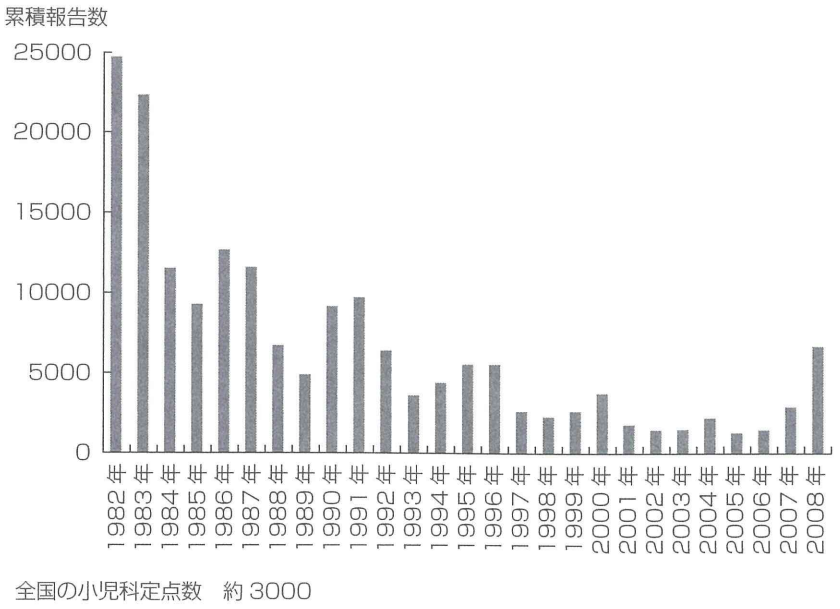

図1．百日咳患者累積報告数の推移（1983－2008年）
（国立感染症研究所感染症情報センター資料より作図）

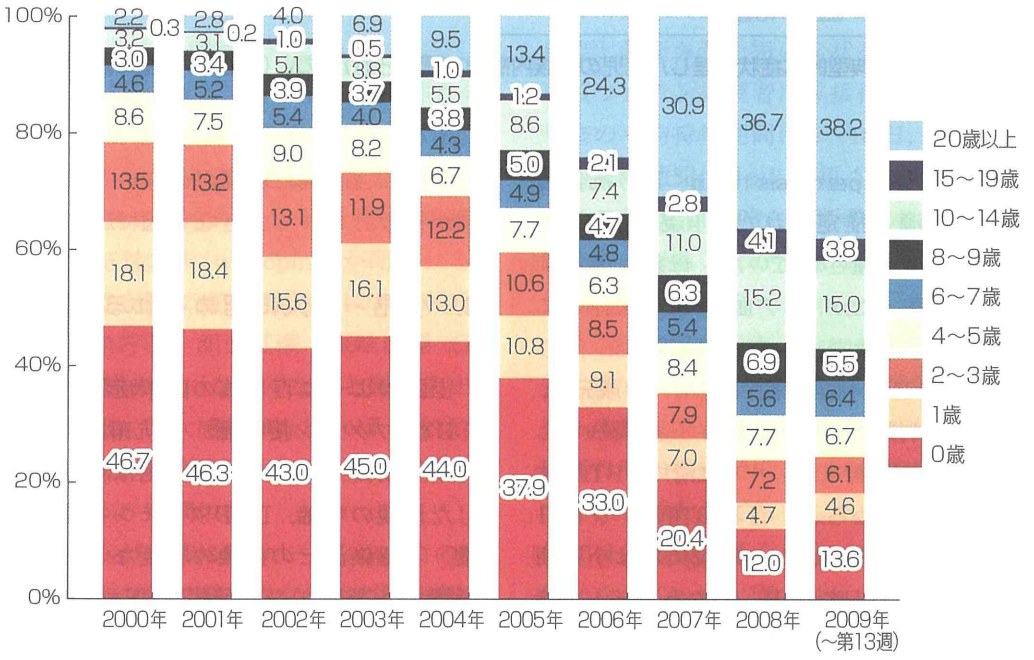

図2．百日咳の年別・年齢群別割合（2000年～2009年第13週）
感染症発生動向調査　週報　2009年第13週

診断した．入院時の問診で，児発病の約3週間前から33歳母親は軽い咳があったが，受診していなかったため，母親の検査も行った．白血球6,400/ul（リンパ球47%）で菌は分離できなかっ

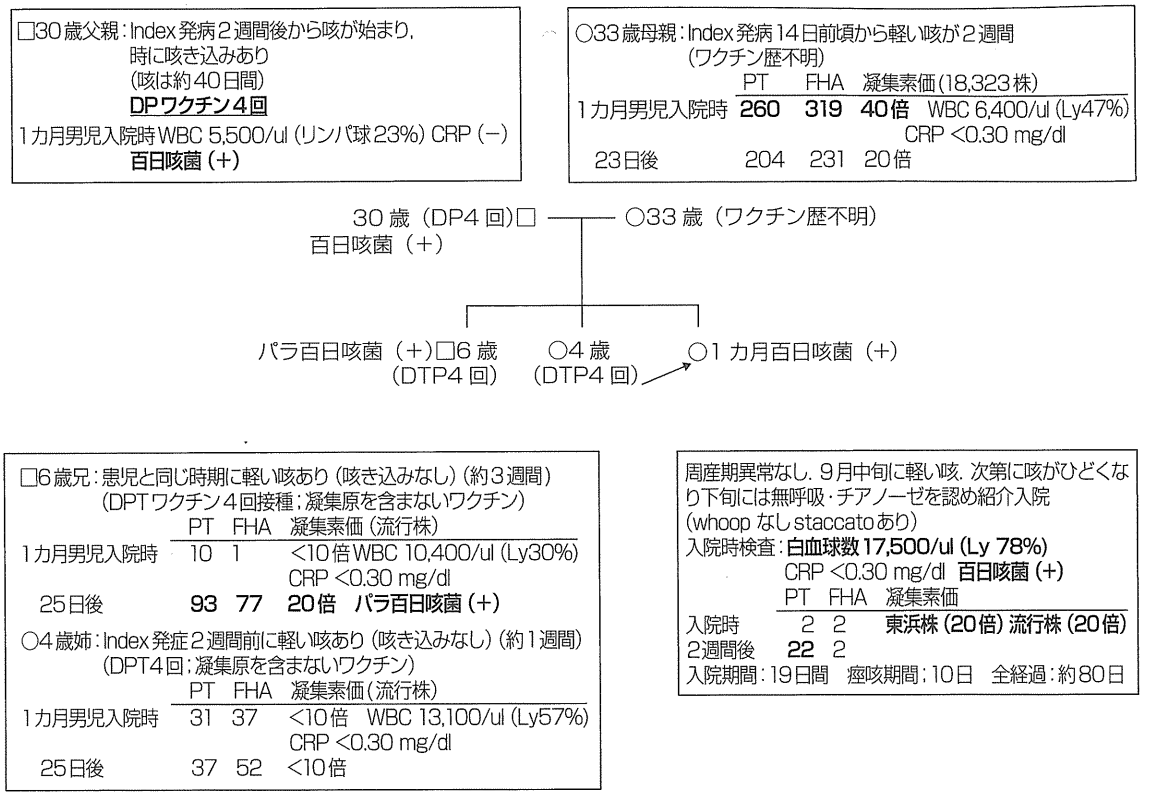

図3．典型的な症状を呈した乳児の家族内感染で認められた成人（両親），同胞の症状

たが，百日咳毒素（pertussis toxin：PT）抗体価は高値で感染源と推定された．4歳姉はDTaPワクチンを4回接種されていた．母親と同じ時期に軽い咳があったが，ペア血清でPT抗体価に変化はなく，感染はなかったと判断した．同じくDTaPワクチンを4回接種されていた6歳兄は，初発児と同じ時期から軽い咳が約3週間続いた．パラ百日咳菌が分離でき，ペア血清で，PT抗体価の有意上昇が認められ，百日咳菌とパラ百日咳菌の重感染と考えられた．30歳父親は小児期にジフテリア・百日咳（DP）ワクチンを4回接種されていた．児発病14日目頃から咳があり，発作性の咳き込みや時に咳込み後の嘔吐および咳による夜間の目覚めなどが認められた．百日咳菌が分離でき，百日咳と診断できた．このように，DPTワクチン接種者や成人が感染を受けても，詳細な家族歴聴取や問診を行わないと，臨床的に百日咳と認識されないことが多く，感染が拡大していく大きな要因である．

3．小児・成人に認められる臨床症状

上記のように百日咳の臨床症状は，①年齢 ②DTPワクチン接種歴 ③抗菌薬の種類，開始時期，期間 ④6カ月未満児は移行抗体を考慮した母親の年齢，DTPワクチン接種の有無，職業 ⑤感染源との接触の程度など多くの因子の影響で多彩である．潜伏期間は，感染後7〜10日が多い（6〜20日）．

1）小児の典型的百日咳の経過と合併症

典型的な経過は，ワクチン未接種の乳幼児に多い．

（1）カタル期（1〜2週間）

軽い咳から始まり，次第に通常の鎮咳薬では

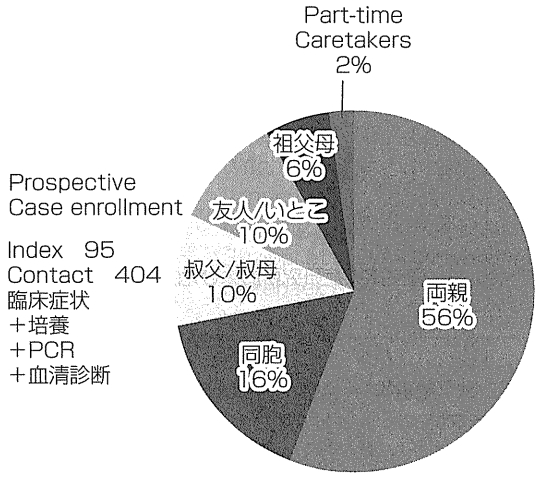

図4. 百日咳の乳幼児への感染源
(Pediatr Infect Dis J 2007. 26：293-299)

