ムンプスの確定診断（実験室診断）には，酵素免疫法（EIA）を用いて血清 IgM 抗体を測定する。ムンプス初感染の多くは，耳下腺腫脹時期にはムンプス IgM 抗体も IgG 抗体も検出されるが，ムンプス IgG 抗体は低値である。ムンプスワクチン後の 2 次性ワクチン不全や再感染では，ときに IgM 抗体が検出されることはあるが，EIA-IgG 抗体は 25.8 EIA 価以上の高値である[1]。唾液からのウイルス分離や，polymerase chain reaction（PCR）法や loop-mediated isothermal amplification（LAMP）法によるムンプスウイルス RNA の検出も診断に有用である。髄膜炎を合併したときは髄液からのウイルス分離やウイルス RNA 検出が診断に有用である。

急性期と回復期（発症 2 週以降）の血清を用いて，IgG 抗体の陽転化または有意上昇も診断に有用である。有意上昇の基準は測定誤差以上の上昇であり，EIA-IgG 抗体では 2 倍以上，赤血球凝集抑制法（HI）や中和法（NT）では 2 管（4 倍）以上の上昇である。

3．ファーストラインの治療戦略

ムンプスウイルスに効果がある抗ウイルス薬はないので，保存的に治療する。耳下腺の痛みが強いときは鎮痛剤を使用し，痛みのために水分の摂取が困難なときは輸液を行う。髄膜炎合併により頭痛や嘔吐が強いときは，髄液を採取し，圧を下げると症状が軽快することがある。精巣炎に対しては，鎮痛剤の投与と局所の冷却が行われている。

ムンプスによる登校停止期間は，日本では耳下腺腫脹が消失するまでであるが，米国での登校停止期間は耳下腺炎出現後 5 日間である[3]。なお，片側が腫脹して 7 日後ごろに反対側の耳下腺が腫脹することがあり，この時も唾液からムンプスウイルスが分離されるので，反対側耳下腺腫脹出現後も 5 日間は登校を停止すべきである[4]。

4．ファーストラインの予防戦略

1．予防の流れと効果のエビデンス（表 2）

ムンプス予防対策の基本はムンプスワクチン接種である。日本では星野株と鳥居株の 2 種類が市販されている。わが国のムンプスワクチンの有効率は 80～90%であり，株による差は認められていない[1]。日本では任意接種であるため 4 年ごとに流行を認めているが，ムンプスワクチンの 1 回定期接種が行われている国では患者数が 90%減少し，2 回定期接種を行っている国では患者数が 99%減少している。欧米の多くの先進国は 2 回接種である。なお，現在欧米や日本で流行している野生株の遺伝子型の多くは G である。

ムンプス患者と接触後の発症予防対策については，ムンプスワクチンの緊急接種は有効率が低く，免疫グロブリンの投与も無効である。ムンプスワクチン接種により特異的免疫が誘導される時期が，麻疹ワクチンや水痘ワクチンよりも遅いこと，免疫グロブリンに含まれるムンプス抗体価が麻疹抗体価よりも低値であることが関係していると考えられている。

表 2　日本のムンプス流行とムンプス対策

ムンプス流行
- 日本ではムンプスワクチンが任意接種のため，4 年ごとに大きな流行がある。
- ムンプスワクチンを 2 回定期接種をしている国では流行が抑制されているが，ときに大学生や成人に流行を認める。
- 現在欧米，日本で主に流行している野生株の遺伝子型は G である。

ムンプスワクチン
- Jeryl-Lynn 株の遺伝子型は A，Urabe 株，星野株，鳥居株の遺伝子型は B である。
- 日本のムンプスワクチンの有効率は 80～90%であり，株による差は認められていない。
- 家族内でのムンプス患者接触後の緊急接種の効果は高くない。
- ムンプスワクチン後 3 週間以内に急性耳下腺腫脹を発症した場合は，唾液からのウイルス分離またはウイルス核酸の検出を行い，由来株を同定する。

ムンプス抗体
- ムンプスの免疫状態を調べる抗体測定方法は EIA-IgG である。
- ムンプス再感染，ワクチン不全を疑うときは，EIA-IgM 抗体と EIA-IgG 抗体を測定する。

EIA：酵素免疫法

2．実際の投与方法

1歳以降の小児を対象に0.5 mL皮下接種する。保育園や幼稚園などの集団生活に入る前に接種が勧められる。また，ムンプス既往歴およびワクチン歴がない思春期以降の人には，男女にかかわらず接種が勧められる。ワクチン接種前に免疫の有無を確認するために抗体測定を希望する場合は，EIA-IgGで測定する。ほかのムンプス抗体測定方法の感度はEIAに比べて低率である。成人に接種しても副反応が増加することはないし，免疫がある人に接種しても副反応は増加しない。

3．投与後の経過観察

ムンプスワクチンによる耳下腺腫脹（3%）や髄膜炎（1/1,000～10,000接種）の合併は，ワクチン接種後18～21日に認められるので，少なくとも接種後21日間の経過観察が必要である。ムンプスワクチン後の精巣炎，脳炎，難聴はきわめてまれである（表1）。なお，ムンプス流行時期にムンプスワクチンを接種し，15日以内に耳下腺腫脹を認めたときは，野生株の感染による臨床症状である[2]。唾液を採取し，耳下腺腫脹をきたした由来株を同定すべきである。

4．判定効果の時期と判定のしかた

ワクチン接種4～6週後に血清抗体価をEIA-IgGで測定すると，ムンプスワクチン接種による効果が判定できるが，ムンプスワクチン接種後の抗体陽転率は90～95%であり，一般に接種後の抗体価測定は行っていない。

ワクチンの臨床上の効果は，園や学校においてムンプス流行に遭遇したときムンプスが発症するかどうかで判定される。ワクチンの有効率は（1－ワクチン接種者の発症率/ワクチン非接種者の発症率）×100で算出される。ムンプスワクチンの有効率は80～90%である。なお，ムンプスワクチンを接種していた人がムンプスを発症したとしても，耳下腺腫脹期間はワクチン非接種者の腫脹期間よりも短く，髄膜炎の合併率も低率である[1]。ワクチンの効果を検討するためには，流行時の疫学的検討が大切である。

5．ワクチン投与時の問題点

ムンプスワクチンは生ワクチンであるので，免疫不全者および妊婦は接種不適当者である。また，37.5℃以上の発熱者も接種不適当者である。ムンプスワクチンはニワトリ胎児細胞を用いてウイルス増殖が行われているが，含まれるオボアルブミンの濃度は1 ng以下である。卵によるアナフィラキシーを発症させる濃度は600 ng/dose以上であるので，現行のムンプスワクチンを卵アレルギーの人に接種してもアナフィラキシーを発症させる危険性はない。

ムンプスワクチンはムンプスが流行すると接種希望者が増加するため，ムンプス流行時のほうがワクチン接種後の耳下腺腫脹者の頻度が増加する[2]。ワクチン後の臨床反応を認めたときは，接種したワクチンのメーカーと相談し，臨床症状を出現させた由来株を同定すべきである。

5．ファーストラインが無効・効果不十分の時の予防戦略

ムンプスワクチンの接触後の発症予防効果は，麻疹ワクチンや水痘ワクチンと比較すると効果は乏しいが，園や学校でのムンプス流行時に流行を早期に抑制する唯一の方法は，ムンプス既往歴およびワクチン歴がない児にムンプスワクチンを接種することである。

世界で多く使用されているムンプスワクチン株であるJeryl-Lynn株は少し病原性を減弱させすぎ（overattenuation）の可能性が指摘されている。実際2回の定期接種を受けた成人においてもムンプス発症が認められている[5]。わが国で開発されたUrabe株は，Jeryl-Lynn株と比べると免疫原性は優れているが，無菌性髄膜炎の副反応発症率はJeryl-Lynn株よりも高率である[6]。わが国で使用されているムンプスワクチン株の免疫原性はUrabe株と同等である。

地域でのムンプス流行排除を考えるならば，90%以上の接種率による2回接種が必要である。わが国は先進国のなかでムンプスワクチンの定期接種が行われていない唯一の国である。なお，世界でムンプス野生株の排除を宣言した国はフィンランドだけである。

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感染症・予防接種レター（第52号）

日本小児保健協会予防接種・感染症委員会では「感染症・予防接種」に関するレターを毎号の小児保健研究に掲載し，わかりやすい情報を会員にお伝えいたしたいと存じます。ご参考になれば幸いです。

