表1　ICTラウンドの進め方

	主任（医長）	副主任（看護師長），他メンバー	専任リスクマネージャー	ラウンド対策の病棟師長	主治医	検査事務薬剤
事前準備	←→	日程調整・連絡	←→	←→		
			＊配布 →			
			MRSA等感染患者リスト作成	← 院内感染対策チェックリスト未提出分提出		MRSA検出患者一覧表（＊）出力
			院内感染対策ﾁｪｯｸﾘｽﾄ提出確認	在院MRSA患者等リストアップ	事前調査票記載	ラウンド
当日	ラウンド＊特記事項診療録記載	ラウンド	ラウンド	事前調査票・カルテ指示表準備	可能ならば同席	ラウンド
終了後		感染防止ﾁｪｯｸﾘｽﾄ・報告書作成・配布	→	→ 指導内容の改善		
	感染対策委員会へ報告					

理由を記載する．

NC調査票（2）（**図1**）の回収：

院内感染と判定された症例については，主治医がNC調査票（2）を，すべての結果が判明次第に記載し，遅くとも4週以内に，院内感染対策委員会（リンクナース→医療安全管理室→検査科細菌室）に提出する．

4. ICTラウンド

2003年1月に，ICTを編成し，毎月1回のラウンドを開始した．

チーム構成は，リンクドクター1名を主任，リンクナース1名を副主任とし，これに，副薬剤科長，業務班長，細菌室検査技師，専任リスクマネージャー，副看護師長（医療安全管理室），を加え計7名からなる．チームは，本館病棟チームと新館病棟チームの2つからなり，本館チームは別館の病棟および中央部門を，別館チームは本館病棟および外来をラウンドするようにした．主任，副主任の任期は半年とし，病棟委員全員が順にICTラウンドに参加するようになっている．ICTラウンドの内容および進め方については，**表1**に示す．2006年4月からは，新たに感染管理認定看護師が配属されたため，これを機にICT活動の再検討，チェックリストの見直しなどを行い，月1回の上記ラウンドに加えて，ラウンドのない週を，MRSAなどの新規発生病棟を含む3ヶ所程度の病棟を重点的にラウンドする方式を開始した．このチームのメンバーは，院内感染対策委員長，感染管理認定看護師，専任リスクマネージャー，副看護師長（医療安全管理室），副薬剤科長，細菌室検査技師とした．これにより，毎週ラウンドを行うようになり，各病棟の院内感染状況が常時把握でき，その対策がもれなく速やかに実施できるようになった．

5. 抗菌薬適正使用

院内感染対策において，抗菌薬の適正使用は，薬剤耐性菌の出現防止などの観点から最重要課題である．当院では，2006年7月より抗MRSA薬3薬剤（塩酸バンコマイシン，テイコプラニン，アルベカシン），広域抗菌薬のカルバペネム系3薬剤（イミペネム，メロペネム，パニペネム），第4世代セフェム系2薬剤（セフォゾプラン，セフェピム），注射用ニューキノロン薬（パズフロキサシン，シプロフロキサシン）を特定抗菌薬として指定し，使用時には使用申請書の提出を義務づけている．

6. 教育活動

●院内（非公開）

1) 教育は，院内感染対策の中でもっとも基本となる対策である．まず，全職種，全職員を対象とした講習会を年３回実施している．この講習会は，すべての職員が参加できるように同じ内容のものを曜日を変えて３回行い，出席者名を把握し，参加できなかった職員には講習会のビデオを見てもらうなど徹底して行うようにしている．

2006年度は，６月；院内感染の経路別対策，標準予防策，手洗いの実際，針刺し事故防止対策．８月；結核の院内感染対策，流行性角結膜炎対策，身だしなみと環境整備．11月；インフルエンザ対策，疥癬について，MRSAの基礎知識を行った．11月の参加者は659名で全職員の90％以上であった．講習会後には理解度，感想，今後希望するテーマなどのアンケート調査を行い，次回の講習会内容の参考とした．この調査から，一般の職員は予想以上に院内感染に対しての興味を抱いているにもかかわらず，基礎的な知識がなく，このため医師を対象とするような内容では理解が得られないことが判った．同じ内容でも平易にわかりやすい言葉での講演が重要で，このため講演者は医師（ICD），看護師（ICN），検査技師，薬剤師など多職種とし，講演内容も重要な内容については異なった職種の講演者から重複して話すようにしている．