咳が治まらず，ひどくなる．この時期での診断は，家族内感染以外は難しいが，適切な抗菌薬療法ができれば，咳症状の軽減に有用とされている．

(2) 痙咳期（3〜6週間）

特徴的な咳が聴かれるようになる．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(whooping)が聞かれる．一連の咳発作は夜間に強く，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（ひどくなると眼球突出）などが見られる．二次感染がなければ，熱はなく咳が激しい割に聴診所見は正常のことが多い．

(3) 回復期（6週間以後）

特有な咳込みが次第に減少してくる．この時期，上気道感染などで再び特有な咳が聴かれることもある．通常3〜6週間で軽快する．

(4) 合併症

米国の28,187例の入院や合併症の報告がある[3]．6カ月未満児に多く，入院率は63.1%，肺炎11.8%，けいれん1.4% 脳症0.2%，死亡0.8% であった．全年齢では脳症26例（0.1%），関連死亡は62例（0.2%）となっている．

2) 乳児の百日咳

6カ月未満の乳児は，月齢，母親からの移行抗体やDTaPワクチン接種の有無などの影響があり症状が多彩である．3カ月未満児は死亡率が高く，無呼吸やけいれんが多く，特有な咳が少ないことが特徴である．生後2カ月以内の児の合併症は，肺炎25%，けいれん3%，脳症1% と報告されている[4]．

3) DTPワクチン接種児の症状

咳の持続や重症度が典型的百日咳ほどではない軽症な百日咳も存在する．とくにワクチン接種児に多い．Yaariらは，5歳〜30歳（平均8.9歳）のワクチン接種者の症状を報告している．咳の持続は4±3.6週間，診断までに平均23日，典型的な症状を示したのはわずか6% であった．平均白血球数は$8.7\pm2.6\times10^3/mm^3$ リンパ球は40±12% であった[5]．Tozziらは，DTaPワクチンの野外試験でDTaP接種児とDT接種児とで，百日咳と診断された児の症状を比較している[6]．百日咳ワクチン接種者は非接種者（DT接種群）より咳の平均持続期間は5〜10日，特徴的な咳込みの平均期間は4〜7日短くなっていた．

この群は，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である．

4) 成人百日咳

成人では咳がひどくない場合は受診しないことも多く，百日咳とほとんど認識されず，乳幼児への感染源となっている[7]．Bisgardらは，乳児百日咳の接触者で7〜20日以前に咳があった者を感染源として調査した．感染源が判明した例では，母親が多く，次いで兄弟，父親，祖父母となっていた（図4）[8]．

(1) 2週間以上の咳で受診した20歳以上の成人を遺伝子診断で診断した場合

当院では，内科と共同で，2週間以上の咳で受診した成人患者を対象に表1に示す百日咳診断の目安に従って，百日咳感染を調査してきた[9]．

LAMP法によるPT遺伝子陽性のA群，PT遺伝

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 40 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（Ball-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 AL2004）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

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	6,188	6,190	7,022
リンパ球（%）	28%	28%	31%
受診までの咳の持続期間 #1	2 週間～ 4 カ月（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（家族癒など）	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

表3．百日咳の診断を培養，PCRおよびPT抗体価に限定した場合の成人の持続咳嗽患者における百日咳感染陽性率

報告者	地域	調査年	陽性率
Mink et al	Los Angels, CA	1986-1989	13
Wright et al	Nashville, TN	1992-1994	16
Jansen et al	San Diego, CA	1993-1994	1
Nenning et al	San Francisco, CA	1994-1995	12
Strebel et al	Mineapolis/St Paul, MN	1995-1996	13
Birkebaek et al	Denmark	1995-1997	17
Vincent et al	Korea	1997-1998	7

（文献10より）

子は検出できなかったが血清診断にて百日咳感染が確認できたB群，LAMP法でも血清診断でも陰性で百日咳とは診断できなかったC群の臨床症状の違いを表2に示す．

各群とも年齢，白血球数，％リンパ球には差がなかった．受診までの咳の持続期間は百日咳感染群（A・B）と非感染群間で有意差があった．症状の出現率では，百日咳に特徴的な「発作性の咳込み」の出現率はA群とB群間で有意な差が認められた．「咳込み後の嘔吐」の率には3群間で差は認められなかった．DTPワクチン未接種の乳幼児患者に特有な咳と考えられていた「吸気性笛声」は，成人でも10.5～50.0％認められた．「咳による夜間の覚醒」・「胸痛」・「息苦しい」・「息が止まりそう」は，A群に多かったが有意差は認められなかった．一方「喘鳴」は，非感染群に多かったが，有意差はなかった．「家族内など周囲の咳」は，百日咳感染群と非感染群とで有意差が認められ，問診上の有用なポイントと考えられる．

(2) 慢性持続咳嗽患者の中の割合

1～4週間続く持続咳嗽患者での百日咳感染の割合は，12～32％であったが咳の持続期間，診断基準などが様々であった．とくに血清診断の抗原で，filamentous haemoagglutinin（FHA），pertactin fimbriaeなどを用いた場合，百日咳菌と*B. parapertussis*，*B. bronchiseptica B. holmesii*などとの抗原交差があるため，陽性率を押し上げている可能性がある．流行のない時期に菌分離とPCRおよび百日咳菌に特異的なPTに対する抗体価のみで診断すると，成人の持続咳嗽患者での陽性率は1～17％〔平均13％〕であった（表3）[10]．

4. 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，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．臨床症状は，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）の1つ以上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）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．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

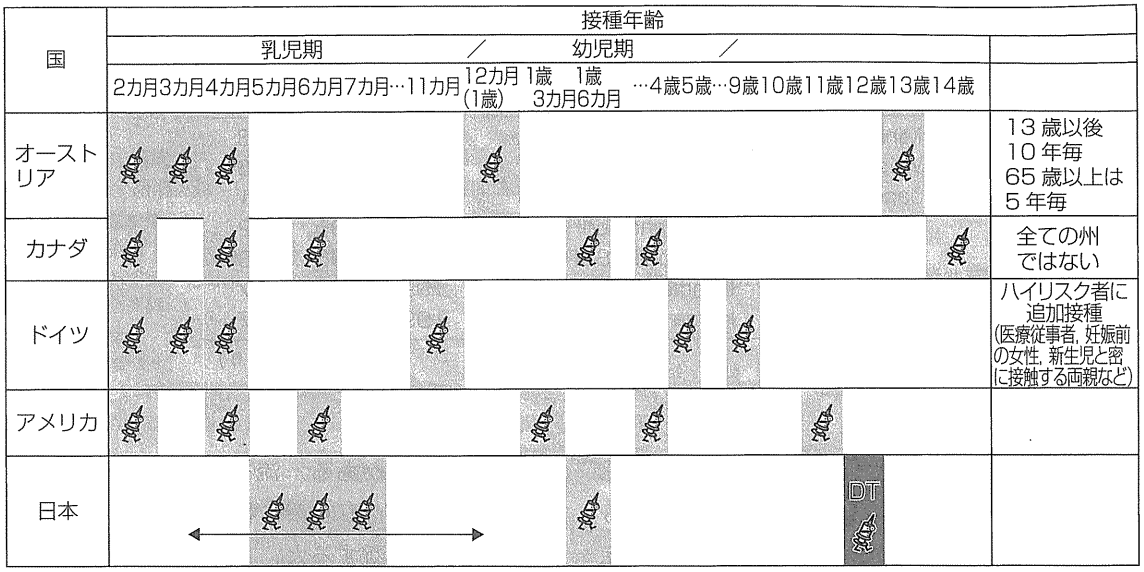

図5. 欧米での百日咳ワクチン接種が6回以上の国々と推奨されている接種年齢およびわが国のDPT/DT接種年齢

きる可能性がある[11].

3) 血清診断法

わが国では凝集素価検査が広く活用されているが，国際的には感度の点であまり推奨されていない．対血清で陽転または4倍以上の上昇が基本である．発症後4週間以上で受診した場合，抗体価がすでに上昇している症例も多く，解釈が容易でない．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（immunoglobulin G）も測定できる．ただ，PTは現行のすべてのDTaPワクチンの主要抗原であり，ワクチン接種により上昇する．そのため，ワクチン接種歴のある患者を診断する場合，DTPワクチン歴を参考にする必要がある．WHOではワクチン接種から3年を経過した患者についてのみ本法の適用を推奨している[12]．対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，94 EU/ml以上を目安としている[13]．

5. 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のカタル期であれば，症状の軽症化に有効であるが，家族内感染や院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，咳の改善効果は低いが，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．

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[14]．「月齢6カ月以上では，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（但し，わが国では百日咳にAZMは保険適用外）．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」．

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．

6. 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[15]．「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．

7. 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，28年が経過した．接種率の向上とともに，小児患者は著明に減少し，優れた効果を示してきたが，近年，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[16]．欧米での百日咳ワクチン接種が6回以上の国々と推奨されている接種年齢を図5に示す．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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Safe and effective booster immunization using DTaP in teenagers

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ABSTRACT

The incidence of reported cases with pertussis has increased in young adults in Japan and the lack of additional booster immunizations containing pertussis components is suspected to be one of the causal reasons. Instead of DT immunization at 11–12 years of age, safety and immunogenicity were investigated using 0.2 ml and 0.5 ml of DTaP. 176 subjects in DTaP 0.5 ml, 178 in DTaP 0.2 ml, and 197 in DT 0.1 ml groups were enrolled in clinical trial. The relative risk of local reactions in the DTaP 0.2 ml group compared to the DT 0.1 ml group was 1.13 (95% CI: 0.97–1.30), and that of the DTaP 0.5 ml to the DT 0.1 ml group was 1.34 (95% CI: 1.18–1.53). The relative risks of local pain and heat were 1.62 (95% CI: 1.33–1.98) and 1.59 (95% CI: 1.19–2.13), respectively, in the DTaP 0.5 ml group compared to the DT 0.1 ml group. Seropositive rates against PT and FHA were 54% and 82% before immunization and increased to >95% for both after vaccination with no significant difference in GMT. Instead of the scheduled DT program, 0.2 ml of DTaP was acceptable and demonstrated efficient immunogenicity.