日本小児保健協会予防接種・感染症委員会

委員長 庵原　俊昭　副委員長 岡田　賢司　宇加江　進　古賀　伸子　住友眞佐美
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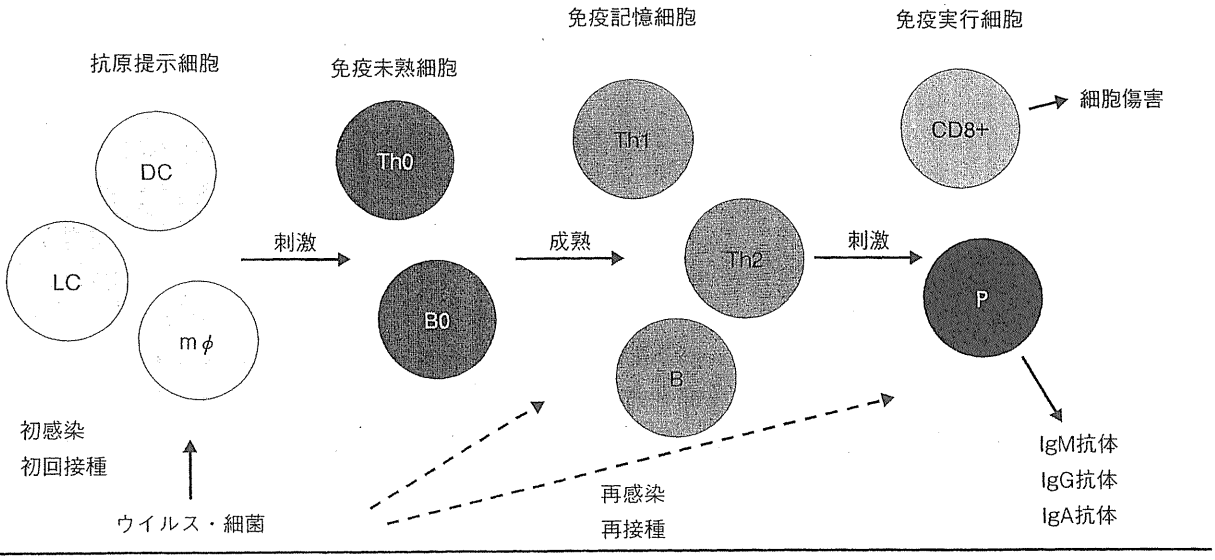
ワクチンと免疫

はじめに

適切な抗原で作成されたワクチンを接種すると，まず各種サイトカインの誘導を含めた自然免疫が働き，同時に特異的細胞性免疫や抗体などの獲得免疫が誘導される。スケジュールから外れたとき，基礎疾患を有する者にワクチンを接種するときなどは，免疫の知識が必要になる。本稿ではワクチンと免疫について解説する。

1．免疫プライミングとブースティング

免疫に関係する細胞群には，抗原提示細胞，免疫未熟細胞，免疫記憶細胞，免疫実行細胞がある。抗原提示細胞は，接種されたワクチン抗原を認識すると同時に免疫未熟細胞に刺激を与え，免疫未熟細胞を免疫記憶細胞に成熟させる働きがある（図1）[1,2]。成熟した免疫記憶細胞は免疫実行細胞を刺激し，抗体を産生させ，特異的細胞性免疫を誘導する。免疫未熟細胞を成熟させ免疫記憶細胞を誘導し，免疫実行細胞により抗体を産生させる段階が免疫プライミングであり，誘導された免疫記憶細胞を刺激し，免疫実行細胞の数を増加させ，抗体を更に高める段階がブースティングである。免疫実行細胞は刺激がないと数は減少するが，一度誘導された免疫記憶細胞は喪失しないため，DPT ワクチ



DC：樹状細胞，LC：ランゲルハンス細胞，mφ：マクロファージ，P：プラズマ細胞，Th0：未熟ヘルパーT細胞，Th1：1型ヘルパーT細胞，Th2：2型ヘルパーT細胞，B0：未熟B細胞，B：B細胞，CD8+：CD8+T細胞
1）一度免疫記憶細胞が誘導されると，抗体価が陰転化しても1回の接種で二次免疫応答が起こる
2）記憶B細胞の誘導には4～6ヵ月が必要なため，追加接種（ブースティング）は初回接種後4～6ヵ月以降に行う

図1　感染・ワクチンと特異免疫の誘導

ン，日本脳炎ワクチンなどの不活化ワクチンで，1期初回終了後の追加接種を忘れたときは，数年後でも気がついたときに1回追加接種をすれば免疫ブーステイングが誘導される。スケジュールから外れたとき，不活化ワクチンでは必要な接種回数を接種することが基本である。

2．生ワクチンとキラーT細胞（$CD8^+$細胞）の誘導

感染からの回復に$CD8^+$細胞が必要な感染症である麻疹，水痘，ムンプス，風疹などでは，$CD8^+$細胞が誘導できる生ワクチンの接種が必須である。生ワクチンを接種すると，MHCクラスⅠが関係する抗原提示細胞が働き$CD8^+$細胞が誘導される。なお，不活化ワクチンや結合型ポリサッカライドワクチンでは特異的細胞性免疫は誘導できるが，誘導できるのはMHCクラスⅡが関係する$CD4^+$細胞だけである。

3．抗体レベルとブースター

抗体を持っている人に生ワクチンを接種すると，接種を受けた人の抗体価に応じて抗体のブースターがかかる人とかからない人がいる。生ワクチンを接種して抗体のブースターがかかるとは，接種したワクチン株が増殖した結果である。低い抗体価だと，接種されたウイルスが増殖して抗体のブースターが誘導され，高い抗体価では接種したウイルスが増殖しないため抗体のブースターが誘導されない。麻疹と風疹では，発症予防レベルやブースターがかからないレベル（感染予防レベル）は示されているが（表1）[3]，水痘やムンプスでは発症予防レベルや感染予防レベルは未確定である。なお，年齢が低いほど感染予防に必要な抗体価が高く（高い抗体価でもブースターがかかる），成人は小児よりも低い抗体レベルで感染が予防される[4]。

不活化ワクチンでも抗体価が低いと抗体のブースターがかかるが，抗体価が高いとブースターがかかりにくい。また，インフルエンザ2009（H1N1）pdmウイルスワクチンの臨床研究結果から，不活化ワクチンでは一度ブースターが誘導されると，3週間後に追加接種しても抗体の更なる上昇は認められない[1]。免疫寛容が働くためと考えられている。

表1　麻疹・風疹の発症予防レベル・感染予防レベル

測定方法	抗体価		
	陽性	発症予防	感染予防
麻疹			
文献（IU/ml）		≧120～200	≧500～1,000
NT（倍）	2	≧4	≧32
PA（倍）	16	≧64	≧512
EIA（EIA価）	2.0	≧4.0	≧16.0
HI（倍）	8	≧8	≧16
風疹			
文献（IU/ml）	4	≧4～10	≧15～25
LA（IU/ml）	4	≧10	≧15～25
HI（倍）	8	≧16	≧32
EIA（EIA価）	2.0	≧5.0	≧7.5～12.5

4．代表的なワクチン予防可能疾患の発症予防レベル

感染防御には，抗体で表わされる液性免疫だけではなく，細胞性免疫や粘膜免疫も関与している。しかし，細胞性免疫や粘膜免疫の測定は手間がかかるため，測定が容易な抗体で感染防御力を示している（表2）[5]。表2で示す抗体価は，多くの人の発症を予防する抗体価であり，曝露されたウイルス量が多いときは，発症予防には高い抗体価が必要である。また，全身感染症では，感染を受けると同時に免疫の二次応答も始まるため，相対的に低い抗体価で発症を予防できるが，局所性感染症では，感染による二次免疫応答が始まるまでに症状が出現するため，発症予防のためには比較的高い抗体価が必要である。インフルエンザでHI抗体価40倍は50％の人の，160倍は90％以上の人の発症を予防する抗体価である[6]。また，麻疹抗体120mIU/mlや風疹抗体4～15IU/mlは95％以上の人の発症予防レベルである。発症者と密接に接触する機会が多い医療従事者は，曝露されるウイルス量が多い危険性があり，発症予防のために表1で示す抗体価よりも高い抗体価が必要である。

5．ワクチンとLow Responder（低反応者）

ワクチンを接種しても一部の人では発症予防レベルの抗体価が誘導できないことがある。このような人はLow Responder（低反応者）と呼ばれ，遺伝的因子が関係している。接種時の抗体価が表2に示した発症予防レベル以下で

表2 代表的なワクチン予防可能疾患の発症予防レベル

ワクチン	抗体測定方法	必要な抗体価
ジフテリア	中 和	0.01～0.1IU/ml
A型肝炎	EIA	10mIU/ml
B型肝炎	EIA	10mIU/ml
Hib 結合型	EIA	0.15μg/ml
インフルエンザ	HI	40倍
日本脳炎	中 和	10倍
麻 疹	マイクロ中和	120mIU/ml
ムンプス		未確定
百日咳	EIA (PT)	5単位
肺炎球菌	EIA, opsonophagocytosis	0.20～0.35μg/ml (小児), 8倍
ポリオ	中 和	4～8倍
狂犬病	中 和	0.5IU/ml
ロタウイルス		未確定
風 疹	免疫沈降	10～15IU/ml
破傷風	中 和	0.1IU/ml
水 痘	FAMA, gp ELISA	64倍, 5IU/ml*
黄 熱	中 和	5倍

Plotkin SA : Clin Vaccine Immunol 2010 ; 17 : 1055-1065.
*参考値

あっても，麻疹ワクチンや風疹ワクチンを追加接種したとき抗体価が発症予防レベル以上に賦活されない場合がある。低い抗体価でも他の免疫機能が働き，接種されたウイルスが体内で増殖しなかったためと考えられ，理論上抗体価が発症予防レベル以下でも発症しない人である。