2) 新人職員については，新入職員研修の一環としての講義，研修医，レジデントについては，新人職員研修のほかに研修医セミナーなどにおいても講義を行っている．

3) 看護部による経年別教育の一環として，必ず院内感染対策を取り上げている．

●院外（公開）

1) 当院は，国立病院の時代から，厚生労働省より委託され，全国の国立病院・療養所職員を対象とした院内感染対策研修会（３日間）を毎年開催してきた．独立行政法人化後も，国立病院機構九州ブロックから委託され，ほぼ同様の研修会を継続して開催している．対象は九州ブロックの職員であるが，アナウンスは全国の国立病院機構施設にも行い，希望があれば全国の国立病院機構施設の職員の参加も受け入れている．この研修会の講師は，本邦での院内感染対策をリードされている著名な大学，研究所，病院の方々に依頼しており，このため県，市など保健行政担当者や一般病院の院内感染対策担当者の参加希望も多く，可能な限り参加いただいている．当院の病棟委員がすべての講義の座長を務め，参加可能な職員はできるだけ傍聴するようにしている．

2) クリティカルパス研究会EBM班による院内感染のEBM発表．３ヶ月ごとに当院で開催される本研究会報告により，術前抗菌薬の投与日数などが著しく改善された．

3) 看護部公開講座にて院内感染を取り上げている．

4) 厚生労働科学研究助成による院内感染対策研究の公開発表を県内医療従事者を対象に行っている．

5) 臨床研究部では，国際医療協力活動の中で，集団研修コース（薬剤耐性菌），パレスチナ，イラク医療支援コースにて院内感染について講義を行っている．

7. 研究活動

1) 薬剤耐性菌による感染症サーベイランス[6-9]

1998年，当院長宮﨑久義はこれまで当院で実施してきた院内感染サーベイランスの手法を用いて，薬剤耐性菌による感染症サーベイランスを行う多施設共同研究を７施設の国立病院機構において開始し（厚生労働科学研究事業），現在（29施設）もそのデータを参加施設にHospネットを通じて毎月フィードバックしている．これにより，全国レベルでの薬剤耐性菌の検出状況が詳細に分析できるようになった．また，本研究には国立感染症研究所に当初より参加していただき，多剤耐性菌の遺伝子分析検査も直ちに可能となっている．本研究成果は認められ，厚生労働省は，これらの手法を用いて全国の病院を対象とした院内感染サーベイランス事業を開始している．

2) 臨床研究部では，院内感染を研究テーマとして，

院内感染についての分子疫学的研究を国立国際医療センター研究所切替照雄部長と共同研究を行っている[10]．また，厚生労働科学研究助成を受け，"諸外国における院内感染対策の応用に関する研究"も行っている．

◇今後の展望とまとめ

DPC，包括医療の導入など，医療制度の変化が継続しているが，医療の質，医療経済の観点からもますます院内感染対策が重要となってきている．院内感染対策の担当者は常に内外の情報に気を配り，最新最良の院内感染対策ができるよう努力が必要である．また院内感染対策の実施においては，院内感染サーベイランスが必須であり，これを用いたICTラウンドは確実に成果が得られる．また，さらに最も重要なことは院内教育であり，きめの細かい教育の継続が必要である．

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〈速　報〉

日本におけるクリティカルパスの普及に関する実態調査報告

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要　旨

日本におけるクリティカルパスの普及状況を調べるために、2003年から毎年３月に200床以上の病院を対象にアンケートを郵送し回収した。対象病院は約2,000病院で当初の回収率は20%前後であったが後半になると40%を越え、信頼性の高い結果を得た。

