がある．単血清の場合，アメリカ人を対象とした報告ではあるが，94～100 EU/mL以上を目安としている．ペア血清が基本となる．

急増する百日咳

国立病院機構福岡病院　小児科
岡田　賢司

日本薬剤師会雑誌　第61巻第１号別刷

セミナー

急増する百日咳

OKADA　Kenji
岡田 賢司*

疫学：患者年齢の変化[1)]

百日咳は，感染症法で5類感染症・定点把握疾患に分類され，全国約3000の小児科定点から毎週報告されている。図1に1982年からの報告数を示す。4～5年毎に小さな増減を繰り返しながら，報告数は着実に減少してきたが2005年から微増してきた。2007年各地で集団感染が報告され，2008年は5月を中心に過去10年にない多くの患者数が報告された(図2)。近年の特徴は報告される患者年齢に変化が認められる。小児科定点からの報告にも関わらず2002年頃から20歳以上が増加し，2008年28週時点では20歳以上は全体の36.6%を占めた（図3)。

現行のわが国の感染症発生動向調査事業では，百日咳は5類感染症・定点把握疾患に分類され，全国約3000の小児科定点から毎週報告されている。成人百日咳の患者は小児科にはあまり受診しないために，これまで報告されている数は，氷山の一角をみているにすぎない。今後，全体像を把握するためには，内科を含めた広い報告システムが必要と考えられる。

臨床症状

1．典型的な症状

ジフテリア・破傷風・百日咳（DTP）三種混合ワクチン未接種の乳幼児では，かぜ症状からはじまり，通常の鎮咳薬では咳が治まらず，次第に痰を伴わない乾性咳嗽が激しくなる。発作性の5～10回以上途切れなく続く連続的な咳込み（paroxysmal cough/staccato）で苦しくなり，大きな努力性吸気の際に狭くなった声門を吸気が通過する時に，吸気性笛声（whoop）が聞かれる。この特有な一連の咳は夜間に強く，咳込みによる嘔吐，チアノーゼ，無呼吸，顔面紅潮・眼瞼浮腫（百日咳顔貌)，結膜充血などが見られる。

その後，咳込みは減少してくるが，上気道感染などで再び特有な咳が聞かれることがある。

2．DTPワクチン接種児の百日咳

DTPワクチン接種により，百日咳の本態である百日咳毒素（pertussis toxin：PT）に対する抗毒素抗体ができているため，特徴的な咳は少ない。

Yaariらは，5歳～30歳（平均8.9歳）のDTPワクチン接種者の症状を報告している[2)]。「咳の持続は4±3.6週間，診断までに平均23日，特徴的な発作性の咳きこみ21%，咳き込み後の嘔吐13%であった」。このように症状や検査所見が典型的でないため，百日咳と診断されることが少なく，乳幼児への感染源となることが問題となる。

3．思春期・成人の百日咳

「百日咳は子どもの病気」という概念があり，診断・治療が遅れ，乳幼児への感染源となっている。

国立感染症研究所細菌第二部（蒲池一成室長）および当院呼吸器内科と協同で2週間以上の咳で受診した20歳以上の成人患者を対象に表1に示す百日咳診断基準（案）に従って，臨床像を調査した。「2週間以上咳が続いた成人患者を，LAMP法によるPT遺伝子陽性群（A群)，PT遺伝子（－)，血清抗体価で百日咳と診断できた群（B群)，PT遺伝子も抗体価でも百日咳とは診断できない群（C群）に分け，臨床症状の違いを比較した（表2[4)]）。各群とも年齢，白血球数などに差はなかった。受診までの咳の期間は，百日咳感染群は有意に短かった。百日咳に特徴的な「発作性の咳込み」や「吸気性笛声」の症状発現率，「家族内などに周囲に咳をしている者がいる」率は，百日咳感染群で有意差が認められた。

Key words　思春期・成人百日咳／長引く咳／三種混合ワクチン

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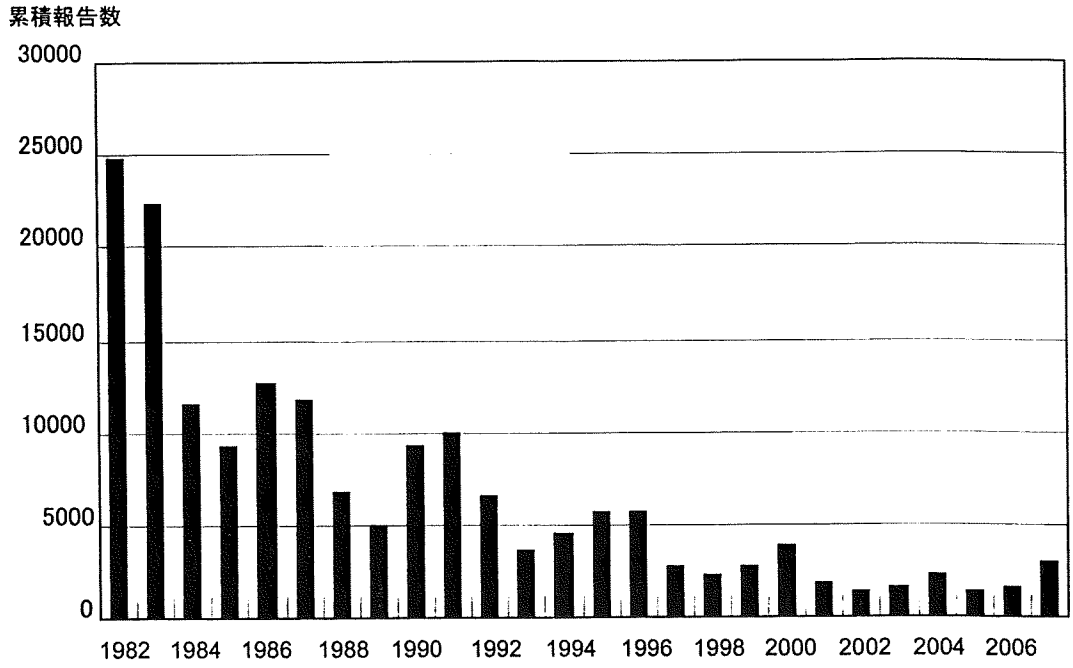

図1 百日咳患者累積報告数の推移(1983－2007年)
(国立感染症研究所感染症情報センター資料より作図)