1. Introduction

Pertussis is still a serious illness in young infants, causing whooping cough, apnea, cyanosis, chocking, and encephalopathy [1]. In Japan, whole cell pertussis vaccine was developed in 1950s and combined with diphtheria and tetanus toxoids (DTwP). DTwP became accepted, resulting in a reduction of reported cases of pertussis [2,3]. Approximately 10% of recipients experienced a febrile illness, with 50–60% showing redness and 20% induration [2]. In 1974–75, two accidental deaths after DTwP administration were reported and, thereafter, DTwP was discontinued for a while. It was re-introduced for children at 2 years of age, but the number of pertussis patients increased because of low vaccine coverage [2,3]. In 1981, a new type of acellular pertussis was developed, and combined vaccine (DTaP) was introduced into recommended immunization practice. Principally, two types of DTaP vaccines were developed: the B-type consisted of two major antigens, pertussis toxin (PT) and filamentous hemagglutinin (FHA) and the T-type contained pertactin and fimbrie besides PT and FHA [4–6]. Nationwide monitoring of clinical adverse events demonstrated low reactogenicity and sufficient antibody responses similar to natural infection. Since 1981, the number of pertussis patients decreased after the acceptance of DTaP. The incidence of pertussis in adults has been increasing gradually from 2002 in Japan, and several outbreaks on college campuses, and in high schools and offices have been reported [7,8]. In addition, the incidence in young infants less than 1 year of age increased as well as adult cases in 2009.

Pertussis is principally an infectious children's illness causing whooping and prolonged cough and the Advisory Committee on Immunization Practices (ACIP) recommended a 5-dose DTaP schedule, at ages 2, 4, 6, and 15–18 months and 4–6 years, instead of the previous DTwP in the US in 1997 [9]. In 1990s, the incidence of pertussis in older age increased in many countries because of waning immunity after primary childhood immunization and antigenic change of pertussis, and adolescent pertussis was identified as the source of transmission of pertussis to young infants through enhanced surveillance studies [10–16]. In 2005, tetanus toxoid, and a reduced concentration of diphtheria toxoid combined with reduced acellular pertussis (Tdap) vaccine was licensed, and the ACIP recommended that adolescents aged 11–18 years should receive a single dose of Tdap for booster immunization [17]. It was now recommended for all generations from 19 to 64 years [18].

It takes several years to obtain a license to introduce a new vaccine from foreign countries into Japan, even though Tdap is

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used worldwide. The immunization schedule in Japan incorporates no booster dose of pertussis components after the completion of the initial primary immunization (three times over 3 months of age and additional dose after approximately 12 months after the third dose), and vaccine containing pertussis components should be scheduled to cope with an outbreak of pertussis. In this study, safety and immunogenicity were investigated in clinical trials using 0.2 and 0.5 ml of DTaP at the age of 11–12 years, in comparison with 0.1 ml of DT.

2. Subjects and methods

2.1. Subjects

The study was conducted from September 2008 to August 2009, involving 29 pediatric outpatient clinics and departments of pediatrics of regional public and university hospitals. Subjects of this study included 555 children, 11–18 years of age, mostly 11–12 years of age, who had completed primary immunization of more than three doses of DTaP and had not undergone DT immunization. The study protocol was checked by the ethical committee of National Mie Hospital as a central organization and also checked by ethical committee of each hospital. Written informed consent was obtained from their parents or guardians. A total of 555 children were enrolled, but four children were excluded: three did not complete the primary immunization (one or two doses of DTaP), and one had already been immunized with DT. They were divided into two study groups: group 1 consisted of 266 subjects undergoing serological examination: 29 receiving 0.1 ml of DT, 119 for 0.2 ml of DTaP, and 118 for 0.5 ml of DTaP. Group 2 comprised 285 immunized without serological examinations, and totaling 551 subjects, with 197 receiving 0.1 ml DT, 178 for 0.2 ml of DTaP, and 176 for 0.5 ml of DTaP, were examined for safety. They are summarized in Fig. 1.

2.2. Vaccines

Five brands of DTaP were on the market in Japan, and the components of each antigen were different for each brand, as shown in Table 1. Subjects were allocated equally to each brand. The B-type (Biken and Kaketsu) vaccine consisted of PT and FHA and the T-type (Takeda, Denka, and Kitasato) contained other components, and the composition of pertussis antigens differed from the brands of DTaP available abroad [5,6,19]. The PT antigen contents varied from 3 to 23.5 μg/dose, and FHA from 23.5 to 51.5 μg/dose, but the amount of diphtheria and tetanus toxoids was 15 and 2.5 Lf/dose, respectively, without a difference among DTaP brands. 0.2 ml of DTaP contained 1.2–9.4 μg of PT, 9.4–20.6 μg of FHA, 6–6.6 Lf of diphtheria toxoid, and 1.0 Lf of tetanus toxoid. Antigen contents of FHA and diphtheria toxoid were slightly higher in 0.2 ml of DTaP than Tdap, Boostrix and Adacel (2.5–8 μg of PT, 5–8 μg of FHA, 2–2.5 Lf of diphtheria toxoid, and 5 Lf of tetanus toxoid) [17]. A 0.2-ml volume of DTaP contained similar amounts to Tdap. The antigen content of tetanus toxoid was lower in 0.2 ml of DTaP than Tdap available abroad, similar to 0.1 ml of DT.

2.3. Study design

The study was designed as a randomized open trial. Subjects were allocated randomly to DT 0.1 ml, DTaP 0.2 ml, and DTaP 0.5 ml groups. They were observed for 30 min for the appearance of anaphylaxis. To assess the safety afterwards, they were asked to check their body temperature and for adverse clinical events based on the healthcare diary every day for 7 days after immunization. In study group I, paired sera were obtained immediately before immunization and principally 4–6 weeks after immunization and kept at −20 °C. The paired sera were divided into two aliquots and transferred to the National Institute of Infectious Diseases, Department of Bacteriology II to examine antibodies against diphtheria and tetanus toxoids and to Kitasato-Otsuka Bio-Medical Assay Laboratories for the examination of pertussis antibodies (PT and FHA).

2.4. Serology

Antibodies against tetanus toxoid were determined with a KPA kit (Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan) [20]. The kit comprised polypeptide artificial carrier particles stained with Reaction Blue solution, sensitized with highly purified tetanus toxoid (3000 Lf/mg PN), and provided in lyophilized form. The test was performed as instructed by the

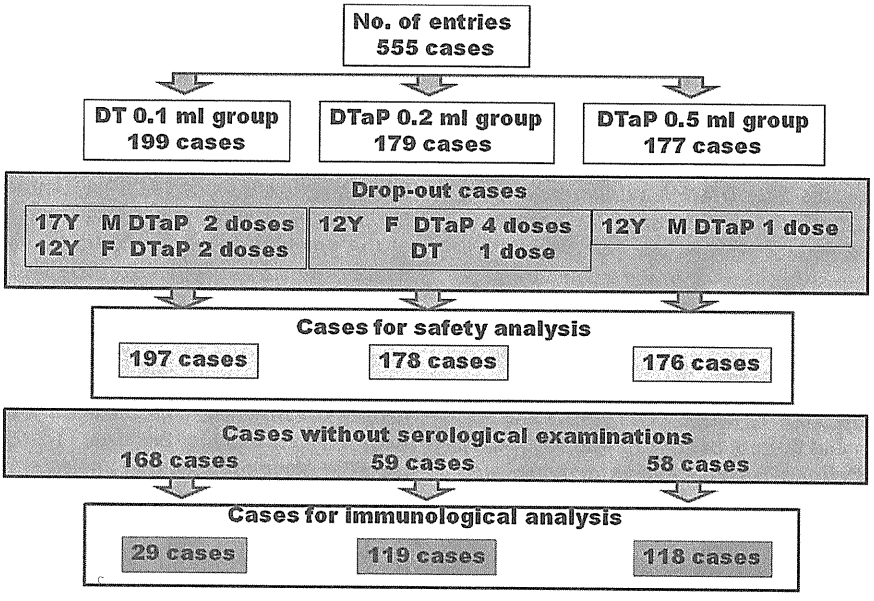

Fig. 1. Number of subjects in the study. A total of 555 subjects were enrolled, of whom four were excluded. Therefore, 551 subjects were evaluated regarding safety. Among the 551, 197 were immunized with 0.1 ml of DT, 178 with 0.2 ml of DTaP, and 176 with 0.5 ml of DTaP. Study group 1 consisted of 266 subjects for serological examination: 29 with 0.1 ml of DT, 119 with 0.2 ml of DTaP, and 118 with 0.5 ml of DTaP.

Table 1
Contents of PT, FHA, and diphtheria and tetanus toxoids.

DTaP/DT (manufacturers)	PT (μg)	FHA (μg)	Pertactin	Fimbrie	D (Lf)	T (Lf)
DTaP 0.5 ml (Kaketsu)	8	32			≦16.7	≧2.5
DTaP 0.5 ml (Biken)	23.5	23.5			≦15	≦2.5
DTaP 0.5 ml (Takeda)	3	34.5	7.5	1	≧15	≧2.5
DTaP 0.5 ml (Denka)	9	32	15	1	≦15	≦2.5
DTaP 0.5 ml (Kitasato)	6	51.5	5	1	≧15	≧2.5
Adacel (Aventis)	2.5	5	3		2	5
Boostrix (GSK)	8	8	2.5		2.5	5
DTaP 0.2 ml	1.2–9.4	9.4–20.6			6–6.6	1.0
DT 0.1 ml					3.2	0.7

Table 2
Background of the subjects.