導入率は５年間で約10%上昇し、2007年には92%にまでなった。病床規模の大きい病院ほど導入率は高い傾向をみた。クリティカルパスの種類は約半数の病院で50種類以上を使用し、200種類以上所有している病院も27病院（３%）あった。

クリティカルパス委員会の開催、作成基準の作成は大半の病院で行われていたが、クリティカルパス研究発表会は約半数の病院で実施されている状況であった。

地域連携クリティカルパスは大きな関心を持たれ、急速に普及しつつある。

日本医療マネジメント学会が医療情報システム開発センターと共同で運営しているクリティカルパス・ライブラリーの認知度は50%に達したが、そのうちの１/３病院が利用しているにとどまっていることがわかった。今後の取り組みを更に強化する必要がある。これからIT化の進むなか、電子化社会におけるクリティカルパス、地域連携クリティカルパスの活用が注目されてくるであろう。

はじめに

クリティカルパスが医療の分野に導入されて久しい。日本においては1990年代に入り一部の医療の現場で使用される様になったが、なかなか普及には至らなかった。日本における普及の導火線になったのは日本医療マネジメント学会の前身であるクリティカルパス研究会による第１回クリティカルパス全国研究交流フォーラム（会長 小関迪筑波記念病院長）の開催であり、以後、燎原に火の走るが如き勢いで普及し始めた。クリティカルパス研究会はその後、日本医療マネジメント学会へと発展し、学術総会、クリティカルパス実践セミナーの開催を行うとともに、学会雑誌、クリティカルパス最近の進歩2003[1)]・2004[2)]をはじめとする各種のクリティカルパス関連書籍[3)4)]の刊行、クリティカルパス・ライブラリー[5)]の開設等を通してクリティカルパスの啓発・普及に努めてきた。

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本学会では、その成果としての普及状況を把握するために、2003年より全国の200床以上の病院を対象としてクリティカルパスに関するアンケート調査を行い、その結果を学術総会で報告するとともに回答病院にフィードバックしてきた[6)7)]。

今般2007年３月に施行したアンケート調査の集計分析を終えたので、2003年から５年間の経年的結果につき報告する。

調査方法

2003年から毎年３月に200床以上の病院を対象にクリティカルパスの普及についてのアンケート調査を行った。各実施年毎の発送数、回答数、回収率は表１に示すとおりである。

表１　クリティカルパスに関する実態調査

調査年月	発送数	回答数	回収率
2003年３月	2187	559	26%
2004年３月	2154	481	22%
2005年３月	2165	338	16%
2006年３月	2116	844	40%
2007年３月	2110	882	42%

調査結果

(1)回収率について

2003年調査の回収率は26%であったが、2004年は22%、2005年は16%と低下した。しかし、2006年は回収率が40%と上がり、2007年は42%とさらに高くなった(表1)。このことはデータを分析する際に十分配慮する必要がある。

(2)クリティカルパス導入病院数とその割合（導入率）(表2)

クリティカルパス導入病院数を回答病院数で除した導入率は2003年調査では81%であったが年を経るに従って増加し2007年は92%と5年間で約10%上昇した。2006年に前年よりいったん1%低下したのは回収率がそれ以前の2倍以上に高くなった為であろう。

病床規模別にクリティカルパス導入率（表3）をみると、病床規模の大きい病院の導入率が高い傾向がみられた。

(3)クリティカルパス導入の目的（図1）

クリティカルパス導入の目的は2004年では①医療の標準化、②医療の質の向上、③業務の効率化と能率化、④インフォームドコンセント、⑤患者さんへのサービス、⑥全職員的取り組みチーム医療、⑦医療経営の効率化、経営改善、⑧意識改革、⑨その他の順であったが、年を経るにつれて少しずつ順番が変わり、③業務の効率化と能率化が2004年の第3位から2007年の第2位へと変化したことが注目される。