不活化ワクチンであるHBワクチンでもLow Responderは認められる。3回接種しても抗体が陽性にならない（HBs抗体＜10mIU/ml）場合は，プライミングしたワクチンと異なる遺伝子型で製造されたワクチンで4回目を接種すると抗体価が上昇することがある。4回接種しても抗体価が上昇しない人は，HBウイルスが感染しにくい人である。

ま と め

ワクチンと免疫について解説した。不活化ワクチンではプライミングとブースティングが大切である。また，発症予防は測定が容易な抗体で評価されているが，細胞性免疫や粘膜免疫も関与しており，抗体価が低くても発症が予防される人は存在する。

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Japanese Guidelines for the Management of Respiratory Infectious Diseases in Children 2007 with focus on pneumonia

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Abstract Members of the Japanese Society of Pediatric Pulmonology and the Japanese Society for Pediatric Infectious Diseases developed the *Guidelines for the Management of Respiratory Infectious Diseases in Children* with the objective of facilitating the appropriate diagnosis and treatment of childhood respiratory infections. To date, a first edition (2004) and a revised edition (2007) have been issued. Many problems complicate the diagnosis of the pathogens responsible for bronchopulmonary infections in children. The *Guidelines* were the first pediatric guidelines in the world to recommend treatment with antimicrobials suited to causative pathogens as identified from cultures of sputum and other clinical specimens collected from infection sites and satisfying assessment criteria. The major causative microorganisms for pneumonia in infants and children were revealed to be *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Mycoplasma pneumoniae*. This manuscript describes the *Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2007*, with a focus on pneumonia.

Key words appropriate use of antimicrobials, causative microorganism, children, guidelines, respiratory infections.

The *Guidelines for the Management of Respiratory Infectious Diseases in Children* were developed by members of the Japanese Society of Pediatric Pulmonology and the Japanese Society for Pediatric Infectious Diseases to facilitate proper management primarily for pneumonia and other childhood respiratory infections. The first edition[1] was issued in 2004, and a revised edition[2] was released in 2007.

The causative microorganisms of bronchopulmonary infections in children have not been sufficiently examined and assessed either in Japan or in other countries. The *Guidelines* were developed to recommend the appropriate use of antimicrobials for treating respiratory infections based on identification of the causative microorganisms. The *Guidelines* were the first pediatric guidelines in the world to utilize sputum cultures and other clinical specimens from infection sites to identify causative microorganisms. Clinical research has scrutinized the appropriateness of the recommendations in the *Guidelines*, and it is hoped that such scrutiny can improve the appropriateness of the recommended use of antimicrobials in childhood respiratory infections. This manuscript focuses on pneumonia, which is addressed in the 150-page *Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2007* that is used in clinical practice in Japan.

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Principles for the development of *Guidelines for the Management of Respiratory Infections in Children*

The *Guidelines* were created with the objectives of: (i) improving the quality of the management and treatment of childhood respiratory infections; and (ii) considering antimicrobial treatment that minimizes the advent of drug-resistant pathogens. The *Guidelines*, which cover childhood respiratory infections, were developed in consideration of age-specific and other characteristics of children.[1] The *Guidelines* are subject to revision when necessitated by trends associated with causative microorganisms, the emergence of resistant pathogens, the occurrence of adverse events, and the development of new drugs. The revised 2007 edition makes more information available about viral infections,

Table 1 Table of contents from *Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2007*

Full color photographs and schematics of key findings	
Dosage recommendations for antimicrobials approved for the treatment of pediatric respiratory infections	
Chapter 1	Principles for the development of guidelines for the management of respiratory infections in children
Chapter 2	Concept and classification of childhood respiratory infections
Chapter 3	Characteristics of childhood respiratory infections
Chapter 4	Pathogens of childhood respiratory infections and their detection: Bacteria, mycoplasma, chlamydia, viruses
Chapter 5	Upper respiratory infections: common cold (nasopharyngitis), pharyngitis/tonsillitis, croup syndrome (epiglottitis)
Chapter 6	Bronchitis: Acute bronchitis, protracted bronchitis
Chapter 7	Bronchiolitis: RSV and other viruses
Chapter 8	Pneumonia: Severity criteria, first-line antimicrobial treatment
Chapter 9	Pleurisy and pyothorax: Diagnosis and treatment
Chapter 10	Pneumonia with underlying disease: Blood diseases, immunodeficiency, neonates, heart diseases
Chapter 11	Nosocomial pneumonia: Fundamentals of infection control, infections from hospital environment/medical practice
Chapter 12	Diseases mainly controlled by vaccination: Influenza, measles, pertussis, diphtheria, tuberculosis
Chapter 13	Pathogenic resistance in community-acquired childhood respiratory infections: Pneumococcus; *Haemophilus influenzae, Moraxella catarrhalis*, Group A Streptococcus, *Staphylococcus aureus*, *Mycoplasma pneumoniae*
Appendix	Table 1: List of reagents for rapid diagnosis of pathogenic microorganisms Table 2: Contact details for organizations supporting the national stockpile of vaccines and antitoxins
Appendix	Chest X-rays of pneumonia

addresses pneumonia in children with underlying diseases and nosocomial pneumonia, and includes tuberculosis and measles in the scope of the *Guidelines*.

Classification of childhood respiratory infections and content of the *Guidelines* (Table 1)

Causative microorganisms of childhood respiratory infections and their detection

Bacteria[3]

1 The problem of identifying the causative pathogens of respiratory infections:[1,2] Identifying the causative bacteria of respiratory infections is more difficult than for other infectious diseases. Deep respiratory infections do not allow non-invasive collection of specimens from the affected site; and bronchopulmonary secretions are unavoidably contaminated by upper respiratory tract and oral flora on expectoration. Thus, isolating bacteria from these clinical specimens is not a reliable method for identifying the causative microorganism(s).

2 Upper respiratory tract flora: The detection of pharyngeal flora and percentage of bacterial colonies in healthy, symptom-free children differ in neonates, infants, preschool children, and school children. *Streptococcus pneumoniae* and *Haemophilus influenzae* are more frequently isolated and accounts for a greater percentage of colonies in infants and preschool children than in other age groups (Fig. 1).

3 Causative bacteria of childhood respiratory infections by disease location: Table 2 lists causative pathogens based primarily on data from the Department of Pediatrics of Chiba University and associated medical institutions.

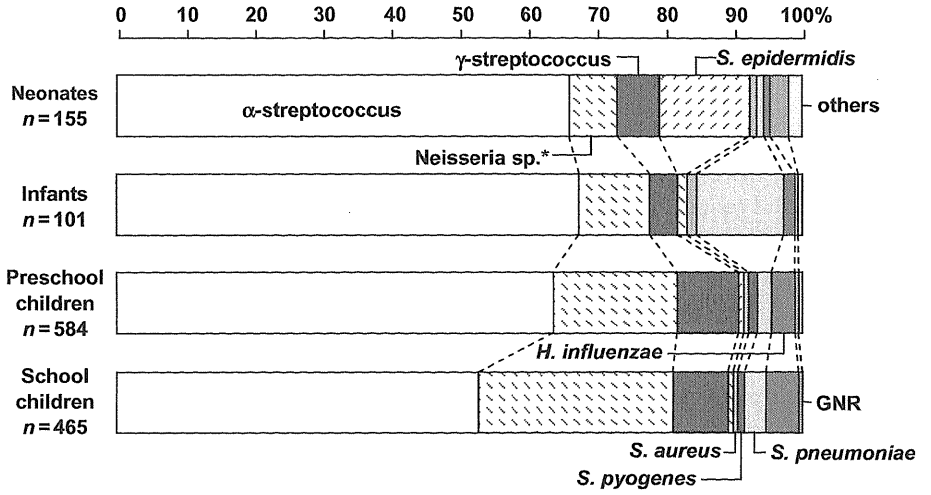

Fig. 1 Distribution of bacteria by age group in throat cultures from healthy children (average % of colonies). **M. catarrhalis* not classified. GNR, gram-negative rods. (Reproduced from *The Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2007*, Uehara and Sunakawa [eds.][2] with permission.)

Table 2 Causative bacteria of childhood respiratory infections by disease location (Adapted from *The Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2007*, Uehara and Sunakawa [eds.][2] with permission)

	Group A Streptococcus	Group B Streptococcus	*Streptococcus viridans*	*Streptococcus pneumoniae*	*Staphylococcus aureus*	*Corynebacterium diphtheriae*	*Moraxella catarrhalis*	*Haemophilus influenzae*	*Bordetella pertussis*	*Pseudomonas aeruginosa*	*Klebsiella*	Anaerobic bacteria	*Mycobacterium tuberculosis*	*Nocardia*	*Actinomycetes*	*Legionella*
Acute nasopharyngitis (common cold)	◎								△							
Acute pharyngotonsillitis	●			○		○		○				○				
Acute laryngitis (croup)						○		○								
Acute epiglottitis	○			○	○			◎								
Acute tracheitis				○	◎			○								
Acute bronchitis	△			○	○		○	○				*Bacteroides*				
Protracted bronchitis				◎			○	◎	○							
Acute bronchiolitis				○				○								
Pneumonia	○	○	○	●	◎		○	●	△	○	○	○	○	△	△	△
Lung abscess			○		○						○	○		○	○	
Pleurisy												○	○			
Pyothorax	○			○	◎			○								

●◎○△: frequency of occurrence from high to low.