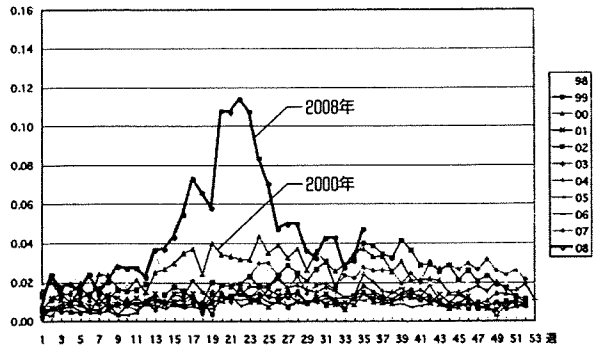

図2 百日咳の定点当たりの年別・週別発生状況(1998～2008年36週まで)

全国の定点数 約3000
(http://idsc.nih.go.jp/idwr/kanja/weeklygraph/09pertus.html)

表1 百日咳診断基準(案)2008

臨床症状 14日以上の咳があり、かつ下記症状を1つ以上を伴う (CDC 1997 WHO 2000)
1 発作性の咳込み 2 吸気性笛声(whoop) 3 咳込み後の嘔吐

実験室診断
発症から4週間以内：培養、LAMP法＋対血清による血清診断
4週間以降： LAMP法＋対血清による血清診断
1 百日咳菌分離
2 遺伝子診断：PCR法または LAMP法
現時点では、LAMP法は全国数カ所の百日咳レファレンスセンター(国立感染症研究所および地方衛生研究所) でしかできない
3 血清診断
(1)凝集素価
1) DTPワクチン未接種児・者：流行株(山口株)、ワクチン株(東浜株)いずれか10倍以上
2) DTPワクチン接種児・者または不明：単血清では評価できない。
対血清での流行株、ワクチン株いずれか4倍以上の有意上昇を確認する必要がある
(2)EIA法： PT(百日咳毒素)-IgG
1) DTPワクチン未接種児・者：1 EU/ml 以上(Bail-ELISA)
2) DTPワクチン接種児・者または不明
対血清：確立された基準はないが、2倍以上を原則とする
単血清(参考)： 94 EU/ml 以上 (Baughman AL 2004) 100 EU/ml 以上 (de Melker HE. 2000)
臨床診断 臨床症状は該当するが、実験室診断はいずれも該当しないとき
確定診断 (1)臨床症状は該当し、実験室診断の1～3のいずれかが該当するとき
(2)臨床症状は該当し、実験室診断された患者との接触があったとき

思春期・成人での長引く咳での百日咳の割合を示す。「成人で6日～1か月続く持続咳嗽患者での百日咳の割合は，流行のない時期に菌分離とPCRおよび百日咳菌特異的なPT抗体で診断すると，陽性率は1～17%（平均13%）であった」[5]。

成人の長引く咳は，乳幼児への感染源となる。Bisgardらは，「乳児患児の接触者で7～20日前に咳があった者を感染源として調査した。両親が多く，次いで兄弟，叔父・叔母，祖父母となっていた」[6]。

診 断

ワクチン接種児や成人例に対する認識が高まってきたが，診断法が具体的に定まっていない。これまでの報告を参考に百日咳診断基準（案）を表1に示す。症状は，14日以上の咳に百日咳特有の咳（発作性の咳込み，吸気性笛声，咳込み後の嘔吐）を伴う場合としている。

確定診断には発症から4週間以内では培養と核酸増幅法（PCR法，LAMP法），4週間以降なら血清診断で確定する。

1．核酸増幅法（PCR法，LAMP法）

培養より感度がよく，時間的にも早く，死菌でも検出できる検査で，有用な検査となるが，まだ実施できる施設が限られている。いずれも新しい診断法であり，とくにLAMP法は特別な機器が必要でないため，今後日常検査として実施できる可能性がある[3]。

2．血清診断法

凝集素価が広く利用され，急性期と回復期のペア血清で4倍以上の上昇を確認することが基本である。

表2「2週間以上の咳」を主訴に受診した成人患者のLAMP法陽性・陰性別の臨床像

	LAMP陽性(n=26)	LAMP陰性(n=43)	
		抗体(凝集素価またはPT-IgG)陽性 (n=26)	抗体価はいずれも陰性 (n=17)
	A 群	B 群	C 群
年齢	51	46.9	47.5
白血球数	6188	6190	7022
リンパ球(%)	28%	28%	31%
受診までの咳の持続期間#1	2週間～4か月(平均 5.0週)*	2週間～5年(平均 4.8週)#1 ∫	2週間～4年(平均11.8週)#1 * ∫
発作性の咳込み	18/20(90.0%)**	8/19(42.1%)**	10/13 (76.9%)
咳込み後の嘔吐	7/20(35.0%)	3/19(15.8%)	3/13 (23.1%)
吸気性笛声	10/20(50.0%) * *	2/19(10.5%) *	1/13 (7.7%) *
夜間覚醒	8/16(50.0%)	10/19(52.6%)	7/13 (53.8%)
胸痛	9/20(45.0%)	4/19(21.0%)	3/13 (23.1%)
息苦しい	7/20(35.0%)	4/19 (21.0%)	4/13 (30.8%)
息が止まりそう	6/20(30.0%)	1/19(5.3%)	2/13 (15.4%)
喘鳴	2/20(10.0%)	2/19(10.5%)	4/13 (30.8%)
周囲の咳(家族歴など)	13/23(56.5%)**	9/19(47.4%) ∫	1/15 (6.6%) ** ∫

#1 平均の算出には受診まで1年以上の症例は除く
** (A VS B) P<0.01 ** (A VS C) P<0.01
* (A VS B) P<0.05 *(A VS C) P<0.05 ∫ (B VS C) P<0.01
検定：年齢・リンパ球(%) は2標本t検定、白血球数・受診までの咳の持続期間(週)は2標本Wilcoxon検定 臨床症状はFisherの直接確率検定