表2　クリティカルパス導入病院数とその割合（導入率）

	2003年	2004年	2005年	2006年	2007年
①導入している	458(81)	413(86)	301(89)	754(89)	808病院(92%)
②導入はしていない	61(11)	43 (9)	24 (7)	65 (8)	51 (6)
③導入予定である	37 (7)	13 (3)	11 (3)	19 (2)	13 (1)
④導入の予定はない	3 (1)	11 (2)	1 (0)	6 (1)	10 (1)
未回答	0	1	1	0	0
計	559(100)	481(100)	338(100)	844(100)	882(100)

( )内は百分率

表3　病床規模別　クリティカルパス導入率の比較

病床数	2004年			2005年			2006年			2007年		
	回答数	クリティカルパス導入病院	導入率	回答数	クリティカルパス導入病院	導入率	回答数	クリティカルパス導入病院	導入率	回答数	クリティカルパス導入病院	導入率
～299床	148	105	71%	81	67	83%	273	211	77%	291	246	85%
300床～399床	133	121	91%	98	89	91%	224	204	91%	245	223	91%
400床～499床	72	67	93%	49	40	82%	137	131	96%	120	117	98%
500床～999床	112	106	95%	96	91	95%	186	183	98%	198	194	98%
1000床以上	15	13	87%	13	13	100%	24	24	100%	27	27	100%
未回答/不明	1	1	—	1	1	—	0	1	—	1	1	—
計	481	413	86%	338	301	89%	844	754	89%	882	808	92%

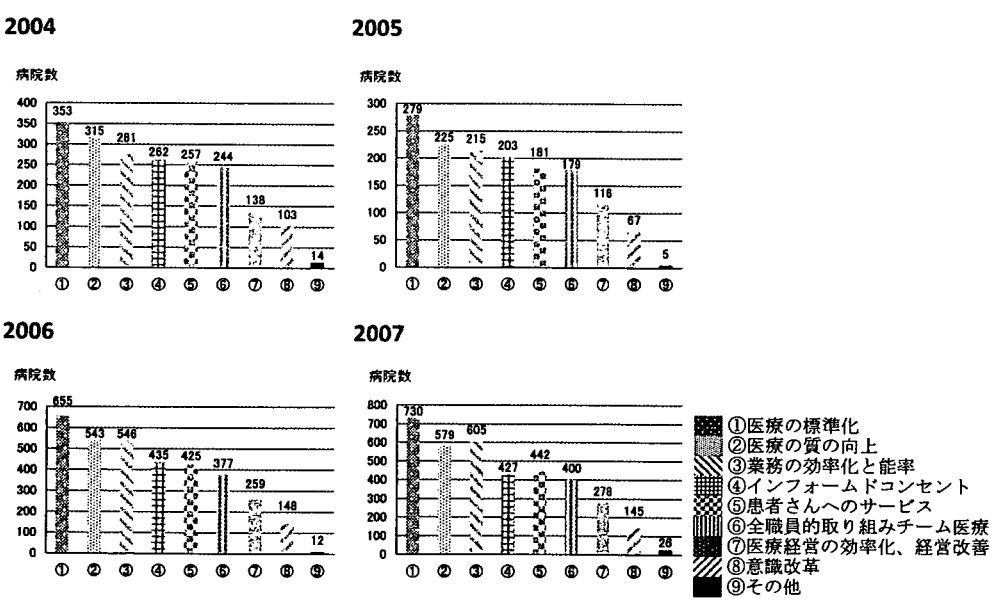

図1　クリティカルパス導入の目的（複数回答）

(4)クリティカルパスの種類（表4）

各病院で導入されているクリティカルパスの種類は調査年を経るに従って増加し、2007年にはほぼ半数の病院が50種類以上のクリティカルパスを使用しており、200種類以上のクリティカルパスを使用していると回答した病院は808病院のうち27病院（3%）であった。

(5)クリティカルパスの使用率（表5）

2004年から退院患者数に対してクリティカルパスを使用した症例数の割合（使用率）について回答を得た。2004年には30%以上の使用率を有する病院が使用率について回答した病院の約半数を占め、翌2005年はその割合はさらに増加している。しかし、2006年になって全体の使用率が低下した値を示したのは回答病院数の急増によるものと思われる。2007年には使用率の高い病院がさらに増加している。2004、2005年は未回答病院が多かったのでデータの取扱に配慮する必要がある。