4 Causative bacteria of upper respiratory infections and their detection: The *Guidelines* describe detection methods for Group A Streptococcus (GAS), including rapid diagnostics, and for *Corynebacterium diphtheriae*.

5 Causative bacteria of bronchopulmonary infections and their detection: The major bacteria responsible for childhood bronchopulmonary infections are *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*. These organisms are isolated with blood agar medium and chocolate agar medium. The clinical laboratory should be contacted in advance about suspected cases of pertussis and *Legionella* infections, which require specialized media for isolation.

6 Selection and determination of causative bacteria of bronchopulmonary infections: As previously stated, contamination with bacteria from the upper respiratory tract is a problem when diagnosing the causative bacteria for bronchitis, pneumonia, and other bronchopulmonary infections. Clinical specimens for culturing the causative bacteria for pneumonia as proposed by Moffet[4] are presented in Table 3. Sputum and nasopharyngeal and throat secretions are categorized as being of dubious value for diagnosing the causative bacteria of pneumonia. Moffet states that bacteria cultured from blood, pleural fluid, and lung puncture are definitive. Blood culture is less sensitive than culture from lung puncture.[5] Surveys conducted by Uehara of the causative bacteria determined from blood, pleural fluid, and lung puncture at pediatric training hospitals throughout Japan showed that the number of cases caused by *S. aureus* became fewer and those caused by *S. pneumoniae* and *H. influenzae* increased, beginning in the 1990s (Fig. 2).[6] It must be noted that only a small number of the total cases were confirmed by these conclusive culture sources. Pneumonia is transmitted via the airways as well as the bloodstream. We were able to raise the significance of sputum from "3. Cultures of dubious significance", which included sputum and nasopharyngeal and throat secretions to "2. Occasionally significant culture sources".

7 Assessment of causative bacteria identified in sputum culture: As sputum consists of bronchopulmonary secretions covered by upper respiratory secretions, it is difficult to differentiate bacteria of bronchopulmonary origin and those of upper respiratory tract when it is cultured as is.[6–8] Washed sputum culture[8,9] and quantitative culture are used to detect the true causative bacteria of bronchopulmonary infections. In washed sputum culture, a sputum specimen is washed with sterile saline solution, airway secretions thought to originate from the lower airway based on cytological evidence are cultured, and the predominant bacterium as determined semi-quantitatively is considered as the causative bacterium.

Table 3 Clinical specimens for identifying causative bacteria for pneumonia (created with modification from Moffet[4])

1. Conclusive Culture Sources
   - blood
   - pleural fluid
   - lung puncture
2. Occasionally Significant Culture Sources
   - transtracheal aspiration
   - tracheotomy aspiration
   - bronchoscopy aspiration
   - (washed sputum)
3. Cultures of Dubious Significance
   - tracheal aspiration
   - sputum
   - throat
   - nose/nasopharynx

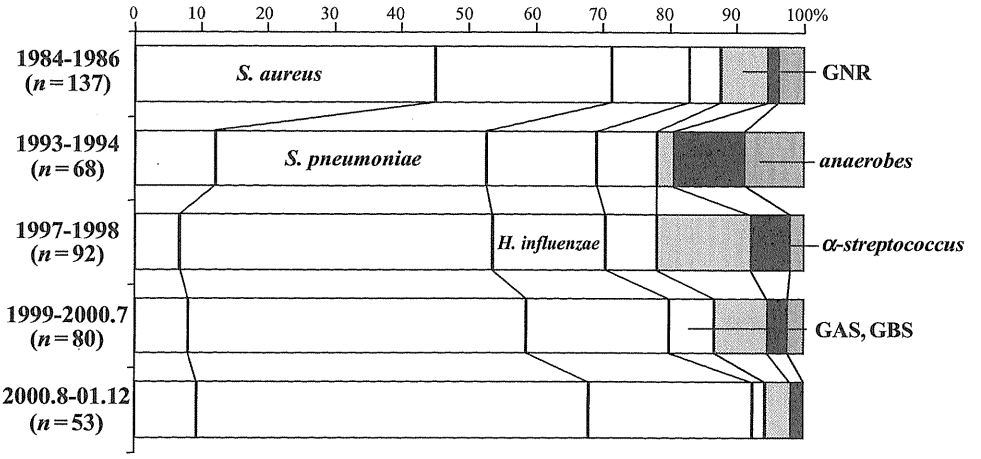

Fig. 2 Causative bacteria detected from blood, pleural fluid and/or lung tissue samples from pediatric pneumonia patients. GAS, Group A Streptococcus; GBS, Group B Streptococcus; GNR, gram-negative rods. (Reproduced from *The Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2007*, Uehara and Sunakawa [eds.][2] with permission.)

Pathogenic respiratory bacteria are predominantly isolated from purulent sputum and are often the likely causative bacterium. However, if the sputum is viscous, the isolated species may be from the oral flora. Broad classification of the causative bacterium can be made by Gram staining of sputum. The classifications defined by Geckler *et al.*[10] are used for the quality control of sputum. Sputum is Gram-stained and observed under weak magnification (×100). Evaluation is based on squamous epithelial cells and neutrophil counts. The predominant organism detected in a Gram-stained smear of a washed sputum culture is of greater significance as the likely causative bacterium of a bronchopulmonary infection when found in close contact with alveolar macrophages (Fig. 3).[9]

Table 4 lists criteria for determining causative bacteria.[8] For *M. catarrhalis* to be confirmed as the causative species, the bacterium must be the predominant species in sputum culture and detected in macrophages by sputum cytology.[7]

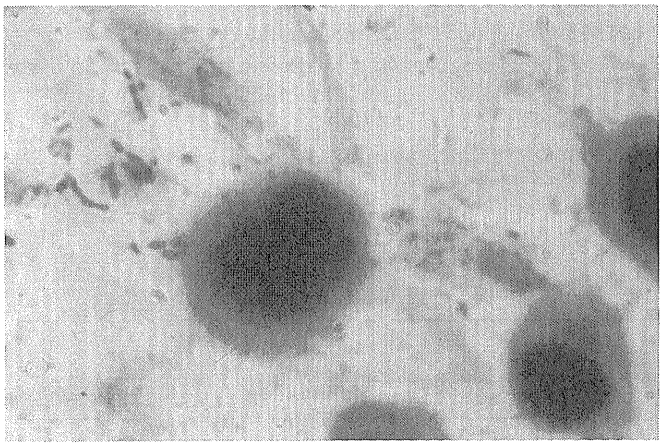

Fig. 3 Alveolar macrophage and perialveolar existence of Gram-positive diplococci (*Streptococcus pneumoniae*) and Gram-negative bacilli (*Haemophilus influenzae*) on gram-stained washed sputum.

Sputum collection in infants and children[7,8] is shown in Figure 4. Sputum collection should be attempted when the patient has a productive cough. If the patient is able to expectorate sputum, they should be instructed to discharge sputum into a sterile Petri dish with saline without contaminating the specimen by further productions of saliva, as far as possible. If the patient is an infant or preschool child who is unable to expectorate, the tongue should be depressed using a tongue depressor with a lamp to induce coughing. When the patient expectorates into the throat, a sterile swab should be promptly swiped around the sputum and placed in sterile saline. Recently, 1-mL disposable syringes have been used to aspirate specimens.[7]

8 The value of sputum washing and nasopharyngeal and pharyngeal culture:[11] Figure 5 shows the results of simultaneous culturing washed sputum, non-washed sputum, and nasopharyngeal and pharyngeal secretions for cases in which the causative bacteria was detected predominantly in washed sputum samples. Washed sputum samples showed better results than non-washed sputum samples. In the same patients, nasopharyngeal swabs showed better results than pharyngeal swabs, though detection was lower than in non-washed sputum samples.[11] Direct culturing of sputum

Table 4 Criteria for determination of causative bacteria in bronchopulmonary infection (adapted from Uehara[8] with permission)

① **Pathogens occupying more than half of the colonies in culture or presenting >10^7 cfu/mL of washed sputum were regarded as "dominant".**
② The same dominant pathogens were grown by repeated cultures.
③ The pathogens were seen perialveorally in smeared specimens.
④ Heavier growth of pathogens was observed with washed sputum than with nasopharyngeal or throat swabs.
⑤ **The pathogens in washed sputum correlated with the clinical course of the disease: signs and symptoms, acute phase reactants, and especially the purulence (neutrophilia) of the sputum.**

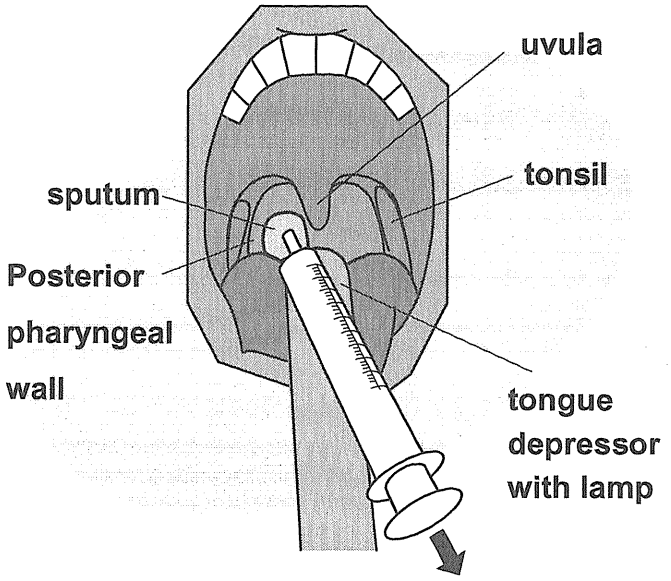

Fig. 4 Placement of instruments for the collection of sputum from pediatric patients.