	DTaP 0.2 ml (*N* = 178)	DTaP 0.5 ml (*N* = 176)	DT 0.1 ml (*N* = 197)	Total (*N* = 551)
Gender				
Male	93 (52.2%)	95 (54.0%)	113 (57.4%)	301 (54.6%)
Female	85 (47.8%)	81 (46.0%)	84 (42.6%)	250 (45.4%)
Age				
11 years	97 (54.5%)	95 (54.0%)	73 (37.1%)	265 (48.1%)
12 years	68 (38.2%)	68 (38.6%)	111 (56.3%)	247 (44.8%)
Others	13 (7.3%)	13 (7.4%)	13 (6.6%)	39 (7.1%)
Mean age ± SD	11.6 ± 0.8	11.6 ± 0.8	11.8 ± 0.8	11.6 ± 0.8
Median age	11.0	11.0	12.0	12.0
Range (min–max)	(11–15)	(11–15)	(11–17)	(11–17)
DPT history				
I-1	178 (100.0%)	176 (100.0%)	197 (100.0%)	551 (100.0%)
I-2	178 (100.0%)	176 (100.0%)	197 (100.0%)	551 (100.0%)
I-3	172 (96.6%)	172 (97.7%)	193 (98.0%)	537 (97.5%)
I-boost	172 (96.6%)	168 (95.5%)	191 (97.0%)	531 (96.4%)

manufacturers. Antibodies against diphtheria toxoid were examined using the micro cell-culture method with Vero cells, and diphtheria antitoxin titers were expressed as international units (IU)/ml [21]. Antibodies against PT and FHA were examined using enzyme-linked immunosorbent assay (EIA) kits (Wako Chemicals, Japan) as instructed by the manufacturers. Positive levels were defined as ≥0.1 IU/ml for antibodies against diphtheria toxoid, ≥0.01 IU/ml for those against tetanus toxoid, and ≥10 EU/ml for those against PT and FHA [22,23].

2.5. Statistical analysis

The sero-positivity rate and the incidence of solicited adverse events (fever as systemic reaction, and redness, swelling, pain, heat, and itching as local reactions) were compared by using Fisher's Extraction test. Geometric mean titers (GMTs) of antibodies before and after immunization were compared by converting to a logarithmic scale using Wilcoxon rank test. The *t* student Welch method was employed to evaluate significance and the significant level was set at $p < 0.05$.

3. Results

3.1. Background of the subjects

The subjects included 555 children aged 11–18 years of age, as shown in Fig. 1. A total of 555 subjects were enrolled, but four were excluded. Therefore, 551 subjects were evaluated for safety. Among the 551, 197 were immunized with 0.1 ml of DT, 178 with 0.2 ml of DTaP, and 176 with 0.5 ml of DTaP. The backgrounds of the subjects are shown in Table 2. A total of 301 (54.6%) were male, and the gender ratio was similar among the three groups with no significant differences in ages, which ranged from 11 to 17 years. They had all completed their primary immunizations (three or four doses of DTaP), confirmed by checking their immunization records.

3.2. Incidence of adverse events

The incidences of adverse events are summarized in Table 3. Febrile reactions were noted in 8 (4.1%) of 197 in the DT 0.1 ml group, 7 (3.9%) of 178 in the DTaP 0.2 ml group, and 7 (4.0%) of 176 in the DTaP 0.5 ml group, and the relative risks in DTaP

Table 3
Incidence of clinical adverse events.

Adverse events	DTaP 0.2 ml (1)	DTaP 0.5 ml (2)	DT 0.1 ml (3)	Risk ratio (95% CI)		
	(*N* = 178)	(*N* = 176)	(*N* = 197)	(2) vs. (1)	(1) vs. (3)	(2) vs. (3)
Fever	7 (3.9%)	7 (4.0%)	8 (4.1%)	1.01 (0.36,2.82)	0.97 (0.36,2.62)	0.98 (0.36,2.65)
Local reactions	123 (69.1%)	145 (82.4%)	121 (61.4%)	1.19 (1.06,1.34)	1.13 (0.97,1.30)	1.34 (1.18,1.53)
Redness	95 (53.4%)	'109 (61.9%)	92 (46.7%)	1.16 (0.97,1.39)	1.14 (0.93,1.40)	1.33 (1.10,1.60)
Swelling	90 (50.6%)	95 (54.0%)	76 (38.6%)	1.07 (0.87,1.30)	1.31 (1.04,1.65)	1.40 (1.12,1.75)
Pain	83 (46.6%)	116 (65.9%)	80 (40.6%)	1.41 (1.17,1.71)	1.15 (0.91,1.45)	1.62 (1.33,1.98)
Heat	50 (28.1%)	74 (42.0%)	52 (26.4%)	1.50 (1.12,2.00)	1.06 (0.76,1.48)	1.59 (1.19,2.13)
Itching	81 (45.5%)	83 (47.2%)	75 (38.1%)	1.02 (0.82,1.28)	1.21 (0.95,1.54)	1.24 (0.98,1.57)

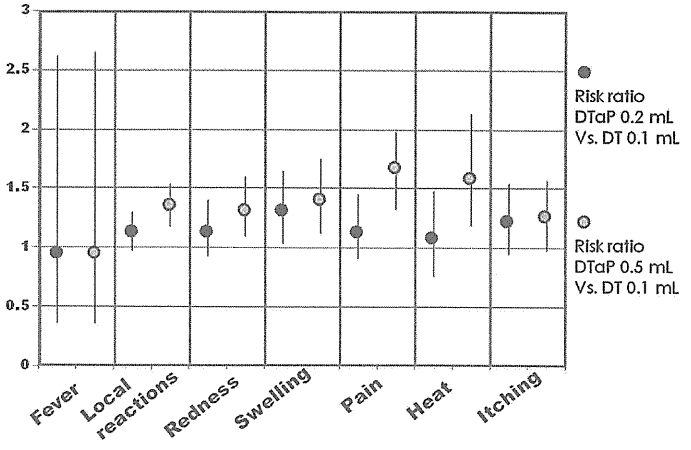

Fig. 2. Summary of the risk ratio regarding the incidence of adverse reactions. The relative risks of the incidence of adverse reactions after immunization with 0.2 ml (●) and 0.5 ml (◎) of DTaP in comparison with those observed after immunization with 0.1 ml of DT are summarized. Vertical lines represent 95% CI.

0.2 ml and DTaP 0.5 ml groups were 0.97 and 0.98, respectively, in comparison with that observed in the DT 0.1 ml group. The relative risk of local reactions after immunization with DTaP at 0.2 ml was 1.13 (95% CI: 0.97–1.30) in comparison with the incidence after immunization with DT at 0.1 ml, and that of the DTaP 0.5 ml compared to the DT 0.1 ml group was 1.34 (95% CI: 1.18–1.53). Relative risks of redness, swelling, local pain, heat, and itching in the DTaP 0.2 ml group compared to the DT 0.1 ml group were 1.14 (95% CI: 0.93–1.40), 1.31 (95% CI: 1.04–1.65), 1.15 (95% CI: 0.91–1.45), 1.06 (95% CI: 0.76–1.48), and 1.21 (95% CI: 0.95–1.54), respectively. However, the relative risks of redness, swelling, local pain, heat, and itching in the DTaP 0.5 ml group compared to the DT 0.1 ml group were 1.33 (95% CI: 1.10–1.60), 1.40 (95% CI: 1.12–1.75), 1.62 (95% CI: 1.33–1.98), 1.59 (95% CI: 1.19–2.13), and 1.24 (95% CI: 0.98–1.57), respectively. The relative risks of the adverse reactions after immunization in the DTaP 0.2 ml and 0.5 ml groups in comparison with those observed after immunization in the DT 0.1 ml group are summarized in Fig. 2. Thus, the incidence of local reactions after immunization with 0.2 ml of DTaP was similar to that observed after immunization with 0.1 ml of DT, but those observed after immunization with 0.5 ml of DTaP were higher than after immunization with 0.1 ml of DT, notably regarding the incidences of local pain and heat, demonstrating the relative risks: 1.62 (95% CI: 1.33–1.98) and 1.59 (95% CI: 1.19–2.13), respectively.

3.3. Onset of adverse reactions

The immunization day was defined as day 0. The onset of adverse reactions was examined, and the results are shown in Fig. 3. Febrile reactions were noted from days 0 to 7 without any case accumulation, but the incidence of local reactions peaked on days 1 and 2. Systemic adverse events were reported sporadically: headache in 25 (9 in DT 0.1 ml group, 9 in DTaP 0.2 ml group, and 7 in DTaP 0.5 ml group), fatigue in 11 (3 in DT 0.1 ml group, 4 in DTaP 0.2 ml group, and 4 in DTaP 0.5 ml group), rhinorrhea in 10 (1 in DT 0.1 ml, 2 in DTaP 0.2 ml, and 7 in DTaP 0.5 ml group), sore throat in 8, cough in 7, and nasal obstruction in 7. Three subjects with urticaria eruption were reported: two on day 0 (one for each DT 0.1 ml and DTaP 0.5 ml group) and one on day 1 in DTaP 0.5 ml group. Generalized eruption was reported on day 1 in DTaP 0.5 ml group. The relative risk of local reactions on day 0 after immunization with 0.2 ml of DTaP compared to that observed after 0.1 ml of DT was 1.08 (95% CI: 0.74–1.58), 1.18 (95% CI: 0.96–1.44) on day 1, 1.09 (95% CI: 0.91–1.30) on day 2, 1.19 (95% CI: 0.97–1.47) on day 3, 1.3 (95% CI: 0.99–1.71) on day 4, 1.56 (95% CI: 1.09-2.23) on day 5, 1.42 (95% CI: 0.87–2.29) on day 6, and 1.54 (95% CI: 0.87–2.72) on day 7. The incidence of local reaction for each day after immunization with 0.2 ml of DTaP was similar to that observed after 0.1 ml of DT. The incidence of local reactions after immunization with 0.5 ml of DTaP was higher than that observed in the DT 0.1 ml group, especially on days 1 and 2, with a relative risk of 1.61 (95% CI: 1.35–1.92) on day 1, and 1.33 (95% CI: 1.13–1.92) on day 2. Most local adverse reactions appeared on day 1 and continued for 3–4 days, but those observed in the DTaP 0.5 ml group became prolonged, showing a relative risk of 2.15 (95% CI: 1.39–3.33) on day 6.