2007/5/22～2008/2/1(LAMP陽性率 26/69 37.7%)
国立病院機構福岡病院呼吸器内科・小児科

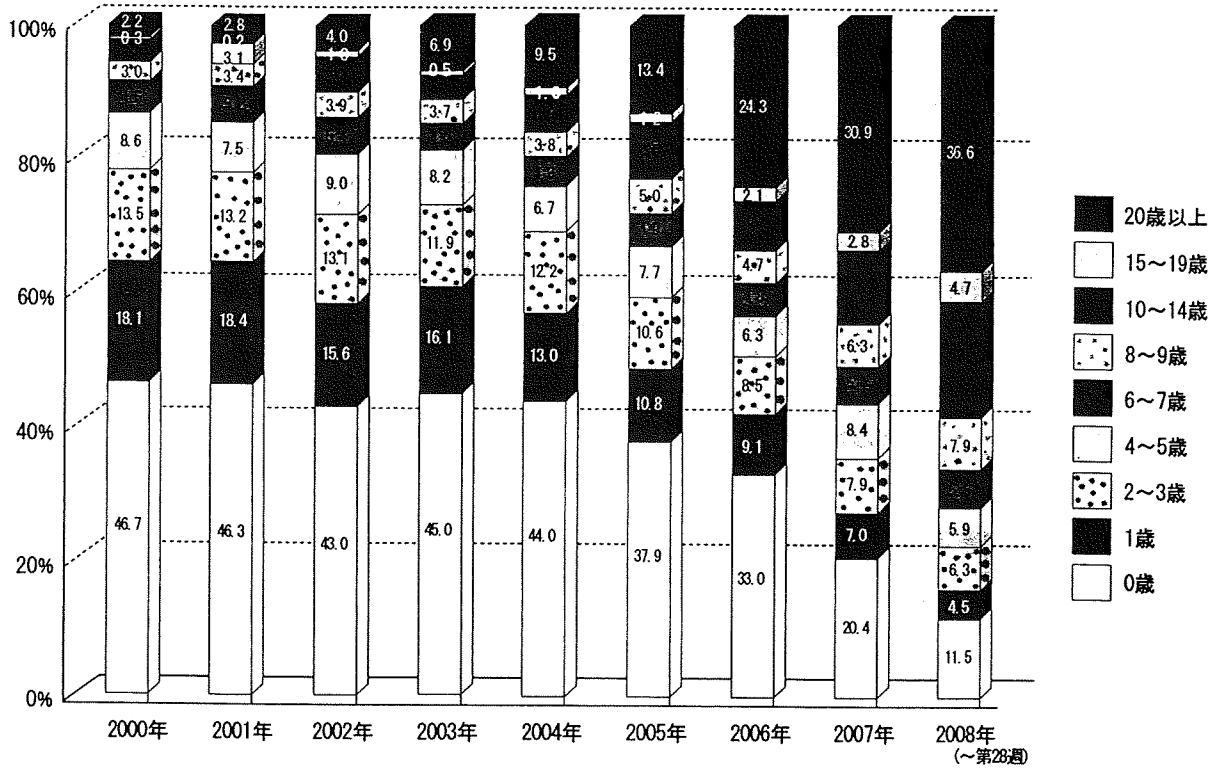

図3　百日咳の年別・年齢群別割合(2000年～2008年第28週)

単血清で高い抗体価の場合は，感染は疑われるが正確な判断ができない。

酵素免役法（EIA）でPT-IgGも測定できる。ペア血清が基本となるが，有意上昇の基準がない。単血清の場合，米国人を対象とした報告ではあるが，94EU/ml以上を目安としている[7]。

治　療

百日咳の多彩な症状は，百日咳菌が気道粘膜に定着後，増殖中に産生する百日咳毒素によると考えられている。このため，抗菌薬は特徴的な咳が出る前であれば，症状の軽症化に有効であるが，家族内感

染などに限られる。多くは，典型的な咳が出始めた頃，あるいは長びく咳などで初めて百日咳を疑われる。この時期の抗菌薬治療は，病状改善効果は低いが，除菌することで周囲への感染を減らせることができるため重要である。通常，治療開始後5-7日で百日咳菌は陰性となる。

治療に関するランダム化および準ランダム化比較試験が報告されている[8]。従来のエリスロマイシン(EM) 14日間治療（長期療法）とクラリスロマイシン（CAM）7日間治療およびアジスロマシン(AZM) 3日間治療（短期療法）とを比較している。菌の消失率は，短期療法と長期療法と同等に有効で，relative risk 1.02であった。副作用は，短期療法が少なく，relative risk 0.66としている。臨床症状の改善および細菌学的再発率も長期療法と短期療法に差がなかった（但し，わが国では百日咳にAZMは保険適用外となっている)。

米国疾病対策センター（CDC）はマクロライド薬の選択に，有効性・安全性・服用性などを考慮したガイドラインを出している[9]。「6カ月以上の乳幼児では，アジスロマイシン（AZM)・クラリスロマイシン（CAM）はエリスロマイシン（EM）と同等な有効性があり，副作用は少なく，使いやすい。CAM・EMはチトクローム p450酵素系の抑制作用があるため，他の薬剤との相互作用を起こしやすい。CAM・AZMは，EMに比較して耐酸性で組織内濃度も高く，半減期も長い。EMは他の2剤より安価。新生児でのAZM・CAMの有効性を実証した報告はないが，肥厚性幽門狭窄症を考慮してEMやCAMよりAZMを暴露後や治療で推奨している」。γグロブリン製剤は痙咳期に効果が認められることがあるが，使用法は確立されていない。

予防接種と最新の動向

わが国は世界に先駆け，発熱など副反応の強かった全菌体百日咳ワクチンを改良した。菌体成分を含まず有効成分のみを単離して，副反応は少なく効果も同等な無細胞百日咳ワクチンを開発した。ジフテリア・破傷風トキソイドと混合し，DTaP（a：acellular 無細胞）として1981年秋から開始し，25年以上が経過した。接種率の向上とともに，百日咳患者は著明に減少し，優れた効果を示してきたが，疫学の項で指摘したように，相対的に10歳以上の患者数が増加している。

米国での増加はわが国より顕著で，対策として新しくジフテリアおよび百日咳の抗原量を減らした思春期・成人用の三種混合ワクチン（Tdap）を2006年1月から11－13歳児にジフテリア・破傷風二種混合（Td）ワクチンに替えて推奨している[10]。フランスは早くから対策をとっており11～13歳にDTaP-不活化ポリオワクチン（IPV）またはTdap-IPVを接種している。ドイツでは9～17歳にTdapまたはTdap-IPVを行っている。