(non-washed) results in inferior identification of causative bacteria, as it is covered with bacteria from upper airway secretions. Sputum specimens should be pretreated to remove contamination from the upper airway as completely as possible before culturing. Use of nasopharyngeal and pharyngeal cultures is only of limited value in etiological diagnosis of bronchopulmonary infections. Nasopharyngeal culture should therefore be conducted when sputum cannot be collected. Nasopharyngeal culture, however, should be used to postulate rather than definitively identify the bacterium responsible for pneumonia.

9 Detection of bacterial antigens in urine: Pneumococcal antigen may show false-positive results in urine because of the high prevalence of *S. pneumoniae* in the upper respiratory tract of children.[12] Urinary antigens are of excellent value in diagnosing legionellosis. Urinary antigen testing for *Legionella* spp. should be performed as a precaution in the critical cases of pneumonia.

10 Blood culture: Although sensitivity is not as high as other methods, blood cultures are of extreme value in selecting drugs for treatment when identifying the causative pathogen. Blood culture should be conducted whenever possible. Blood culture is discussed in detail in *Cumitech 1C: Blood Cultures IV*, a publication of the American Society for Microbiology.[13]

Mycoplasma, Chlamydia

Mycoplasma pneumoniae and *Chlamydia* infections are diagnosed by: (i) confirming significantly elevated or abnormally high serum antibody titers; and (ii) performing isolation culture, antigen detection, and nucleic acid detection on specimens from the infection site.

1 *Mycoplasma*: *M. pneumoniae* is the only significant pathogen involved in childhood respiratory infections. *Mycoplasma* infections are diagnosed by detection of *Mycoplasma* from the infection site and confirmation of increased antibody titers. *Mycoplasma* is detected in nasopharyngeal swab specimens, sputum, and pleural fluid. Detection is accomplished with direct fluorescent antibody assay, isolation culture, enzyme immunoassay, DNA probe assay, polymerase chain reaction (PCR), and other methods. Liquid pleuropneumonia-like organism (PPLO) media and other special media are used for isolation culture, which typically requires at least 7 days. PCR features excellent sensitivity and specificity. Serological diagnosis is accomplished with methods including particle agglutination (PA), cold agglutinin titer, complement fixation, indirect hemagglutination assay, and enzyme immunoassay.[14] Although serum antibody titer is at least fourfold higher in the acute and convalescent phases, increased immunoglobulin (Ig)M antibody levels must be identified to reach a definitive diagnosis. Infection may be strongly suspected if a PA titer of at least 320 or a complement fixation titer of at least 64 is detected in single serum. Infections in infants show poor antibody response.

2 *Chlamydia*: The three species *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, and *Chlamydia trachomatis* are the causes of childhood *Chlamydia* respiratory infections. *Chlamydia* infections are diagnosed by detection of *Chlamydia* from

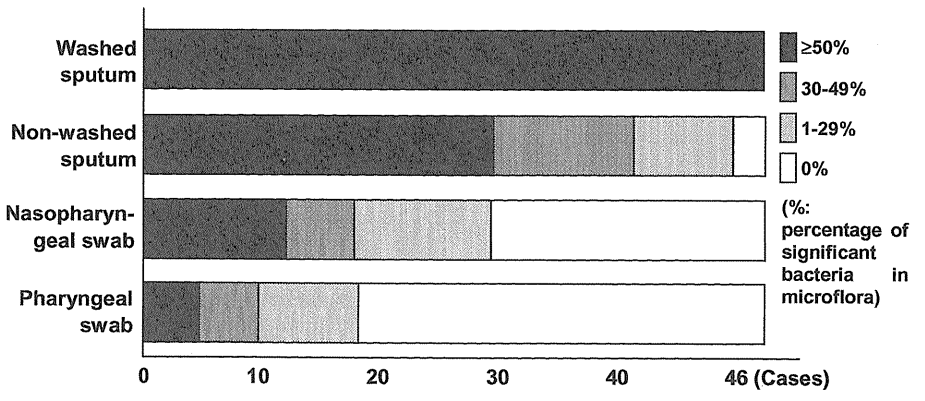

Fig. 5 Simultaneous culturing of washed and non-washed sputum specimens and nasopharyngeal and pharyngeal swabs from cases in which causative bacteria could be identified from washed sputum cultures. (Reproduced from Takeda *et al.*,[11] with permission.)

the infection site and confirmation of significantly increased antibody titer. *Chlamydia* is detected in nasopharyngeal swab specimens, sputum, and pleural fluid. Direct fluorescent antibody, enzyme immunoassay, PCR, and other techniques are used for detection. Isolation culture in cell culture requires at least 7 days. PCR offers good sensitivity and specificity. The Committee on Serological Diagnosis of *Chlamydophila pneumoniae* infection (chaired by Toshio Kishimoto) sets related diagnostic standards in Japan.[15]

Although serum antibody titer is at least fourfold higher in the acute and convalescent phases, increased IgM antibody levels must be identified to achieve serological diagnosis. For initial infections, a diagnosis can be reached in a relatively early stage using IgM antibody assay. Infections in infants show poor antibody response.

It should be noted that legionellosis is attributable to aspiration of *Legionella pneumophila* and other *Legionella* spp. from water coolers and other climate-control equipment. Only a few infants have acquired legionellosis in a neonatal intensive care unit. Legionellosis is more often diagnosed through rapid antigen diagnostics of urine specimens (61%) than it is from serum antibody titers. Rapid antigen diagnostics should therefore be attempted in cases of critical pneumonia. Isolation culture requires special media (B-CYEα medium, World Health Organization [WHO] agar medium).

Viruses

The characteristics of the viruses often isolated in childhood respiratory tract infections differ according to the infection site. Determining causative microorganisms according to symptoms alone is often difficult. The flow of testing is presented in the original *Guidelines*.

Medical staff collecting specimens for testing must be careful to perform collection at initial presentation in the early stage of the disease and to place specimens in a preserving solution for specimens for isolation (such as those designated by testing facilities). Specimens should be stored at low temperature (often 4°C). Specimens should be promptly shipped refrigerated to the testing facility. Serum specimens must be collected as paired sera once during the acute phase and again during the convalescent phase, 14–21 days after onset. A definitive diagnosis is reached when antibody titer is increased at least fourfold. The microplate method used by Numazaki *et al.* at the Virus Research Center of Sendai National Hospital[16] is well suited for the co-detection of viruses, is recommended by the WHO, and is increasingly used at Prefectural Institutes of Public Health in Japan, but the method is not feasible in all cases and must be selected according to the reason for culturing. The *2007 Guidelines* refined the list of rapid diagnostic testing, isolation culturing, nucleic acid detection testing, and serological detection methods for influenza virus, respiratory syncytial virus (RSV), and adenovirus pathogens.

Testing for rapid diagnosis of childhood respiratory infections

The *Guidelines* summarize: (i) trends in testing for the rapid diagnosis of childhood respiratory infections; (ii) the strengths and limits of immunochromatography; (iii) reagents for blood assay for *Mycobacterium tuberculosis* (BAMT), including whole-blood interferon-γ assay for diagnosing tuberculosis; and (iv) points to consider when performing rapid diagnostic testing.

Upper respiratory infections

1 Common cold (nasopharyngitis): Colds, which are caused primarily by viruses, are not treatable with antimicrobials. Antimicrobials fail to improve the course or prognosis of colds and have been found not to protect against lower respiratory tract infections. Fever alone with no respiratory symptoms is differentiated based on the presence of occult bacteremia, urinary tract infections, and other conditions.

2 Pharyngitis/tonsillitis: These conditions are often of viral origin. Antimicrobial treatment is indicated for primarily GAS infections. The *Guidelines* now recommend penicillin (PC)-based antimicrobials[17] as first-line treatments for GAS based on the discussions of GAS treatment that have taken place since 2004, but also list cephem antimicrobials for short-term therapy. Cephem or macrolide antimicrobials are recommended for children with penicillin allergies, but some children are also allergic to cephem antimicrobials. Not a few GAS isolates in Japan show resistance to macrolide antimicrobials, making cross-resistance a concern.