In this study, the extents of redness and swelling were monitored when they appeared and the degree of adverse reactions was evaluated (Fig. 4). There was no significant difference in the incidence of redness and swelling of <2.0 cm and 2–5 cm among the

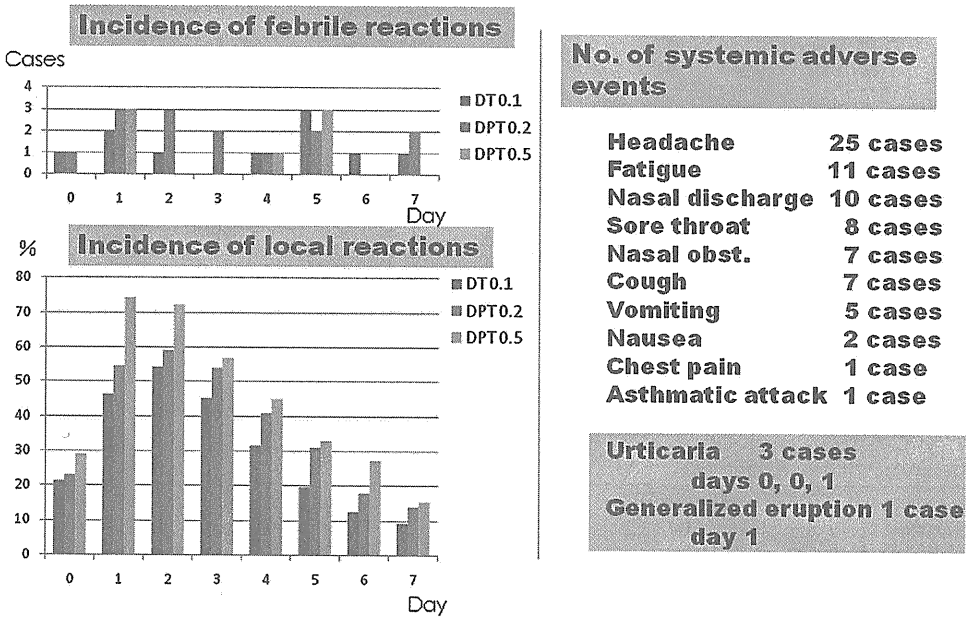

Fig. 3. Onset of febrile and local reactions within 7 days after immunization and the no. of cases with systemic adverse events.

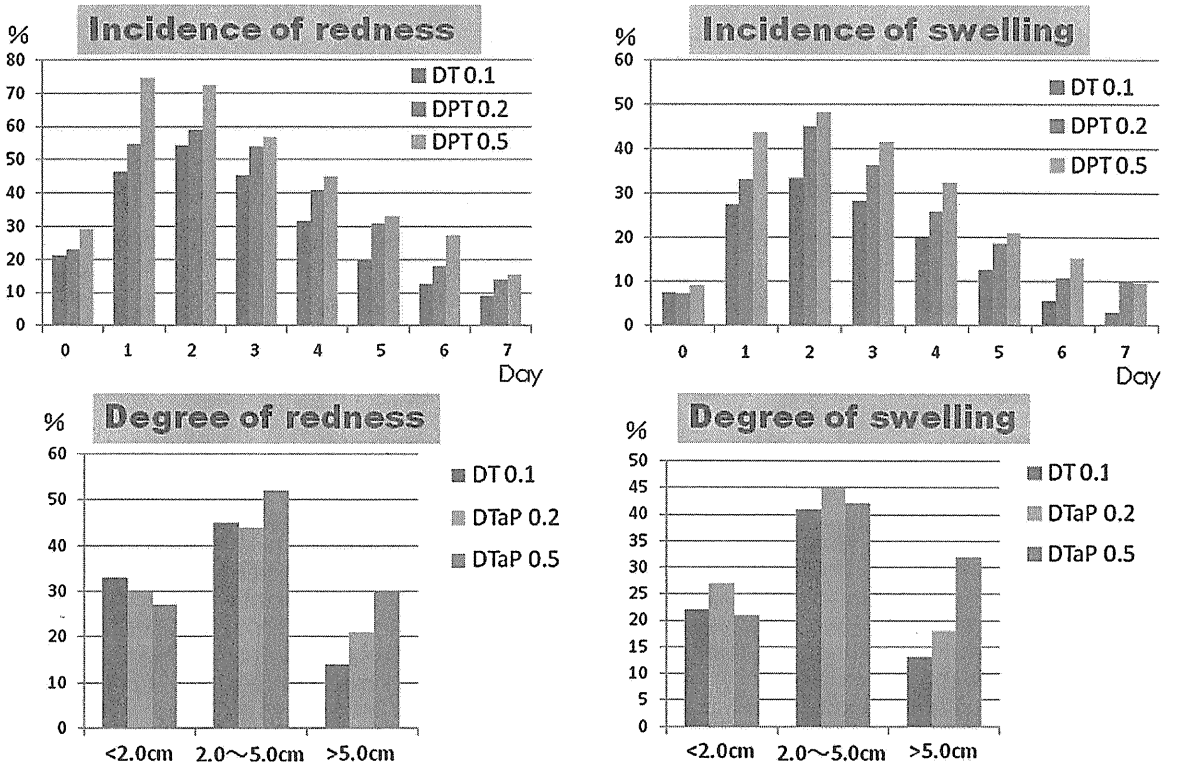

Fig. 4. Onset of local redness and swelling, and the severity of adverse events.

three groups, but 0.5 ml of DTaP had a tendency to induce a serious local reaction (redness and swelling) >5.0 cm.

3.4. Immunogenicity

Study group 1, in whom paired serum samples were examined, consisted of 266 subjects with serological examination, 29 with 0.1 ml of DT, 119 with 0.2 ml of DTaP, and 118 with 0.5 ml of DTaP. The sero-positivity of antibodies for diphtheria toxoid >0.1 was 60.9% (162/266), 90.6% (241/266) for tetanus toxoid >0.01, 54.13% (144/266) for PT >10, and 82.33% (219/266) for FHA > 10 EIA units. Antibodies against PT were markedly reduced at the age of 11–12 years.

The results of sero-positivity and GMT are shown in Table 4. The sero-positivity of PT and FHA and their GMT were the same before and after immunization in the DT 0.1 ml group. After immunization, the sero-positivity against PT increased from 52.1 to 95% in the DTaP 0.2 ml group and from 55.1 to 95.8% in the DTaP 0.5 ml group. The GMT of PT antibodies after immunization with 0.2 ml of DTaP was 89.05 (95% CI: 70.54–112.41), and there was no significant difference after immunization with 0.5 ml of DTaP, being 102.74 (95% CI: 82.91–127.32). Sero-positivity against FHA increased from 85.7 to 100% in the DTaP 0.2 ml group and from 78.8 to 98.3% in the DTaP 0.5 ml group. The GMT of antibodies against FHA was 252.82 (95% CI: 214.29–298.27) after immunization with 0.2 ml of DTaP and 302.06 (95% CI: 254.2–358.93) after immunization with 0.5 ml of DTaP, without a significant difference. Sero-positivity against diphtheria toxoid was 55.9–66.4% before immunization and increased to 100% in all three groups. The GMT of antibodies against diphtheria toxoid was 40.14 (95% CI: 28.28–56.96), 45.17 (95% CI: 35.59–57.32), and 46.78 (95% CI: 35.73–61.24) in the DT 0.1 ml, DTaP 0.2 ml, and DTaP 0.5 ml groups, respectively. As for the antibodies against tetanus toxoid, 86.2–94.1% sero-positivity before immunization increased to 100%. The GMT of antibodies against tetanus toxoid after vaccination with 0.2 ml of DTaP was 18.02 (95% CI: 14.90–21.80), similar to the 20.96 (95% CI: 13.37–32.84) after immunization with 0.1 ml of DT. However, the GMT of antibodies against tetanus toxoid was 27.12 (95% CI: 22.79–32.27) after immunization with 0.5 ml of DTaP, higher than those in DT 0.1 ml and DTaP 0.2 ml groups.

3.5. Difference in immunogenicity of different brands

There was no significant difference in immunogenicity against PT and FHA after immunization with 0.2 or 0.5 ml of DTaP. Risk ratios of a local reaction to 0.5 ml of DTaP compared to 0.1 ml of DT were higher than that to 0.2 ml of DTaP. GMTs after immunization with different brands of DTaP are shown in Fig. 5. A volume of 0.2 ml of DTaP contained 1.2–9.4 μg of PT, 9.4–20.6 μg of FHA, 6–6.6 Lf of diphtheria toxoid, and 1.0 Lf of tetanus toxoid. A volume of 0.1 ml of DT contains similar amounts of tetanus and diphtheria toxoid antigens in different brands and compared with 0.2 ml of each DTaP brand. 29 were immunized with 0.1 ml DT, 26 with 0.2 ml of Takeda DTaP, 26 with Biken, 19 with Kaketsu, 19 with Kitasato, and 29 with Denka. There was no significant difference in GMTs of antibodies against diphtheria toxoid after immunization with the five different brands in comparison with that induced after immunization with 0.1 ml of DT. The GMT against tetanus toxoid after immunization with Kitasato was higher than that after 0.1 ml of DT. As for the pertussis antigens, the GMT of PT antibodies after immunization with Takeda or Denka vaccine was lower than those induced after the other brands. These two brands contained lower amounts of PT antigen. The GMT against FHA after immunization with Denka was slightly lower than the others, not reflecting the concentration of vaccine material.