(6)クリティカルパス委員会、研究発表会、作成基準の有無について

クリティカルパス委員会を定期的に開催している病院は2003年は69%であったが、2007年は81%まで増加している（表6）。しかし、研究発表会は約半数の病院で開催されているのみである（表7）。作成基準を設けている病院は2003年は52%であったが、2007年には68%まで増加した（表8）。

表4　クリティカルパスの種類

	2003年	2004年	2005年	2006年	2007年
①10種未満	84(18)	67(16)	28 (9)	115(15)	104病院(13%)
②10～49種	231(51)	198(48)	119(40)	292(39)	307(38)
③50～99種	114(25)	112(27)	104(35)	229(30)	225(28)
④100～199種	18 (4)	30 (7)	46(15)	103(14)	138(17)
⑤200種以上	1 (0)	3 (1)	3 (1)	7 (1)	27 (3)
⑥未記入	10 (2)	3 (1)	1 (0)	8 (1)	7 (1)
計	458(100)	413(100)	301(100)	754(100)	808(100)

( )内は百分率

表5　クリティカルパスの使用率

	2004年	2005年	2006年	2007年
①0%～10%未満	17(10)	4 (3)	135(21)	137病院(19%)
②10%～20%未満	26(16)	21(14)	161(25)	152(21)
③20%～30%未満	35(21)	33(23)	128(20)	142(20)
④30%～40%未満	46(28)	48(33)	101(15)	110(16)
⑤40%以上	39(24)	40(27)	128(20)	168(24)
計	163(100)	146(100)	653(100)	709(100)

( )内は百分率

表6　クリティカルパス委員会

	2003年	2004年	2005年	2006年	2007年
①開催している	314(69)	324(78)	250(83)	584(77)	656病院(81%)
②開催していない	140(31)	89(22)	51(17)	165(22)	150(19)
未記入	4 (1)	0	0	5 (1)	2 (0)
計	458(100)	413(100)	301(100)	754(100)	808(100)

( )内は百分率

表7　クリティカルパス研究発表会

	2003年	2004年	2005年	2006年	2007年
①開催している	206(45)	206(50)	173(57)	372(49)	379病院(47%)
②開催していない	244(53)	206(50)	123(41)	376(50)	424(52)
未記入	8 (2)	1 (0)	5 (2)	6 (1)	5 (1)
計	458(100)	413(100)	301(100)	754(100)	808(100)

( )内は百分率

表8　クリティカルパスの作成基準の設置

	2003年	2004年	2005年	2006年	2007年
①いる	240(52)	242(59)	203(68)	512(68)	552病院(68%)
②いない	203(44)	169(41)	94(31)	225(30)	234(29)
未記入	15 (3)	2 (0)	4 (1)	17 (2)	22 (3)
計	458(100)	413(100)	301(100)	754(100)	808(100)

( )内は百分率

表9　地域連携クリティカルパスについて

	2006年	2007年
①作成し、実施している	43 (6)	168病院(21%)
②作成準備中である	187(25)	211(26)
③まだ取り組んでいないが関心がある	476(63)	389(48)
④関心はない	11 (1)	15 (2)
⑤知らない	34 (5)	17 (2)
未回答	3 (0)	8 (1)
計	754(100)	808(100)

( )内は百分率

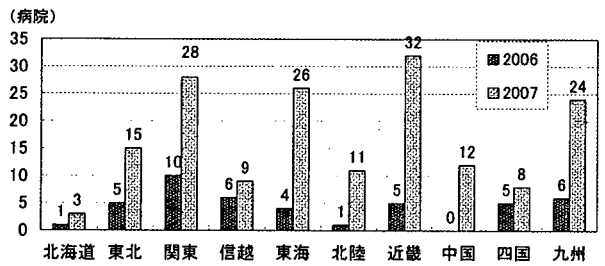

図2　地域連携クリティカルパス導入施設数
(2006年、2007年の推移)