3 Croup syndrome
   (1) Viral croup: Viral croup is to be treated symptomatically. Dexamethasone therapy is an option for severe cases.
   (2) Acute epiglottitis: The course of this serious disease can include asphyxiation occurring 10 h after onset. A tongue depressor must not be used. Securing the airway is an urgent priority. Lateral radiography of the neck can show any epiglottic enlargement. *H. influenzae* type b (Hib) is the causative microorganism in ≥90% of all cases. The disease is treated with the antimicrobials: ceftriaxone, cefotaxime, meropenem, or tazobactam/piperacillin. Now that the Hib vaccine (approved in January 2007 in Japan) has been found to be safe and effective, Hib epiglottitis can be almost completely prevented through vaccination.[18]
   (3) Laryngeal diphtheria: Although very rare (only one case has been officially reported over the past several years), the possibility of laryngeal diphtheria must be kept in mind in unvaccinated and older children. Antitoxin therapy should be administered first and foremost.
   (4) Bacterial tracheitis: Although very rare, bacterial tracheitis can cause asphyxiation. *S. aureus* and other organisms cause this disease.

Bronchitis

1 Acute bronchitis:[19] Although acute bronchitis is usually viral, oral antimicrobials (consistent with those used for pneumonia) are used when bacterial bronchitis (*H. influenzae*, *S. pneumoniae*) is suspected based on fever, productive cough, or purulent sputum.

2 Protracted bronchitis (protracted, recurrent, and chronic bronchitis):[7] If infection is confirmed, the causative bacteria (*H.*

influenzae > *Streptococcus pneumoniae*) should be identified from the sputum and treated with the appropriate antimicrobial(s). Any underlying diseases (e.g. sinusitis, immunodeficiency) must be identified and superinfection by *Pseudomonas aeruginosa* or other organisms must be avoided.

Bronchiolitis

Acute bronchiolitis[20] is common in infants and is primarily caused by RSV (45–75%). Fever infrequently exceeds 38.5°C, and chest radiography often shows hyperinflated lungs. Some serious cases in infants under 3 months old require respiratory management. Antigen testing is useful. Some infections are caused by the human metapneumovirus, which has become a recent focus of attention.[21] No consensus has been reached on the value of PCR detection of the human bocavirus. Palivizumab is an effective prophylactic for RSV infection in high-risk infants.

Pneumonia

1 The definition of pneumonia: This acute respiratory infection is characterized by fever, rhinorrhea, and cough. Chest radiography, computed tomography (CT), and other imaging modalities show acute new infiltration in the lungs. Adventitious breath sounds and decreased respiratory sounds on chest auscultation can be observed in pneumonia.

2 Diagnosis of pneumonia: Patients suffering primarily from fever, cough, and dyspnea and who are suspected of having pneumonia based on chest findings should undergo chest radiography. Viral and *Mycoplasma* pneumonia are characterized primarily by interstitial lesions, and may show no abnormalities on chest auscultation. Once a definitive diagnosis of pneumonia is made based on imaging, the causative microorganisms should be identified in the blood and sputum (or in nasopharyngeal secretions). The need for antimicrobial(s) is determined in reference to pulmonary radiographs, acute phase reactants, and in consideration of the presumed causative microorganism. It must be remembered that infants and preschool children often cannot report dyspnea. When evaluating severity, features to check in addition to chest imaging include tachypnea (≥50 breaths/minute in children 1 year old and younger and ≥40 breaths/minute in children aged 2–5 years old) and retractions, nasal alar breathing, shoulder breathing, grunting, and cyanosis as signs of dyspnea (discussed later).

3 Causative microorganisms and examination

(1) Incidence of causative microorganisms: Based on the limited number of pneumonia cases for which the causative bacterium was confirmed through blood or pleural fluid culture in a nation-wide survey, the incidence of infections caused by *S. pneumoniae* and *H. influenzae* have exceeded those caused by *S. aureus* since the 1990s (Fig. 2).[6] Trends in *S. aureus* infection must be monitored.

Of the washed sputum cultures from bronchopulmonary infections, predominant bacteria were identified in about 30% of cases, and recent trends show that *H. influenzae* became more common than *S. pneumoniae*, and *M. catarrhalis*, in that order. *S. pneumoniae* pneumonia has been increasing since 1995 and accounted for about 30% of cases in which a causative organism was identified in 2005 (Fig. 6). For cases in which the causative pathogen of pneumonia was identified by washed sputum culture, about 30% of cases were attributed to bacterial pneumonia, 10–20% were attributed to *M. pneumoniae*, about 20% were viral, and the cause of the remaining 30% could not be determined. Trends in causative pathogens identified in washed sputum culture at three medical institutions associated with Chiba University showed *H. influenzae* and *S. pneumoniae* to be the major culprits since 1965, with some cases attributed to *M. catarrhalis*.

(2) Causative microorganisms and age distribution: The *Guidelines* summarize evidence about the age distributions associated with the causative microorganisms of pneumonia from the publication of McIntosh.[22] The Japanese evidence is similar. Although *C. pneumoniae* is well characterized, the data on other microorganisms do not differ substantially from those listed in medical texts, and no frequencies are stated. An investigation of the relationship of age in childhood pneumonia at Chiba Kaihin Municipal Hospital (1998–99) showed that of the 634 cases of childhood pneumonia treated, 170 (26.8%) were in 1-year-old children, 115 (18.1%) were in 2-year-old children, and 84 (13.2%) were in 4- to 11-month-old infants. A total of 512 (80.8%) were in children 4 years old and younger. Bacterial pneumonia was confirmed in washed sputum culture in 163 cases (25.7%). All cases were attributable to *H. influenzae*, *S. pneumoniae*, or combinations of these two, with the exception of three cases caused by *M. catarrhalis*, one caused by *Bordetella pertussis*, and two caused by GAS. Pneumonia was more commonly of bacterial origin in the younger age groups of hospitalized patients at Chiba Children's Hospital, while the incidence of *Mycoplasma* pneumonia increased with age (Fig. 7).

Although *C. pneumoniae* infections are relatively common beginning at young ages outside Japan, the prevalence of *C. pneumoniae* IgG antibody in Japanese children increases with age starting with an increased prevalence in 4–7-year-olds, a sharp increase to 44% in 8–11-year-olds, and about 50% above the age of 11 years.[23] The data provided by Kishimoto[24] on antibody incidence similarly indicate an increase in prevalence beginning at 6 years old. Grayston,[25] who stated that the incidences of bronchitis and pneumonia are about equal from 5 to 9 years old and that pneumonia is more common from 10 years old, reported that most cases of pneumonia are attributed to *C. pneumoniae* in older children.

4 Clinical symptoms, laboratory test findings, and antimicrobial selection

(1) Clinical symptoms and physical findings encountered with different causative pathogens: Investigation of many

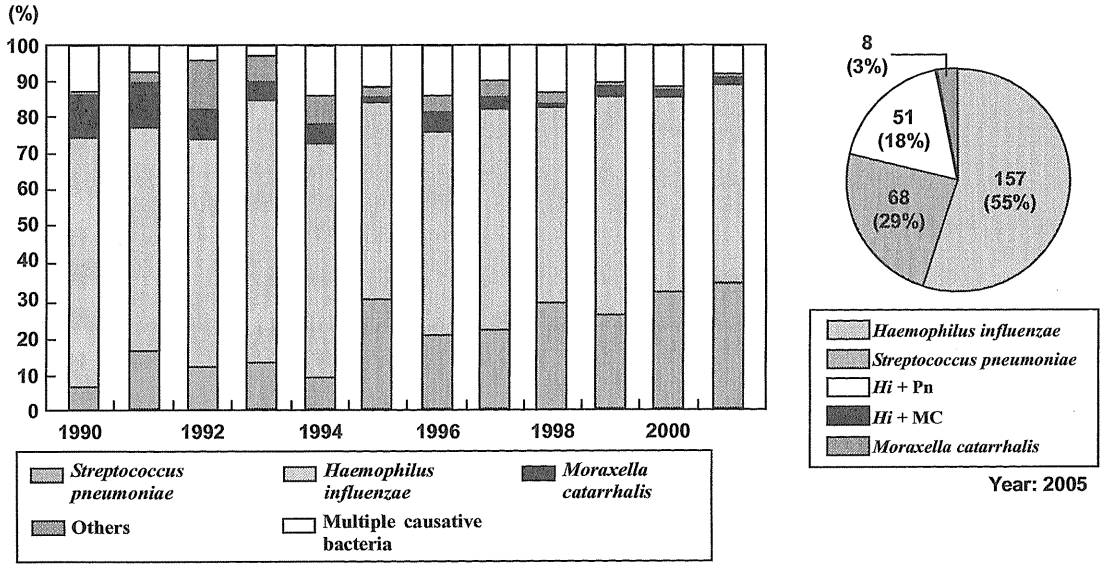

Fig. 6 Trends in causative bacteria in childhood bronchopulmonary infections based on washed sputum culture (percentages among cases of known pathogens). MC, *Moraxella catarrhalis*; Pn, *pneumococcus*. (Prepared from data provided by Dr. Kurosaki of Chiba Municipal Kaihin Hospital; reproduced from *The Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2007*, Uehara and Sunakawa [eds.][2] with permission.)