日本でも，増加してきた思春期・成人の百日咳対策が必要な時期となっている。現行2期接種(11～12歳）のDTワクチンに替わり，百日咳ワクチンを加えたDTaPが有益と考えられ，DTaPとDTとの比較試験で有効性と安全性の検討を開始している。

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Effectiveness of an acellular pertussis vaccine in Japanese children during a non-epidemic period: a matched case-control study

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SUMMARY

The number of pertussis cases in Japan has decreased dramatically following the nationwide use of an acellular pertussis vaccine combined with diphtheria-tetanus toxoids (DTaP vaccines) which began in 1981. However, the effectiveness of the DTaP vaccine has not been systematically evaluated using appropriate epidemiological methods during a non-epidemic period in Japan. We evaluated the vaccine effectiveness (VE) of the Kaketsuken DTaP vaccine which contains two-component pertussis antigens in Japanese children from 1999 to 2001 using a matched case-control design and data from the Basic Resident Registration and Maternal and Child Health Handbooks. The DTaP vaccination history of 15 children with pertussis and 59 controls was obtained. The VE of 3 or 4 pertussis vaccinations compared with non-vaccination (baseline) was 96·9% for coughing attacks that lasted ⩾7 days, 96·4% for those lasting ⩾14 days, and 95·9% for those lasting ⩾21 days. These findings suggest that DTaP vaccination effectively prevented pertussis during a non-epidemic period in Japan.

INTRODUCTION

Acellular pertussis (aP) vaccination in Japan was introduced in 1981 after confirmation of antibody production in vaccinees and demonstration of the vaccine's clinical safety [1] and prophylactic effect on secondary infection in family members [2]. A number of randomized controlled trials (RCT) were conducted later, mainly in Europe, to evaluate aP vaccines. Since then, aP vaccines have been used in many countries [3, 4].

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Several observational studies have been conducted worldwide to evaluate the effectiveness of aP vaccine. However, most studies evaluated vaccine effectiveness (VE) during pertussis epidemics. Effectiveness of aP vaccine in a non-epidemic period has been evaluated in only a few studies [5, 6]. By 1987, a Japanese observational study on secondary infection in family members reported the effectiveness of aP vaccine during an epidemic. The National Epidemiological Surveillance of Infectious Diseases showed that the number of reported cases of pertussis decreased dramatically as the vaccination rate increased, suggesting the effectiveness of the aP vaccine. No increases in the number of infected patients suggestive of apparent pertussis outbreaks have been reported since 1997 [7].

No observational study to directly evaluate the effectiveness of aP vaccine has been conducted since the number of reported cases of pertussis started to decrease in Japan.

In addition to the fact that pharmacoepidemiology in Japan is still an underdeveloped discipline, the lack of a database of personal vaccination histories may explain why so few observational studies of VE have been conducted in Japan. Accurate information about individual vaccination status is indispensable for observational studies of VE. In the United States, influenza vaccination information is recorded in the HealthPartners computerized influenza vaccination database and has been used for a cost-effectiveness study [8]. The General Practice Research Database (GPRD) in Great Britain contains vaccination information which has been used for a case-control study [9]. However, such an electronic database has not been developed in Japan. Instead, all parents living in Japan are required to keep their children's vaccination records in their Maternal and Child Health (MCH) Handbooks according to the Maternal and Child Health Law. Parents in Japan therefore have reliable information on their children's vaccination status [10]. Data from the MCH Handbooks could be used to check vaccination status and therefore be used in research studies.

Another limitation on observational studies to evaluate VE in Japan is the need for population sampling. In order to conduct an observational study in the general population, researchers need to check the personal vaccination statuses of individual residents. A telephone survey might be an effective way to collect such information; however, it requires tremendous time and effort to select appropriate subjects based on their age and sex. Many of the existing Japanese observational studies were therefore conducted in patients seeking treatment at hospitals without attempting to survey a representative and unbiased population sample. Fortunately, information such as individual residents' address, name, age, and sex can be obtained for each household from the Basic Resident Registration in Japan. Therefore, efficient random sampling of study subjects is possible if a copy of the resident card is available [11]. We therefore conducted a matched case-control study in Japanese children to evaluate the effectiveness of aP vaccine during a non-epidemic period based on data from MCH Handbooks and the Basic Resident Registration.

METHODS

Paediatricians at 57 medical institutions and paediatric general practitioners participated in the study. We recruited the paediatricians from the members of the Kitakyushu City Medical Association, via an invitation explaining the purpose and plan of our study. Of the paediatricians belonging to the Kitakyushu Medical Association, 66% (57/86) collaborated with our study. Cases and controls were selected from children who lived in Kitakyushu City (population 1·01 million in 1999). Based on a VE of 0·96, which was estimated in a previous small-scale pilot study (K. Okada *et al.*, unpublished data), three controls were selected for each case to ensure a statistical power of 90%.

Vaccine studied

aP vaccines combined with diphtheria-tetanus (DT) toxoids (DTaP) were available in Japan from six manufacturers when the study was conducted. The DTaP vaccine produced by The Chemo-Sero-Therapeutic Research Institute (Kaketsuken; Kumamoto, Japan) was estimated to have been given to >95% of children in Kitakyushu City. The rate of use of the Kaketsuken vaccine was estimated from the total number of units supplied by the manufacturer in the city of Kitakyushu divided by the total number of DTaP vaccines that children received in the city of Kitakyushu. The Kaketsuken vaccine, a two-component aP vaccine, contains a modified formulation of the original aP vaccine; its pertussis toxin (PT) and filamentous haemagglutinin (FHA) were isolated by affinity chromatography to obtain a constant ratio of 1:4 PT to FHA [12]. The standard immunization schedule for DTaP in Japan is an initial dose given three times from ages 3 to 12 months followed by a single booster injection given between 12 and 18 months.