(7)地域連携クリティカルパスについて（表9）

2006年から地域連携クリティカルパスの導入についても調査を開始した。地域連携クリティカルパスを作成し、実施している病院数は2006年の43病院から2007年の168病院へと急激な増加をみた。作成準備中も含めると回答病院のほぼ半数が取り組んでいることとなる。

地域連携クリティカルパスへの取り組み病院数を地域別にみる（図2）と、近畿地方が最も多く、ついで関東、東海、九州の順で、北海道は少ない。母数の違いの影響も大きい。

(8)クリティカルパス・ライブラリーについて

1）認知度について（表10）

クリティカルパス・ライブラリーの認知度は毎年向上し、われわれの努力が認められた感があるが、54%の認知度は低い。

2）利用について（表11）

クリティカルパス・ライブラリーを知っていて利用している回答病院の割合は、回答病院数の約1/3と、まだまだ低い結果であった。

表10　クリティカルパス・ライブラリーの認知度について

	2004年	2005年	2006年	2007年
①知っている	173(36)	140(47)	379(50)	432病院(54%)
②知らない	258(54)	156(51)	359(48)	364(45)
③未回答	50(10)	5 (2)	16 (2)	12 (1)
計	481(100)	301(100)	754(100)	808(100)

( )内は百分率

表11　クリティカルパス・ライブラリーの利用について

	2004年	2005年	2006年	2007年
①利用している	55(32)	54(39)	146(39)	153病院(35%)
②利用していない	116(67)	85(61)	226(60)	276(64)
③未回答	2 (1)	1 (0)	7 (1)	3 (1)
計	173(100)	140(100)	379(100)	432(100)

( )内は百分率

考　察

この種のアンケート調査としては回収率は高く、本報告の信頼性は高い。特に医療連携との関わりから地域連携クリティカルパスが注目され、改正医療法に明記されるとともに診療報酬上も算定できるようになった影響が大きいと思われる。

クリティカルパスの導入率は2003年の81%から2007年の92%へと11%の増加をみた。特に2007年の回収率が42%と高いことから、回答していない病院でクリティカルパス導入がされていないと仮定しても、クリティカルパスの導入はかなり進んでいるとみて良い。しかし導入率を病床規模別にみると、病床数の多い病院群で高く、病床規模の小さい病院群で低いことから、今後は200床規模以下の病院における導入率調査も必要であろう。

クリティカルパス導入の目的は2004年では、①医療の標準化、②医療の質の向上、③業務の効率化と能率化、④インフォームドコンセント、⑤患者さんへのサービス、⑥全職員的取り組みチーム医療、⑦医療経営の効率化、経営改善、⑧意識改革の順であったが、年を経るに従って②と③の回答数が接近し、2006年から逆

転し、2007年には更にその差は大きくなるという興味ある結果であり、導入目的が変わりつつあることを表している。

運用されているクリティカルパスの種類は約半数の病院が50種類未満であるが100種類以上運用する病院数、特に200種類以上を運用する病院が毎年増加しつつあることは大変興味深い。

クリティカルパスの使用率については2004年から調査を開始したが、最初の2年間は未回答の施設が半数以上あり比較するには適当でない。2006年からはほとんどの病院から回答があり、使用率への関心が高まってきたといえる。使用率は2006年よりも2007年において低い病院が減少し、高い病院が増加する傾向を示し、各病院における使用率向上を読み取ることができる。

クリティカルパス委員会の定期開催は組織としてクリティカルパスを運用するには重要であり、約80%の病院で行われるようになっているが、研究発表会を開催している病院は約半数と少なく、研究発表会をいかにして開催し、成功させるかが関心の高いところである。研究発表会の目的を明らかにして、成果を上げる取り組みをする必要があろう。

クリティカルパス作成基準を設けて運用している病院は回答病院の68%であり、2003年の52%からみるとかなり増加している。作成基準は更新され、進歩するものであり、関心の高いところである。