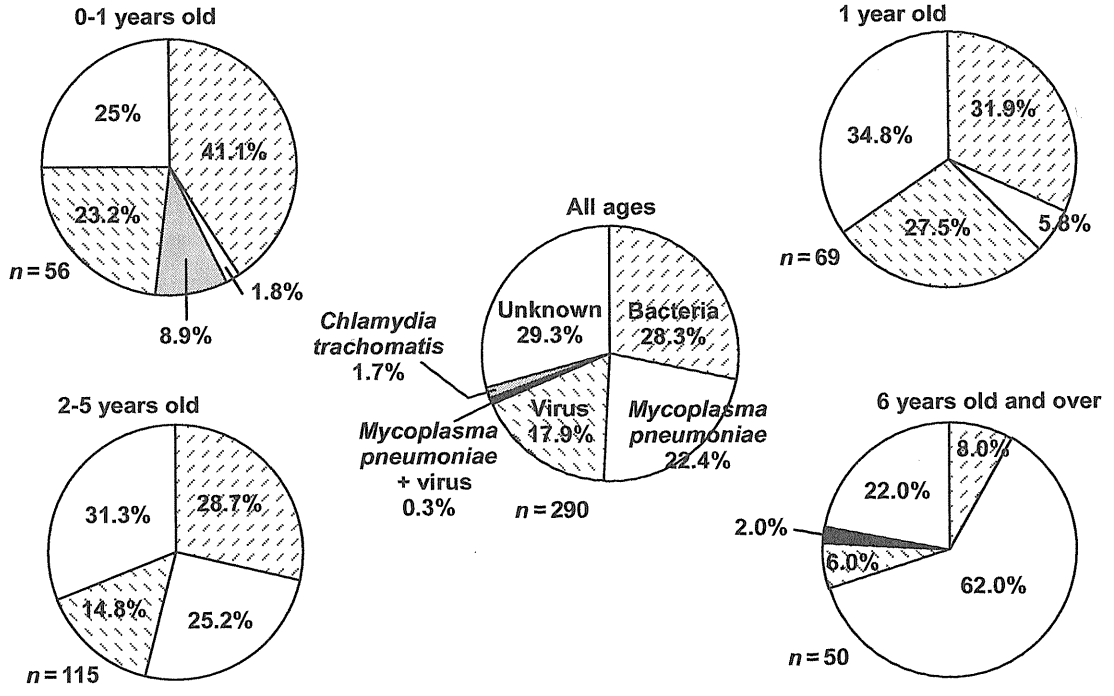

Fig. 7 Causative bacteria of community-acquired pneumonia in children. (Data collected October 1988–March 2002 by A. Nakamura of Chiba Children's Hospital; reproduced from *The Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2007*, Uehara and Sunakawa [eds.][2] with permission.)

Table 5 Community-acquired pneumonia: determining severity through physical and laboratory observations

	Mild	Moderate	Severe	Critical
General condition	Good		Poor	
Cyanosis	Absent		Present	
Respiratory rate†	Normal		Rapid (over normal range)	
Forced respiration (grunting, nasal alar breathing, retraction)	Absent		Present	
Extent of infiltration on chest X-ray examination	≤1/3 of one lung		≥2/3 of one lung	
Pleural effusion	Absent		Measurable quantity	
SpO_2	>96%		<90%	
C-reactive protein (mg/dL)	<3.0		>15	
Neutrophils: Infant	4000–8000		<500 or >10 000	
Preschool-age child	2500–5500		<500 or >10 000	
School-age child	3000–5000		<500 of >10 000	
Criteria	All of the above criteria are met	Not mild or extreme	Any one of the above conditions are met	Accompanied by circulatory failure or when artificial respiratory care is required

†Respiratory rate by age: (breaths/min): neonate, <60; infant, <50; preschool-age child, <40; school-age child, <30.

cases in which the causative pathogen has been identified has revealed that bacterial pneumonia often involves productive cough and that *M. pneumoniae* disease often lacks labored breathing and abnormalities on auscultation. *C. pneumoniae* infections result in low-grade fever and prolonged coughing. Diagnostics for causative organisms, however, are required because postulating the causative microorganism according to symptoms is difficult in individual patients.[26,27]

(2) Causative microorganisms and laboratory test findings on admission: Bacterial and viral pneumonia had been considered distinguishable by the intensity of the inflammatory response. In blood culture-negative bacterial pneumonia, although white blood cell counts, C-reactive protein levels, and erythrocyte sedimentation rates were significantly different from those of viral pneumonia ($P < 0.01$), overlap is seen in about one-third of patients, making differentiation of cause impossible in individual cases.[27] Bacterial culture is therefore necessary before antimicrobial treatment. The possibility of *Mycoplasma* pneumonia should be considered when C-reactive protein levels and erythrocyte sedimentation rates are high, but white blood cell counts are not elevated.

(3) Causative pathogens and findings from chest radiography: The cause of pneumonia cannot be clearly differentiated based on chest radiography performed on admission using the differentiation methods of Swischuk and Hayden[28] or the scoring method of Khamapirad and Glezen.[29]

(4) Classifications of pneumonia severity: Tachypnea: The WHO established management criteria for pneumonia in developing countries, with a focus on tachypnea and labored breathing. Kurosaki[27] compared respiratory rates (≥50 breaths/minute in children 1 year old and younger and ≥40 breaths/minute in children under 5 years old) to findings from washed sputum cultures and reported that tachypnea can be used as an index for determining the appropriateness of antimicrobial treatment before culture results become available for 1–4-year-old children.[30] Assessing the severity of pneumonia is a first step toward determining whether the patient should be treated as an outpatient or admitted, whether antimicrobials should be administered, and whether oral or intravenous (i.v.) administration is appropriate. Criteria for assessing pneumonia severity are shown in Table 5.

(5) Hospitalization eligibility criteria: Patients with a severity classification of mild should be treated on an outpatient basis, while patients with moderate or severe infections should be admitted for treatment.

(6) Important factors when considering initial antimicrobial therapy

(i) Intensity of bacterial pathogenicity: *S. pneumoniae* has the strongest pathogenicity of the three causative organisms of bronchopulmonary infections: *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Antimicrobial therapy that considers *S. aureus* is occasionally recommended for infants and children with underlying diseases.

(ii) Relationship between age and causative organism: The organisms primarily responsible for pneumonia differ with age of children as follows.

Neonates: Group B Streptococcus, *Escherichia coli*, and other intestinal flora.

Infants to children aged 5 years old: viruses, *H. influenzae*, and *S. pneumoniae*.

Children 6 years of age and older: *M. pneumoniae*, *C. pneumoniae*, *H. influenzae*, and *S. pneumoniae*.

Macrolide antibiotics should be considered first in children at least 6 years old who do not exhibit productive cough.

(iii) Pharmacokinetics of oral antibiotics: The pharmacokinetics-pharmacodynamics (PK-PD)

theory indicates that new cephem antibiotics, when recommended, should be administered at a high dose.

(iv) Minimizing drug resistance: Care must be taken to use antibiotics appropriately (particularly oral cephem antibiotics).

(v) Synthetic penicillin therapy for *S. pneumoniae* and *H. influenzae*: The Drug-Resistant *Streptococcus pneumoniae* (DRSP) Therapeutic Working Group of the Centers for Disease Control and Prevention of the USA, reasoning that pneumonia in children under 5 years of age is often bacterial in origin, advocates a β-lactam antibiotic (amoxicillin, amoxicillin/clavulanic acid, or cefuroxime for outpatient cases) for the initial treatment of pneumonia.[31,32] We set dosages for the treatment of cases for which *S. pneumoniae* was the predominant organism isolated from washed sputum based on the breakpoint for i.v. ampicillin defined by the Japanese Society of Chemotherapy of 2 μg/mL. Treatment with oral amoxicillin (30–40 mg/kg/day) and i.v. ampicillin (80–150 mg/kg/day) showed no significant differences for pneumonia with the following: penicillin-susceptible *S. pneumoniae* (PSSP), penicillin-intermediate resistant *S. pneumoniae* (PISP), and penicillin-resistant *S. pneumoniae* (PRSP).[32] (Note: The 2007 edition of the *Guidelines* lists penicillin G [PcG] resistance criteria that were revised in 2008. Following are the criteria in the 2007 edition of the *Guidelines*: PSSP, PcG-minimum inhibitory concentration [MIC] ≤ 0.06 μg/mL; PISP, PcG-MIC, 0.12–1 μg/mL; and PRSP, PcG-MIC ≥ 2 μg/mL). The *H. influenzae* ampicillin resistance criteria of the Clinical Laboratory Standards Institute (CLSI) of the USA[33] defines sensitivity as ≤1 μg/mL, moderate resistance as 2 μg/mL, and resistance as ≥4 μg/mL by the broth microdilution method. Most bronchopulmonary infections caused by β-lactamase-non-producing ampicillin-resistant (BLNAR) strains in Japan are treatable with i.v. ampicillin. Piperacillin, cefotaxime, and ceftriaxone offer reliable antibiotic activity against BLNAR strains. The response rate to piperacillin was 95%.[34] There are few patients with pathology caused by β-lactamase-producing *H. influenzae* strains that have shown clinical deterioration when treatment is initiated with oral amoxicillin or i.v. ampicillin. There is still time to switch antibiotics if resistance is identified after treatment is initiated.