Patients, controls, and diagnosis

From April 1999 to March 2001, the participating paediatricians registered 116 children with clinically suspected pertussis who had attended their hospital or paediatric clinic, and definitive diagnoses were made by another paediatrician responsible for case diagnosis. Clinically suspected pertussis was determined by the participating paediatricians according to the reporting standards used for Japan's pertussis

surveillance, i.e. coughing lasting >1 week with either: (*a*) coughing episodes with staccato, whooping, or paroxysmal cough at night and/or (*b*) neonates or children with otherwise unexplained vomiting or apnoea after cough. For these cases, we examined bacterial isolates from nasopharyngeal swab samples, PT paired serum, and levels of antibody to the fimbriae antigen which is not included in the two-component vaccine, in addition to WBC count and lymphocyte count. After these tests, the paediatrician responsible for case diagnosis reviewed the diagnosis of pertussis on the basis of patient files and test results supplied by the participating paediatricians, and definitively diagnosed pertussis in 15 children. Definitive diagnosis was based on the following: (1) characteristic coughing attacks (repeated staccato, whoop or paroxysmal cough that lasted $\geqslant$7 days and (2) either isolation of *Bordetella* pertussis, serodiagnosis (at least fourfold increase of PT-IgG or agglutinin titre) or contact with a family member with confirmed pertussis.

Controls were randomly selected from the Basic Resident Registration of Kitakyushu City. In Japan, all citizens are registered on the Basic Resident Registration. Individuals can view details including names, dates of birth, sex and address. Controls [matched by age ($\pm$6 months of the date of birth) and sex] were selected who were living in the same residential area as the cases during the study period.

The number of vaccinations was defined as the number of vaccinations received at least 28 days before definitive case diagnosis. A period of 28 days was chosen as the valid period to allow for the development of antibodies (around 14 days) and the normal incubation period (14 days). The age of cases at the time of the valid period was used in the data analysis.

Study method and questionnaires

The study description and a questionnaire with a manual were sent to parents of potential controls between October and December 2005. In a previous small-scale pilot study (using the same method), a 43% valid response rate from the parents of 30 children was achieved. Based on this response rate, we randomly selected nine candidates, which included 'reserves' if additional mailing of questionnaire forms was needed, for each case from the Basic Resident Registration. Questionnaire forms were sent according to the selection order to the first six consecutive candidates per case. If valid responses from three or more controls for each case were not received within 2 weeks, questionnaires were sent to the three 'reserve' candidates. The study description and general information on pertussis were posted on the Kitakyushu Medical Association website to provide information for parents.

The questionnaire sent to the parents of candidate controls included questions on: (1) the history of DTaP vaccination (date, vaccine manufacturer and lot number), (2) whether the control child was born in Kitakyushu City or had moved from another city (in which case the date of arrival was requested), and (3) any history of pertussis, including the date of diagnosis and name of diagnosing institution if available. Parents who consented to taking part in the study also copied the history of DTaP vaccination from their MCH Handbooks. Questionnaires could be returned to the Kitakyushu Medical Association by fax or mail.

The same definitions of number of vaccination and age used for the cases were applied to the controls. The exclusion criteria for controls were as follows: (1) onset of pertussis before the definitive diagnosis of pertussis in the matched case, (2) moving to Kitakyushu City after the onset of pertussis in the matched case, and (3) use of vaccines other than Kaketsuken DTaP vaccine.

The reason for this 4-year delay in surveying controls after the identification of the cases is that there was a change in the method of identifying control subjects. Initially, we planned to collect hospital-based controls, but we received advice from our statistician that the collection of community-based controls would be more appropriate. However, the method of collecting community-based controls in Japan was not established at that point, and it took some time to change the research protocol. Moreover, due to the enactment of the Protection of Personal Information Act in Japan, obtaining permission to view the Basic Resident Registration from the local government also takes a long time. Therefore, there was a delay between collecting the cases and starting to identify suitable controls.

The controls were surveyed in accordance with the 'Ethical Guidelines for Epidemiological Studies' issued by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare in July 2002. The study protocol was approved by the ethical committee of the Public Health Research Foundation.

Table 1. *Age of children and number of DTaP vaccinations*

	0†		1		2		3		4		Total	
Age*	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
<1 yr	7	20	0	4	0	3	1	5	0	0	8	32
1 yr	3	0	0	0	0	1	1	12	0	2	4	15
2 yr	1	0	0	0	0	0	0	2	0	5	1	7
3 yr	1	0	0	0	0	0	0	0	0	1	1	1
5 yr	0	0	0	0	0	0	0	0	0	2	0	2
6 yr	0	0	1	0	0	0	0	0	0	2	1	2
Total	12	20	1	4	0	4	2	19	0	12	15	59

* Age of children.
† Number of DTaP vaccinations.

Statistical analysis

We used SAS software (SAS Institute Inc., Cary, NC) and a conditional logistic regression model to calculate the matched odds ratio (OR) and two-tailed 95% confidence interval (CI) for pertussis events by number of vaccination [1–2 vaccination(s) or 3–4 vaccinations]. The formula $(1-\mathrm{OR}) \times 100$ was used to calculate VE. This was stratified according to the duration of coughing attacks: ≥7 days, ≥14 days, or ≥21 days.

RESULTS

Questionnaires for cases

During the study period, 15 children, aged 4 months to 6 years, received a definitive diagnosis of pertussis. Eight of the children were aged <1 year [their ages were 4 and 10 months (one case each) and 5, 6 and 7 months (each in two cases)], four were aged 1 year, and the remaining three were aged 2, 3, and 6 years (Table 1). Six were boys and nine were girls. Twelve had never been vaccinated, while one child had been vaccinated once and two children had been vaccinated three times.

Ten children had persistent staccato cough, six whooped, 14 had nocturnal paroxysmal cough, two had cyanosis (lasting 1 day and 3 days respectively) and one patient presented with apnoea. Coughing attacks lasted 10–90 days, with one child having coughing attacks that lasted 7–13 days, two children having attacks that lasted 14–20 days, and 12 children having attacks that lasted >21 days. One patient was admitted to hospital. The WBC count was ≥15000/μl in 11 children, and the percentage of lymphocyte was ≥70% in three.

The definitive diagnosis of pertussis was based on *Bordetella* pertussis isolation in two children, on positive PT-IgG antibody titre or significant increase in antibody level in 10 children, and on positive agglutinin titre or its significant increase in three children. No child had contact with a family member with confirmed pertussis. However, of the 15 confirmed cases, 10 had siblings, and among these, three had a sibling who showed signs of pertussis (i.e. consistent coughing lasting ≥14 days), and could have been an infection source.

Questionnaires for controls

For four cases, valid responses were not received within 2 weeks of sending questionnaires from three or more matched controls, so questionnaires were also sent to the parents of the 'reserve' candidates until valid responses were received from three or more controls for each case.