4. Discussion

Pertussis is an infectious disease affecting young infants and children, leading to severe illness in very young infants,

Table 4
Immunogenicity of DT and DTaP.

	DT 0.1 ml		DTaP 0.2 ml		DTaP 0.5 ml	
	Sero+ rate GMT pre (95% CI)	Sero+ rate GMT post (95% CI)	Sero+ rate GMT pre (95% CI)	Sero+ rate GMT post (95% CI)	Sero+ rate GMT pre (95% CI)	Sero+ rate GMT post (95% CI)
Anti-PT	58.6% 10.8 (6.38–18.29)	58.6% 13.93 (8.98–21.61)	52.1% 12.11 (9.21–15.94)	95% 89.05 (70.54–112.41)	55.1% 10.88 (8.27–14.32)	95.8% 102.74 (82.91–127.32)
Anti-FHA	82.8% 24.92 (16.34–38.00	86.2% 31.2 (22.43–43.42)	85.7% 33.73 (27.32–41.64	100% 252.82 (214.29–298.27)	78.8% 25.83 (20.67–32.28)	98.3% 302.06 (254.2–358.93)
Anti-D	58.6% 0.23 (0.11–0.471)	100% 40.14 (28.28–56.96)	66.4% 0.22 (017–0.30)	100% 45.17 (35.59–57.32)	55.9% 0.16 (0.12–0.24)	100% 46.78 (35.73–61.24)
Anti-T	86.2% 0.47 (0.28–0.81)	100% 20.96 (13.37–32.84)	94.1% 0.87 (0.70–1.09)	100% 18.02 (14.90–21.80)	88.1% 0.59 (0.44–0.79)	100% 27.12 (22.79–32.27)

causing whoop, staccato, apnea, and choking with sputa. To prevent the disease, acellular pertussis vaccines have been used in many developed countries. However, the acellular vaccine did not confer a long-lasting antibody response after vaccination and so in the late 1990s several pertussis outbreaks occurred in young adults [10–16]. The diagnosis of pertussis in adults was difficult because they only demonstrated mild atypical symptoms, showing a prolonged cough without whooping [24–26]. The adult patients showing a prolonged cough were not suspected to have pertussis because general physicians believed that pertussis was a disease only affecting children. They were, therefore, undiagnosed, and the number of patients with pertussis was underreported. In addition, they were not treated and transmitted pertussis to young infants before DTaP immunization [27]. The adult pertussis vaccine trial was conducted in 2781 subjects consisting of 1391 received the acellular pertussis vaccine and 1390 received the control vaccine. Ten patients of pertussis were diagnosed by culture, PCR, or serological responses and nine were in the control group and one in acellular pertussis vaccine group. An incidence of 370–450 cases per 100,000 person-years was noted in the control group aged 15–65 years and the acellular pertussis vaccine was protective in the same age group [28]. These adult patients with pertussis were considered to be an infectious source for transmission to young infants in household contact. Through such household contacts, even vaccinated children who had been completely immunized showed typical pertussis, and the most likely source of infant

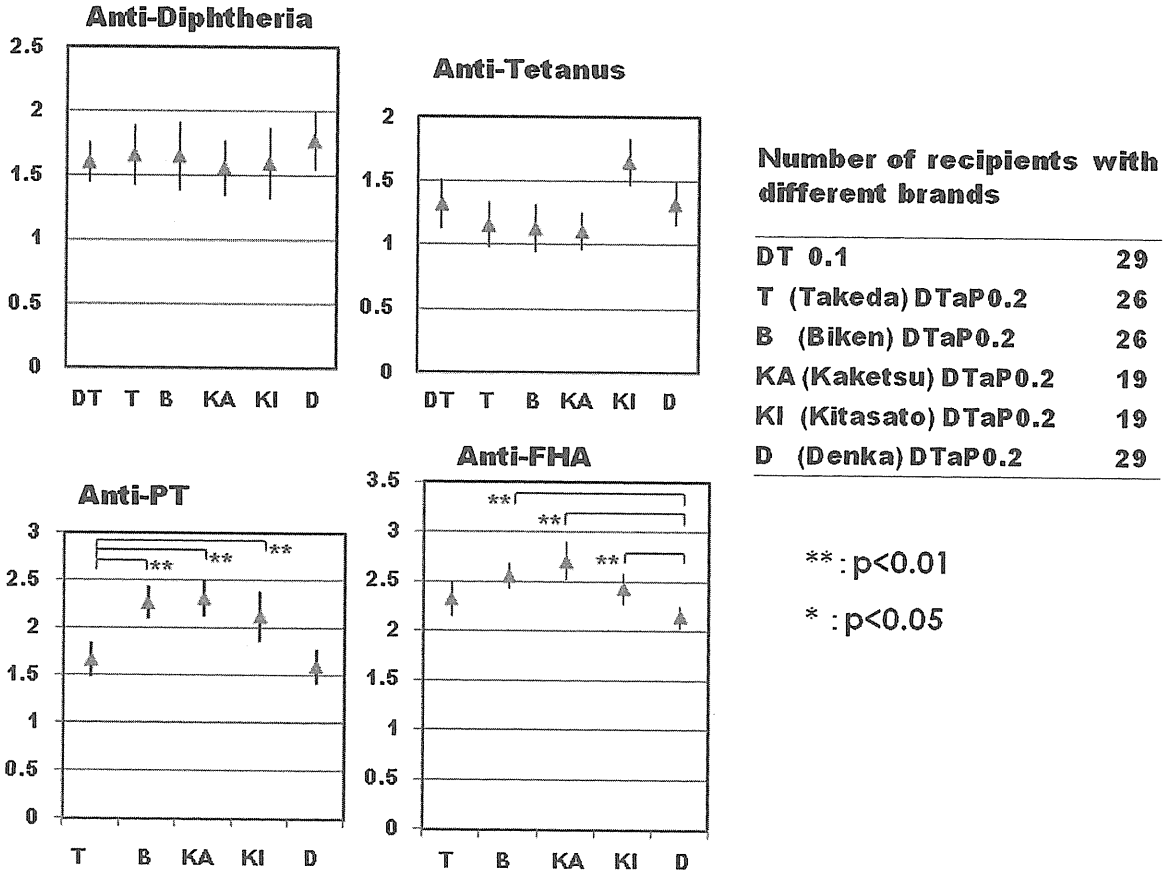

Fig. 5. GMTs of anti-D, T PT, and FHA antibodies after immunization with different brands of DTaP at 0.2 ml.

infection was reported, being a sibling (41%), mother (38%), and father (17%). To control pertussis, Tdap was developed and recommended as the booster in teenagers and young adults [15]. It is necessary to maintain a high level of immunity in all generations [29,30]. Thus, Tdap was newly recommended for all generations from 19 to 64 years as well as teenagers [17,18].

DTaP was first developed in Japan and has been used since 1981 [4]. Some pertussis patients were reported sporadically in Japan, and a survey of 89 households showed that the source of infection was an adult in approximately 11% and the secondary attack rate was 10%, confirmed by serological responses with asymptomatic infection [31]. The estimated efficacy of DTaP was 84% (95% CI: 71–91%) in children aged 2–8 years. Since vaccine-induced immunity waned 6–10 years after immunization, immunization with vaccines including pertussis components was proposed for both children and adults [32]. Adult patients with pertussis have gone undiagnosed and, therefore, the disease burden of pertussis has been neglected. In 2007–08, there were several outbreaks in universities, schools, and other facilities, and the number of reported cases of pertussis increased. Most of the patients were over 15 years of age and, the number of patients aged less than 1 year increased.

To control pertussis, an active immunization strategy should be implemented. Some ideas were considered to import Tdap, as well as change the immunization schedule. The immunization schedule of DTaP in Japan is 4 doses in young children only, being one or two times fewer doses in comparison with the schedule of DTaP in the EU and US. The components of Tdap (Adacel and Boostrix) were 2.5–8 μg of PT, 5–8 μg of FHA, 2.5–3 μg of pertactin, 2–2.5 Lf of diphtheria toxoid, and 5 Lf of tetanus toxoid. The five brands of DTaP in Japan have different formulations of components, as shown in Table 1. The B-type DTaP has only two components (Biken and Kaketsu) and T-type vaccines contain several other components besides PT and FHA (Takeda, Denka, and Kitasato). A dose of 0.1 ml of DT was scheduled at the age of 11–12 years. The concentration of tetanus toxoid in 0.2 ml of DTaP was similar to that in 0.1 ml of DT, but that of diphtheria toxoid was higher than that in 0.1 ml of DT. In comparison with Tdap used abroad, 0.2 ml of DTaP contained higher amounts of diphtheria toxoid and there was no significant difference in the incidence of adverse local reactions and serological response. Also, 0.2 ml of DTaP contains lower contents of tetanus toxoid and they induced efficient antibodies against tetanus toxoid. As for the antigen content of pertussis components, the PT antigen content varies from 1.2 to 9.4 μg, and the FHA content from 9.4 to 20.6 μg in 0.2 ml of different brands of DTaP. The GMT of antibodies against PT and FHA showed no significant difference after immunization with 0.2 or 0.5 ml of DTaP, but when comparing the GMT after immunization among different brands with different antigen concentrations, DTaP with higher antigen content did not always induce higher antibody titers. A lower-level serological response was observed in those immunized with a lower antigen content, but sero-positivity (protection levels > 10) was almost 100% after immunization with different bands of DTaP. DTaP with higher antigen content induced more marked serological responses at 4 years of age on booster immunization, but the difference was ten-times for PT antigen and five-times for FHA [33].