(vi) Synthetic penicillin therapy for *M. catarrhalis*: Synthetic penicillin is clinically effective in treating *M. catarrhalis* infections even though the microorganism produces β-lactamase and is bacteriologically resistant to amoxicillin[35,36] because the produced β-lactamase has low activity.

(vii) Penicillin-binding protein (PBP) mutations: PBP of *S. pneumoniae* readily mutate in the presence of cephem antibiotics.[37] Mutation leads to increased resistance to β-lactam antibiotics and consequently DRSP strains. PBP mutations also underlie BLNAR and β-lactamase-producing amoxicillin-clavulanate resistant (BLPACR) *H. influenzae* strains. The increase in the prevalence of BLNAR strains is attributable to the widespread use of oral cephem antibiotics, which reaches a concentration that is only a fraction of that of amoxicillin.[37]

(7) Initial antimicrobial therapy when etiological pathogen is unknown: Antimicrobial agents recommended for initial treatment when the pathogen is unknown are shown for different age groups and for hospitalized patients and outpatients in Table 6. Agreement has been reached[38,39] on the appropriateness of the selections of initial antimicrobial agents given in the 2004 edition of the *Guidelines*. These selections must be continuously evaluated to take trends in causative microorganisms and drug resistance into account.

(8) Selection of antimicrobial agents when the etiological pathogen of pneumonia is known (monotherapy as a starting point): When the pathogen responsible for the pneumonia is known, the antimicrobial agent is selected in consideration of drug susceptibility and pharmacokinetics. Macrolide-resistant *Mycoplasma* strains have been increasing since 2000 (this is discussed later).

(9) Assessment of antimicrobial agent efficacy and duration of use: Antimicrobial agents for treating community-acquired pneumonia are normally sufficiently effective when administered for 3 to 7 days. Efficacy is assessed after 2 or 3 days (48–72 h after start of administration). Efficacy should be initially assessed after 2 days in younger children and severe cases. Assessment is performed to determine whether the initial antimicrobial agent is effective and whether the drug should be continued or switched. The duration of use will vary among individual patients. For common bacteria, use can be discontinued 3 days after the patient's fever breaks. A longer duration is required for *S. aureus* pneumonia. For *Mycoplasma* and *Chlamydia* infections, 10 days of new macrolide (clarithromycin) treatment or 3 days of azithromycin treatment (5 days in the USA) is recommended.

(10) Actions to take and selections to make when no response is achieved

(i) Actions to take when the patient does not respond to antimicrobial therapy: The correctness of the pneumonia diagnosis and the possibility of another disease producing pneumonia-like findings on imaging should be considered in order to distinguish pneumonia cases due to causative microorganisms other than common causative bacteria, such as viruses, tuberculosis, and fungi.

Table 6 Initial antimicrobial therapy in children for unknown etiological pathogen

	Severity	2 months to 5 years old*1*2*5	≥6 years old
Outpatient	Mild	AMPC ± CVA or SBTPC p.o. or Broad-spectrum cephem p.o.*3	Macrolide p.o. or Tetracyclin p.o.*4
Inpatient	Moderate to Severe	ABPC ± SBT i.v. or PIPC i.v. or Broad-spectrum cephem i.v.*3	ABPC ± SBT i.v. or PIPC i.v.*2 or Broad-spectrum cephem i.v.*3 ± Macrolide p.o./d.i.v. or Tetracycline p.o./d.i.v.*4
	Critical	Carbapenem d.i.v. ± Macrolide p.o./d.i.v.*6	

When the causative pathogen has been identified, change to the appropriate antimicrobial agent.
*1: With concomitant macrolide when *Chlamydia trachomatis* infection is identified.
*2: With concomitant macrolide when *Mycoplasma/Chlamydophila pneumoniae* infection is strongly suspected.
*3: The following offer superior antibacterial activity against *S. pneumoniae* and *H. influenzae*: Representative oral drugs: CDTR-PI; CFPN-PI; CFTM-PI. Representative intravenous drugs: CTRX; CTX.
*4: Use in children <8 years old only when other agents are ineffective or cannot be used.
*5: In principal, children <1 year old are hospitalized.
*6: With concomitant macrolide when Legionellosis cannot be ruled out.
AMPC, amoxicillin; CDTR-PI, cefditoren pivoxil; CFPN-PI, cefcapene pivoxil; CFTM-PI, cefteram pivoxil; CTRX, ceftriaxone; CTX, cefotaxime; CVA, clavulanic acid; d.i.v., drip intravenous; i.v., intravenous; PIPC, piperacillin; p.o., per os; SBTPC, sultamicillin.

(ii) Selection of antimicrobials when the patient does not respond to antimicrobial therapy:
- If a β-lactam antibiotic was initially used: Pneumonia is often caused by *H. influenzae* and *S. pneumoniae*, against which ampicillin and amoxicillin are recommended. These drugs are reportedly effective even against BLNAR and PRSP. For mild and moderate non-responsive cases, *Mycoplasma* or *Chlamydia* infection should be suspected, and the initial antimicrobial agent should be switched to or used in combination with a macrolide. A broad-spectrum i.v. cephem antibiotic or i.v. carbapenem antibiotic should be used when response is insufficient. For rapidly progressive, severe cases and critical cases, a carbapenem antibiotic and macrolide antibiotic should be used in combination. Addition of an anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agent is to be considered.
- If a macrolide antibiotic was initially used: Treatment should be switched to a β-lactam antibiotic to treat macrolide-resistant *S. pneumoniae* and *H. influenzae*. Treatment should be switched to the optimal antimicrobial agent once the causative pathogen is identified. Table 6 provides recommendations for critical cases. When the condition of the patient is good and a *Mycoplasma* infection is suspected, switching to a tetracycline antibiotic should be considered to treat possible macrolide-resistant *Mycoplasma* infection.

(11) Outpatient parenteral antimicrobial therapy (OPAT): OPAT is sometimes used to treat patients with moderate pneumonia who are unable to be admitted. Such patients must visit the medical institution daily and be carefully monitored. Once-daily ceftriaxone has a long half-life and is commonly used.[40] A first-line treatment for bacterial meningitis, ceftriaxone should not be used readily and widely until the Hib vaccine has substantially reduced the prevalence of meningitis.

Pleurisy and pyothorax

Although pyothorax prevalence in Japan has decreased with the waning incidence of *S. aureus* pneumonia, vigilance is required because the disease is still on the increase in countries outside Japan, despite widespread use of the pneumococcal conjugate vaccine.

Pneumonia in patients with underlying diseases

The 2007 edition discusses pneumonia with accompanying underlying conditions (blood diseases, immunodeficiency, neonates, and cardiac diseases).

Nosocomial pneumonia

Nosocomial pneumonia is defined as pneumonia acquired after a hospital stay of at least 48 h. Measures must be taken to prevent children from becoming infected due to the hospital environment and medical acts (including those leading to ventilator-associated pneumonia) as well as from other patients, attendants, visitors, and medical personnel. The *Guidelines* present measures for preventing respiratory infections acquired through different routes and discuss the person-to-person transmission of respiratory infections. The *Guidelines* also recommend the vaccination of medical personnel.

Main diseases controlled by vaccination

The *Guidelines* discuss influenza, measles, pertussis, diphtheria, and tuberculosis. Also proposed are draft diagnostic criteria for pertussis based on epidemiological data that factor in the relative increase in the disease among older children and adolescents and DTP-vaccinated children and adults. Although affected older children and adults exhibit prolonged and severe coughing, no characteristic symptoms can be identified in children without a detailed interview. The disease lacks elevated white blood cell and lymphocyte counts. A novel trivalent vaccine for adolescents and adults (Tdap) has been developed in Europe and the USA.

Pathogen resistance in community-acquired childhood respiratory infections

A classification system for *S. pneumoniae* and *H. influenzae* based on the analysis of antibiotic resistance genes is presented.[41] Antimicrobial agents currently used to treat resistant pathogens are listed (note: the antimicrobial susceptibility of *S. pneumoniae* and *H. influenzae* is discussed in Ubukata[37]). Most strains with an ampicillin-MIC ≤ 2 μg/mL are treatable using oral amoxicillin or i.v. ampicillin, but when therapy must be changed, oral faropenem, cefditoren, or cefcapene or i.v. panipenem or vancomycin are recommended for resistant *S. pneumoniae*, and oral cefditoren or azithromycin or i.v. piperacillin, ceftriaxone, or meropenem are recommended for BLNAR strains. Clindamycin resistance among GAS and *S. aureus* and macrolide-resistant *Mycoplasma* is a problem. Macrolide-resistant *Mycoplasma* was first detected in culture and by PCR in 2000, and many strains are highly resistant to erythromycin.[42,43] Although the period of fever following macrolide administration is significantly longer than that for infections by susceptible strains (mean duration of fever: 4.3 days for resistant strains vs 1.4 days for susceptible strains), the clinical symptoms are not more severe.[43] Changing treatment to a tetracycline antibiotic should be considered if fever persists for more than 48 h after macrolide antibiotic initiation.

The *Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2007* are summarized here with a focus on pneumonia. Only selected tables and figures to illustrate the *Guidelines* could be reproduced here due to limited space.

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Evaluation of ELISA Kit for Detection of Pertussis-associated IgG Antibodies

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