The questionnaire return rate was 69·6% (71/102). We received valid responses from the parents of 59 children; this amounted to three controls for six cases, four controls for four cases, and five controls for five cases. The age of the control children ranged between 4 months and 6 years: 32 were aged <1 year; 15 were aged 1 year; seven were aged 2 years; one was aged 3 years; two were 5 years and two were 6 years (Table 1). Of the controls, 25 were boys, and 34 were girls. Twenty had never been vaccinated, four had been vaccinated once, four twice, 19 three times, and 12 four times.

Twelve children were excluded from the efficacy analysis: one had an onset of pertussis before the onset in the matched case, four had moved to Kitakyushu City after the onset of pertussis in the

Table 2. *Effectiveness of aP vaccine*

Case definition	No. of subjects		No. of vaccinations	OR*	95% CI	VE* (%)	95% CI
	Case	Control					
⩾7 days cough	15	59	1–2	0·132	0·010–1·690	86·8	−69·0 to 99·0
			3–4	0·031	0·003–0·378	96·9	62·2 to 99·7
⩾14 days cough	14	56	1–2	0·140	0·011–1·742	86·0	−74·2 to 98·9
			3–4	0·036	0·003–0·465	96·4	53·5 to 99·7
⩾21 days cough	12	46	1–2	0·161	0·013–2·075	83·9	−107·5 to 98·7
			3–4	0·041	0·003–0·539	95·9	46·1 to 99·7

* Effectiveness of acellular pertussis vaccinations compared with non-vaccination.

matched cases, and seven had been vaccinated with vaccines other than the Kaketsuken DTaP vaccine.

Age of children and number of vaccinations

The rate of vaccination with Kaketsuken DTaP was 87% (comprising a total of 136 injections) in the 67 children (obtained from the 71 completed questionnaires excluding the four children who had moved to Kitakyushu City after the study period).

Vaccination status by age (defined as having received at least one vaccination) was 1/8 in children aged <1 year, 1/4 in children aged 1 year, 0/1 in the children aged 3 or 5 years, and 1/1 in the child aged 6 years (Table 1). Vaccination status in control children was 12/32 in those aged <1 year, 15/15 in those aged 1 year, 7/7 in those aged 2 years, 1/1 in the child aged 3 years, and 2/2 in children aged 5 or 6 years. Based on the number of vaccinations by age, the vaccination rate was lower in the cases than in the controls.

Effectiveness of pertussis vaccine

The cases were divided into three groups based on the duration of coughing attacks characteristic of pertussis: ⩾7 days, ⩾14 days, and ⩾21 days. The cases were further divided into two groups, depending on whether they had received one or two vaccination(s), or three or four vaccinations, to estimate VE by using a conditional logistic regression model (Table 2). The VE of three or four vaccinations compared with non-aP vaccination (baseline) was 96·9% (95% CI 62·2–99·7) for coughing attacks that lasted ⩾7 days, 96·4% (95% CI 53·5–99·7) for ⩾14 days, and 95·9% (95% CI 46·1–99·7) for ⩾21 days. The point estimate of VE for one or two vaccination(s) was 86·8–83·9%. However, the number of subjects who received only one or two vaccination(s) was small, and therefore the confidence interval was large. Therefore, comparing the effectiveness of one or two with three or four vaccinations was difficult.

DISCUSSION

The effectiveness of DTaP vaccine has never previously been evaluated using appropriate epidemiological methods in Japan. We surveyed the DTaP vaccination history of children with pertussis who had coughing attacks that lasted >7 days and of controls who were matched by age and sex in Kitakyushu City. The effectiveness of the DTaP vaccine used in more than 95% of children living in the region for prevention of pertussis was 95·9–96·9% in children who had received three or four vaccinations, equivalent to VE of 96·0% (95% CI 67·4–99·5) in the practice-based controls (children who, for reasons other than pertussis, visited the hospital where the cases received treatment for pertussis around the same time and had the same background as the cases) in the previous study.

A case-control study on DTaP vaccine was conducted in Munich, Germany, from 1993 to 1995. In the cases who were defined as having continual cough for at least 21 days, the VE of three DTaP vaccinations was 93% (95% CI 63–99) [13], which is comparable to the VE of three or more DTaP vaccinations in patients who had continual cough for ⩾21 days estimated in our study (95·9%, 95% CI 46·1–99·7). The Centers for Disease Control and Prevention (CDC) in the United States conducted a case-control study in children aged 6–59 months in seven states and territories by using two types of whole-cell pertussis vaccines combined with DT toxoids (DTwP) and three types of DTaP vaccines

from 1999 to 2000 [14]. The VE estimated in the US study was also comparable to that in our study: 95·4% (95% CI 88·7–98·2) with three DTaP vaccinations and 96·7% (95% CI 90·8–98·8) with four vaccinations.

Since 1991, large-scale field RCTs and cohort studies on DTaP vaccines including aP vaccines developed in Japan have been conducted in children in Europe and Africa. These studies used different designs and case definitions. When evaluated based on the case definition most similar to that used by the World Health Organization (WHO), most DTaP vaccines (with two or more components) showed >80% effectiveness [15].

Thus, the VE reported in the case-control studies are higher than that reported in the RCTs or cohort studies. Pertussis symptoms are often milder in vaccinated children than in their unvaccinated counterparts. VE may therefore be overestimated if the definition 'moderate-to-severe pertussis' is used in the study [16]. Liese *et al.* estimated VE separately based on two sets of definitions, 'pertussis with paroxysmal cough' and 'pertussis with cough', and reported a higher VE among patients who met the stricter criteria [13]. The high VE estimated in our study may be due to the fact that the majority of patients included in the analysis had more severe forms of pertussis (Table 2).

We consider the wide confidence intervals and relatively high point estimates for the effectiveness of one or two doses of vaccine are due to the small number of cases included. However, a similar case-control study conducted in the United States reported the effectiveness of a single vaccination to be 70%, and two doses to be 89%; and they therefore reported similar effectiveness for one or two doses as the present study, i.e. 86% [14].

The effectiveness of aP vaccines in the Japanese population was evaluated based on secondary infection within families in the studies conducted during the pertussis epidemic in the 1980s [17, 18]. However, no placebo-controlled RCT or cohort study was done. In overseas studies, effectiveness of aP vaccines has been evaluated by individual brands. However, other than the study conducted by Kato *et al.* [18], previous Japanese studies on secondary infection within families did not distinguish vaccines by brand.