In the late 1990s, the resurgence of pertussis might have been associated with multi-factorial events: waning immunity, increased awareness, inappropriate vaccination schedule, improved diagnostic methods, and variant strains evading immunity acquired by immunization [8,34–36]. There have been several reports on mutation of the PT gene and it is still controversial which antigens are related to promoting immunity or reducing the severity of symptom [37,38]. Antibodies against PT reduced susceptibility to pertussis and those against pertactin or Fim2/3 were protective antibodies [39]. Protective immunity was considered to be induced by multiple components [40].

In many developed countries, the control of pertussis is complicated because of the difficulty in case identification, limited persistence of vaccine-acquired immunity, and transmission from unrecognized very mild patients or asymptomatic cases. In Japan, the number of pertussis patients has been increasing and resurgence in very young infant due to household contact was reported [41]. In this report, safe and effective immunization was achieved by 0.2 ml of DTaP instead of 0.1 ml of DT. The booster immunization with pertussis components should be implemented to achieve more effectively control the epidemiology of pertussis in Japan.

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第41回日本小児感染症学会ICD講習会

百日咳，結核を中心とした細菌感染症の院内制御

岡田賢司*

要旨　百日咳に関しては，国内外の施設内における百日咳感染の現状および最近の百日咳患者の年齢の変化について紹介した．米国が勧奨している百日咳の感染管理についてもまとめた．結核に関しては，最近出された感染症法に基づく接触者健診の流れおよび小児結核患者への対応について概説した．

Ⅰ．百　日　咳

1．医療従事者における百日咳感染

1993年Cincinnatiでの集団発生の報告では206人の医療従事者を検査し，87人（42.2%）が百日咳感染の基準に合致し感染と確認され，79/87が5日間の予防内服を行った[1]．米国UCLAメディカルセンターの医療従事者の血清疫学研究では，看護師，他51名の5年間にわたる百日咳に対する血清抗体価（IgG，IgA）の変動が観察されている[2]．5年間で抗体価の有意上昇（範囲：1〜7回）が認められた割合は，90%（46/51）と高率であった．年平均でも33%と高かった．

国内の小児科医療従事者における百日咳に関する調査では，2003年10月〜2004年2月の5カ月間，全国12医療機関（6病院・6診療所）の小児科医25名，看護師24名（平均年齢42.5±11.6歳）を対象に月1回の後鼻腔培養とペア血清で抗体価の変動が調査された[3]．調査期間中5医療機関の外来に百日咳患児が受診し16名（33%）の医療従事者に患児との接触歴があった．ペア血清で1名だけ凝集素価が4倍以上上昇した．感染率は2.2%（1/46）であった．培養では220検体中，百日咳菌・ジフテリア菌はいずれも分離されなかった．PCRもともに陰性であった．百日咳抗体（PT-IgG）価は10 EU/ml以上が50%（23/46）であった．

百日咳の流行状況，百日咳の診断方法などによって医療従事者の感染率は異なるが，乳幼児への感染源となる場合があり，注意が必要である．

2．百日咳の罹患年齢の変化

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．百日咳ワクチンを含むDTaP（Diphtheria-Tetanus-acellular Pertussis）三種混合ワクチン開始後の感染症発生動向調査における百日咳患者報告数を示す（**図1**）．1982年から4〜5年ごと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年から増加してきた．2007年いくつかの大学や高校での集団発生が報告され，2008年は過去10年にない多くの報告があった．

近年の特徴に患者年齢の変化がある．2000年，乳児は46.7%，1歳18.1%，2〜3歳13.5%と3歳までが約80%で20歳以上は2.2%であった．次第に10〜14歳以上，特に20歳以上が増加してきた．20歳以上の割合は2002年4.0%，2004年9.5%，2006年24.3%，2008年36.7%，2009年

Key words：百日咳，結核，感染管理，ワクチン
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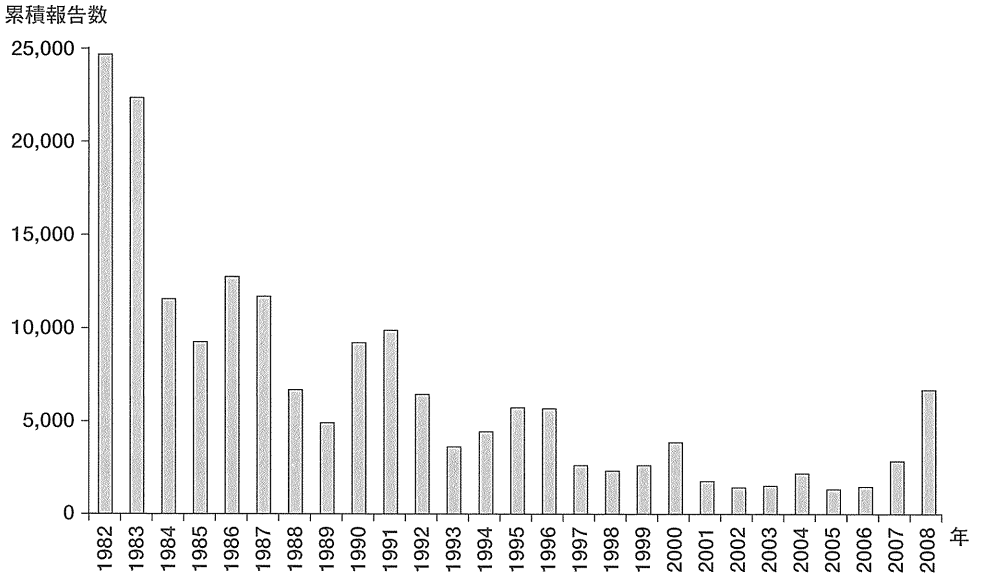

図 1 百日咳患者累積報告数の推移（1983～2008 年）
全国の小児科定点数 約 3,000.（国立感染症研究所感染症情報センター資料より作図）

13 週時点で 38.2%となっている（**図 2**）[4]. この報告は，小児科の定点医療機関に受診した患者報告である点に注意が必要である．成人は小児科を受診することは少なく，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となってきた．このため，国立感染症研究所感染症情報センターのホームページに，百日咳を診断した医師なら誰でも報告できるシステムが整備されている[5].

3．医療従事者における百日咳感染対策

米国の CDC では，サージカルマスクなしで百日咳患者の咳を 3 フィート（約 90 cm）以内で曝露を受けた時（face-to-face contacts）や百日咳患者の分泌物に直接接触した，あるいは狭い部屋で 1 時間以上一緒にいた場合（close contacts），発症予防のためにマクロライド（AZM）内服を推奨している．初日に 500 mg，2～5 日目までは 250 mg 内服となっている[6].

米国小児科学会では，① 百日咳患者との接触者で 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 医療従事者は，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[7].「濃厚接触者」とは“face to face contacts”や“close contacts”などの状況をあげている．

小児医療機関における医療従事者対策としては，小児の百日咳患者来院に伴い，適切な予防措置（抗菌薬の使用）を行えば，曝露リスクを少なくできるが，費用と効果の面からはワクチン接種が望ましい[8]. 米国小児科学会でも，無防備で曝露を受けた場合，適切な抗菌薬開始後 5 日間の就業制限を勧奨している．さらに，CDC と合わせて患者と接するすべての医療従事者に Tdap ワクチン（思春期・成人用に新たに調整された三種混合ワクチンで，小児用に比較して百日咳およびジフテリアの抗原量を減量している）を勧奨している[9]. ACIP では，特にハイリスク従事者（救急部，感染症部門，呼吸器部門，放射線部門）には Tdap ワクチン接種を勧奨しているが，まだ広く普及していないのが現状である．

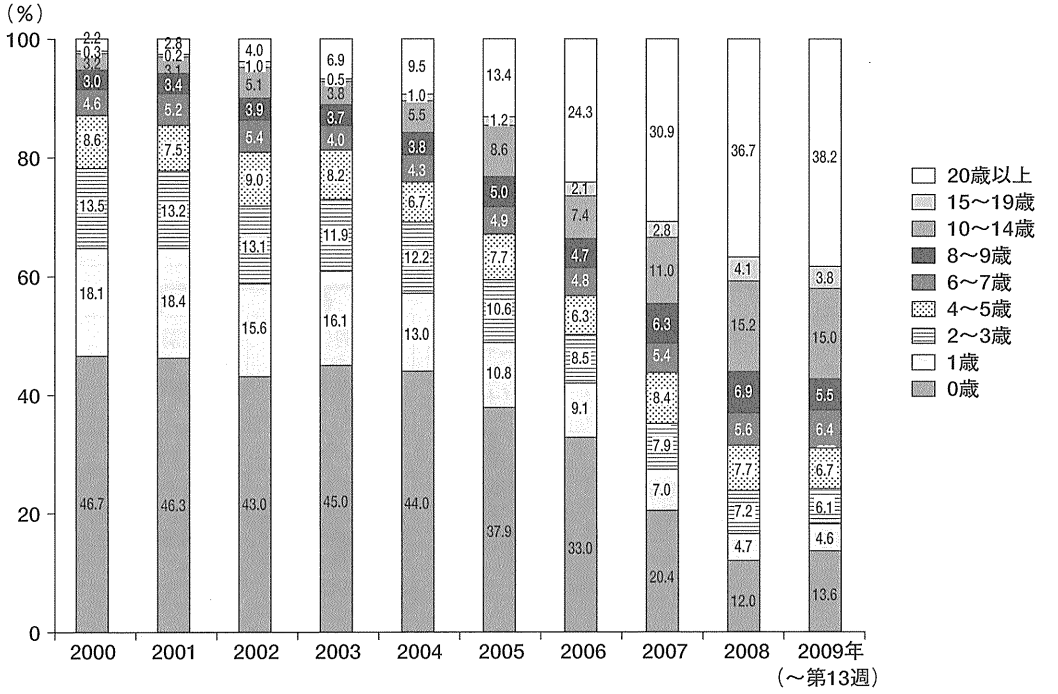

図 2　百日咳の年別・年齢群別割合（2000～2009 年第 13 週）（感染症発生動向調査週報　2009 年第 13 週）

II. 結　　核

小児の結核における感染源としては，両親や祖父母など周囲の大人からの感染が多い．

1. 診　　断

感染症法に基づく結核の接触者健康診断

目的は，潜在性結核感染症患者の発見と進展防止，新たな結核患者の早期発見および感染源および感染経路の探求とされている．結核患者の接触者から「潜在性結核感染者（LTBI）」をできるだけ非感染性の段階で早期発見し，治療に導く．治療（通常は INH 単剤；従来の化学予防）により，結核患者（確定例）への進展を防止する．