An RCT or cohort study is ideal for evaluating aP VE. However, because the number of pertussis cases in Japan has decreased substantially due to the increased vaccination rate [19], conducting a cohort study is difficult. Additionally because infant pertussis vaccination is generally recommended in Japan, a randomized study would be unethical. Fine pointed out that the study design for evaluation of secondary infection within families included potential biases that might affect study results [20]. Thus, in the present study, we believe that our use of a case-control design using aP vaccine was the most appropriate to evaluate the effectiveness of DTaP vaccine during a non-epidemic period.

We inspected a copy of the Basic Resident Registration to identify a random sample of control candidates from the community. Sampling efficiency with this method was considered far superior to a telephone survey since control candidates could be matched with cases based on their date of birth and sex provided in the Basic Resident Registration. Unlike authors of studies conducted in Europe and the United States where databases of personal vaccination statuses are available, we used MCH Handbooks kept by parents of study participants as information sources. In Japan, all pregnant women receive an MCH Handbook, and these are retained by most parents or guardians at least until the child reaches the sixth grade of elementary school, which is the end of last required periodical vaccination in Japan. Several reports have been published on epidemiological studies in which MCH Handbooks were used [21, 22]. Documentation of health-care records of mothers and their children including infant vaccination status (including a record of the type of vaccine, manufacturer, lot number, date of vaccination, and administering physician) in MCH Handbooks by physicians is required under Japanese law. Since we asked the parents to copy the details such as manufacturer, lot number and date of vaccination from their MCH Handbooks onto questionnaire forms, the information obtained in the survey was thought to be more reliable than that which could have been obtained from telephone interviews. The study method based on the Basic Resident Registration and MCH Handbooks used in this case-control study on paediatric aP vaccine could therefore be used in Japan as an alternative to the database-oriented study method used in Europe and the United States. The Basic Resident Registration and MCH Handbooks could also be used in other epidemiological studies in Japanese children.

Our study suggests that the Kaketsuken DTaP vaccine effectively prevented pertussis in Japanese children during a non-epidemic period. However,

because this study was conducted in a specific region and had a small number of cases, further research is needed to reach a definitive conclusion.

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DECLARATION OF INTEREST

None.

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疾病に対する取り組み

成人百日咳流行に伴う問題と対策

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要旨 長引く咳に発作性の咳込み，咳込み後の嘔吐，吸気性笛声の一つ以上を伴い，家族内に咳をしている方がいれば，臨床的に百日咳と診断できる．確定には，感染症の基本である百日咳菌分離やLAMP法による抗原検出，血清診断ではペア血清による有意上昇を確認する．疫学の変化，臨床症状の特徴，診断上の問題点とその対策について概説した．

■疫学[1]の変化と今後の課題

百日咳は，感染症法5類感染症・定点把握疾患に分類され，全国約3,000の小児科定点から報告されている．図1に1982年からの定点あたりの報告数を示す．4～5年ごとに小さな増減を繰り返しながら，報告数は着実に減少してきたが2005年から微増，2007年各地で集団感染が報告され，2008年は5月を中心に過去10年にない多くの患者数が報告された（図2）．近年の特徴は患者年齢に変化が認められる．2002年頃から20歳以上が増加し，2008年28週時点では20歳以上は全体の36.6%を占めた（図3）．

現行のわが国の感染症発生動向調査事業では，百日咳は小児科の定点把握疾患であり，報告されているのは氷山の一角である．今後，思春期・成人症例を含めた全体像を把握するためには，内科を含めた報告システムが必要である．

■臨床症状

DTPワクチン未接種の乳幼児に認められる典型的症状に変化はない．通常の鎮咳薬では咳が治まらず，次第に乾性咳嗽が激しくなる．特有な発作性の5～10回以上途切れなく続く連続的な咳込み（paroxysmal cough/staccato）で苦しくなり，大きな努力性吸気の際に狭くなった声門を吸気が通過する時に，吸気性笛声（whoop）が聞かれる．一連の特有な咳は夜間に強く，咳込みによる嘔吐，チアノーゼ，無呼吸，顔面紅潮・眼瞼浮腫（百日咳顔貌），結膜充血などが見られる．その後，咳込みは減少してくるが，上気道感染などで再び特有な咳が聞かれることがある．

1. DTPワクチン接種児の百日咳

特有な咳は少ない．Yaariらは，5～30歳（平均8.9歳）のDTPワクチン接種者の症状を報告している[2]．「咳の持続は4±3.6週間，診断までに平均23日，特徴的な発作性の咳込み21%，咳込み後の嘔吐13%であった」．症状や検査所見が典型的でないため，百日咳と診断されることが少なく，感染源となることが問題となる．

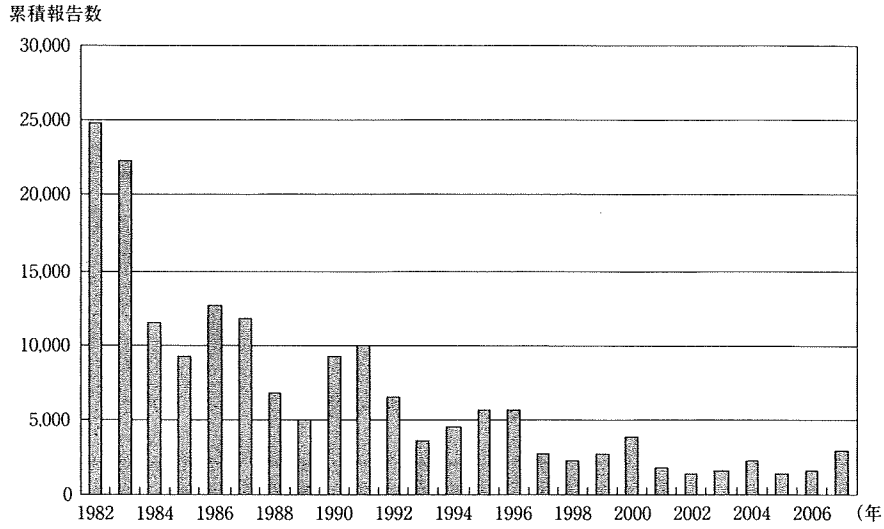

図1　百日咳患者累積報告数の推移（1983～2007年）
（国立感染症研究所感染症情報センター資料より作図）

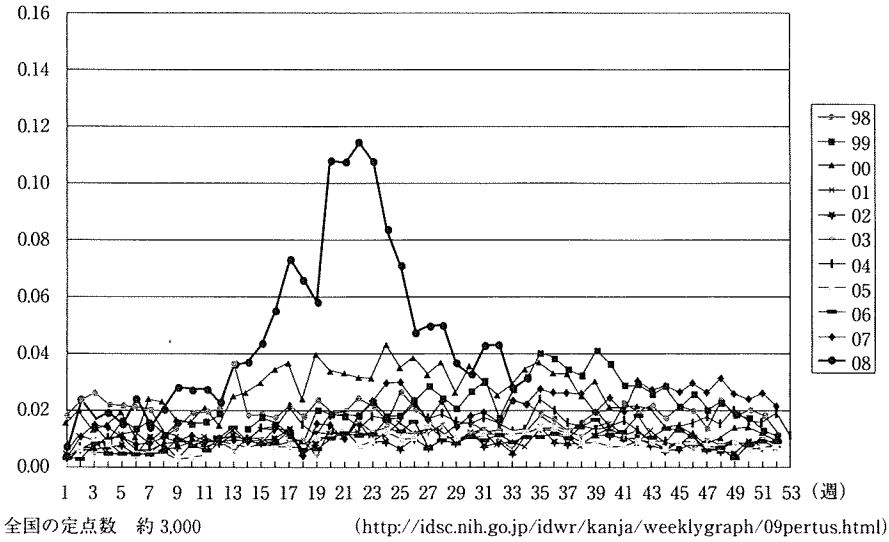

図2　百日咳の定点当たりの年別・週別発生状況（1998～2008年35週まで）

2. 思春期・成人の百日咳

長引く咳などが多いため，診断・治療が遅れ，乳幼児への感染源となっている．国立感染症研究所細菌第2部（蒲地一成室長）および当院呼吸器内科と協同で2週間以上の咳で受診した20歳以上の成人患者を対象に表1に示す百日咳診断基準（案）に従って，臨床像を調査した．「2週間以上咳が続いた成人患者を，LAMP法によるPT（百日咳毒素）遺伝子陽性群（A群），LAMP陰性，血清診断陽性群（B群），LAMP陰性，血清診断陰性で百日咳と診断できなかった群（C群）に分け，臨床症状の違いを示した[3]．各群とも年齢，白血球数，%リンパ球に差はなかった．受診までの咳の期間は，百日咳感染群（A群およびB群）

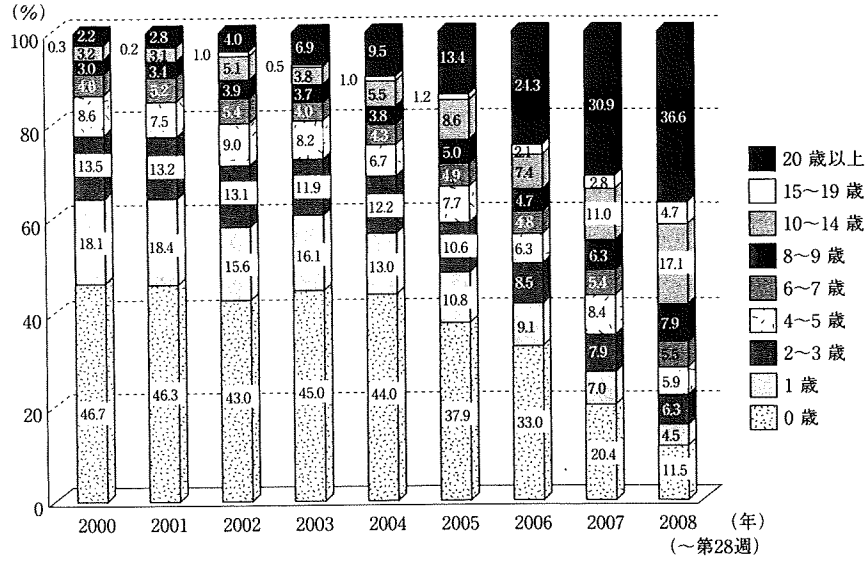

図3　百日咳の年別・年齢群別割合（2000年～2008年第28週）
http://idsc.nih.go.jp/idwr/douko/2008d/28douko.html#chumoku1

は有意に短かった．百日咳に特徴的な「発作性の咳込み」は感染群と非感染群（C群）間で有意差が認められた．「咳込み後の嘔吐」には両群間で差は認められなかった．「吸気性笛声」は感染群間，および感染群・非感染群間で有意差があり，成人百日咳でも10.5～50.0%認められている．「家族内など周囲」の咳は，百日咳感染群と非感染群で有意差が認められた．

「成人で6日～1か月続く持続咳嗽患者での百日咳の割合は，流行のない時期に菌分離とPCRおよび百日咳菌特異的なPT抗体で診断すると，陽性率は1～17%（平均13%）であった」との報告もある[5]．

成人の長引く咳は，乳幼児への感染源となる．Bisgardらは，「乳児の百日咳患児の接触者で7～20日前に咳があった者を感染源として調査した．両親が多く，次いで兄弟，叔父・叔母，祖父母となっていた」[6]．

■診断上の問題点

ワクチン接種児や成人例に対する認識が高まってきたが，実験室診断法が具体的に定まっていない．これまでの報告を参考に百日咳診断基準（案）を表1に示す．症状は，14日以上の咳に百日咳特有の咳（発作性の咳込み，吸気性笛声，咳込み後の嘔吐）を伴う場合としている．確定診断には発症から4週間以内では培養と核酸増幅法（PCR法，LAMP法），4週間以降なら血清診断で行う．

1. 培　　養

患児の後鼻腔から柔らかい針金の付いたスワブを用い検体を採取し，選択培地に塗布する．分離率は，第3病週までが高い．典型的な症状の場合，菌分離率は約52%と高く，早期診断法として有用である．選択培地のため，検査室に目的菌を事前に知らせておく必要がある．

2. 核酸増幅法（PCR法，LAMP法）

培養より感度がよく，時間的にも早く，死菌でも検出できる．特にLAMP法は特別な機器が必要でないため，今後日常検査として実施できる可能性がある[3]．