「特に患者が小児および若年者の場合は，最近 2 年以内（とりわけ 1 年以内）の接触者から感染を受けて発病する可能性が高いため，積極的疫学調査と健診を組み合わせて感染源および感染経路を探求する意義は大きい」とされている．

① 結核患者の感染性の評価

感染源となった結核患者の感染性をまず評価することが必要となる（**表 1**）．喀痰塗抹陽性例および空洞が認められる例の感染性が相対的に高い．**図 3** に結核患者の感染性の評価に基づく接触者健診の基本的な流れを示す．患者の診断名や喀痰塗抹の結果などを基準に接触者のリスクを評価していく．**図 4** に初発患者が「高感染性」の結核であった場合の接触者健診の優先度設定の流れを示す．接触者が小児の場合，最優先接触者となる．

表 1　感染性の結核患者の特徴

感染源になり得る結核は？〔診断名〕	肺結核，喉頭結核 結核性胸膜炎*，粟粒結核*
結核患者の「感染性の高さ」の評価方法は？	① 喀痰検査 →喀痰塗抹陽性例は，陰性例（培養陽性例）に比べて感染性が高い
	② 胸部 X 線検査 →空洞性病変を認める肺結核患者は，相対的に感染性が高い

*：肺実質病変を伴い，喀痰検査で結核菌が検出された場合（小児ではまれ）．

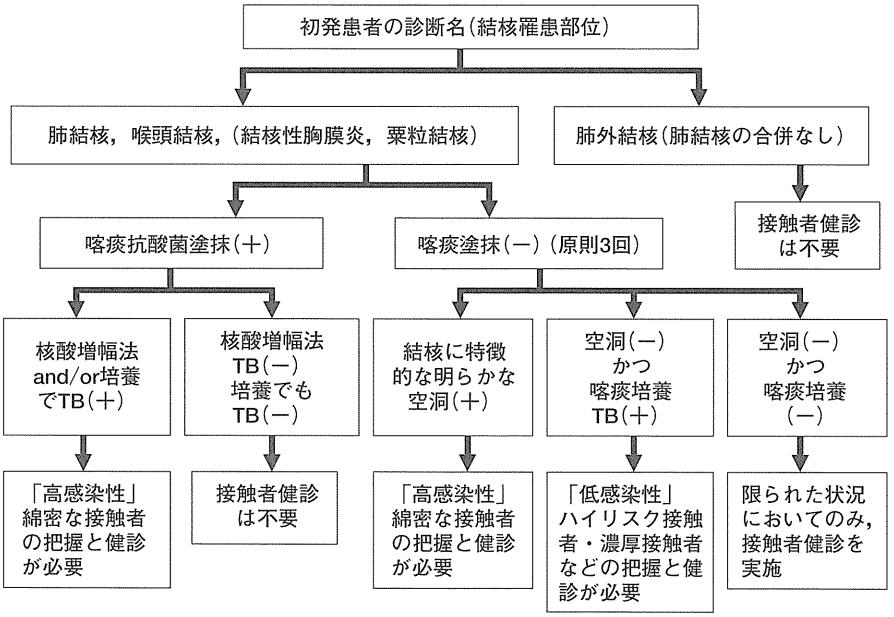

図 3　結核患者の感染性の評価に基づく接触者健診の基本的な流れ

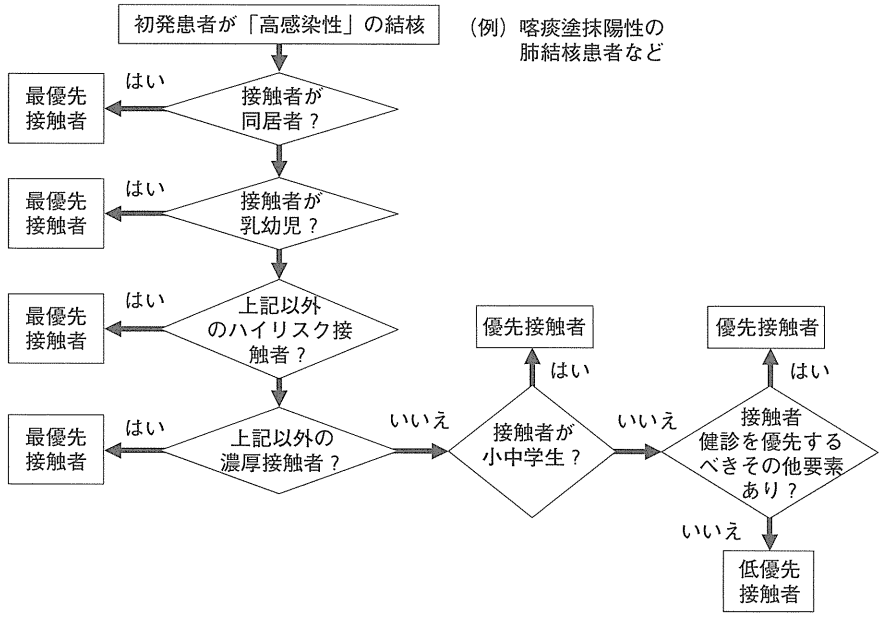

図 4　初発患者が「高感染性」の結核であった場合の接触者健診の優先度

図 5 に初発患者が「低感染性」の結核であった場合の接触者健診の優先度を示す．この場合でも小児は，最優先接触者となる．

② 接触者の優先度などに応じた健診の流れ (表 2)

接触者が乳幼児の場合 (表 2)，ツベルクリン反応検査が基本となる．2006 年日本結核病学会予防委員会から出されたツ反結果に基づく潜在性結核

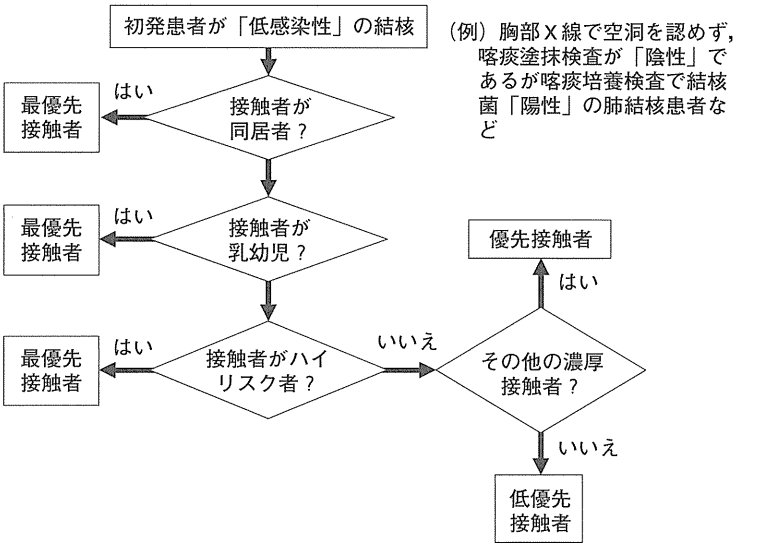

図 5　初発患者が「低感染性」の結核であった場合の接触者健診の優先度

表 2　接触者の優先度などに応じた健診の実施時期・内容・事後対応

接触者の年齢など：乳幼児（未就学児）

健診目的	健診の実施時期	第一同心円		第二同心円
		最優先接触者	優先接触者	低優先接触者
LTBI の発見と進展防止	登録直後 2 カ月後	ツ反検査が基本 →陽性者に胸部 X 線検査	—	—
	事後対応	・上記のツ反の結果，感染あり（疑い）と診断→LTBI としての治療を指示 ・直後のツ反陰性でも，BCG 歴なしの場合などは，ウインドウ期を考慮→LTBI としての治療を検討 ・最終接触から 2 カ月後も，ツ反陰性（未感染と判断）→ここで健診は終了		
患者の早期発見	6 カ月後～2 年後まで	・上記で感染あり（疑い）と診断したが，LTBI としての治療を実施できなかった場合→胸部 X 線検査（概ね 6 カ月間隔）	—	—

※LTBI：潜在性結核患者

感染の判断基準を**表 3** に示す．BCG 接種児の評価が難しい．ツ反の結果，感染あり（疑い）と診断した場合は潜在性結核感染者としての治療を行う．直後のツ反が陰性でも，BCG 接種歴なしの場合は，潜伏期を考慮して潜在性結核感染者としての治療を考慮する．最終接触から 2 カ月後のツ反が陰性なら“未感染”と判断し，健診を終了する．接触者が小学生の場合を**表 4** に示す．感染の評価にツ反に加えて，クォンティフェロン（QFT）が追加されている．さらに，接触者が 12～17 歳までの場合（**表 5**）は，18 歳以上と同じように感染の評価には QFT を基本として対応するようになっている．

③ 小児結核感染診断における QuantiFERON TB-2 G 使用指針（**表 6**）

小児潜在性結核感染例診断（≒接触者健診例で