地域連携クリティカルパス[8]への関心は高く、作成している病院数は調査を開始した2006年から2007年にかけて急増している。本報告書作成中も恐らくは新しく取り組んでいる病院数が増加していることであろう。改正医療法への記載、現在は大腿骨頸部骨折に限定されているが診療報酬上に算定が認められたことは大きな進歩である。診療報酬上は大腿骨頸部骨折に限定されているが、近い将来は適応拡大が予想されている。日本医療マネジメント学会としては地域連携クリティカルパス分科会の開催、学術総会における特別枠の設定、学会雑誌での特集、啓蒙のための単行本「クリティカルパスの新しい展開」[9][10][11]の出版等々、情報提供、情報交換をすすめている。医療の質改善、良質の医療を国民へ提供するツールとして発展が期待される。

クリティカルパス・ライブラリーの認知度は50%まで高まったが、それに比して利用率は低い。新しいクリティカルパスの情報を日々更新し、認知度、利用率ともに高め、魅力あるライブラリーにする努力が必要である。関係各位の助言を期待する。

おわりに

クリティカルパスの普及は200床以上の病院においてはかなり普及していることがわかった。そして、その種類、使用率とも病院間で格差が大きいもののまだ増加傾向にあり、今後の展開に興味が持たれる。

特に地域連携クリティカルパスへの関心は高く、2007年調査時点で既に実施している病院と現在作成準備中の病院も合わせると、約1/2の病院では近く運用されることになることが示唆された。

これからIT化の進むなか、電子化社会におけるクリティカルパス、地域連携クリティカルパスの活用が注目されてくるであろう。

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Spanish Influenza in Japanese Armed Forces, 1918–1920

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With the recent outbreaks of avian influenza A (H5N1), the risk for the next influenza pandemic has increased. For effective countermeasures against the next pandemic, investigation of past pandemics is necessary. We selected cases diagnosed as influenza from medical records and hospitalization registries of Japanese army hospitals during 1918–1920, the Spanish influenza era, and investigated clinical features and circumstances of outbreaks. Admission lists showed a sudden increase in the number of inpatients with influenza in November 1918 and showed the effect of the first wave of this pandemic in Tokyo. The death rate was high (6%–8%) even though patients were otherwise healthy male adults.

Because of the emergence of avian influenza A (H5N1) virus in Southeast Asia, potential evolution of a novel type of influenza in the near future is of great concern (*1,2*). If an outbreak of a novel form of influenza occurs, a major worldwide pandemic is predicted because humans would not have immunity against this virus. To take effective countermeasures against new pandemics, investigation of past pandemics is essential.

Four pandemics occurred in the 20th century: Spanish flu in 1918, Asian flu in 1957, Hong Kong flu in 1968, and Russian flu in 1977 (*3,4*). Spanish influenza was the largest pandemic, and Japan was seriously affected. Despite abundant public records related to Spanish influenza, few primary documents, such as medical records, remain in Japan. Recently, medical records from the early 20th century were found in the depository of the International Medical Center of Japan (IMCJ) Hospital, Tokyo. We used these records to investigate the clinical characteristics of Spanish influenza. To help prepare countermeasures, we investigated the outbreak situation, clinical findings, and outcomes of Spanish influenza in the Japanese military during 1918–1920.

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Patients and Methods

The documents were stored at the medical history depository of IMCJ Hospital, at the medical records and hospitalization registries of Tokyo First Army Hospital (a predecessor of IMCJ Hospital), and at the Fifth Japanese Army Garrison Hospital, Krasnoyarsk, Russia. Medical records in which influenza was diagnosed between January 1918 and December 1920 were selected. Because the influenza virus had not yet been discovered at that time, no serologic or virologic diagnostic methods for influenza infection were available, and no examinations such as chest radiographs were performed. Thus, the diagnosis flu (*kanbo* in Japanese) was defined as clinical influenza.

Three types of documents were investigated. The first type was the hospitalization registry of Tokyo First Army Hospital, in which records of 127 patients from January 1918 through November 1918 were included. Because these records were bound, it was assumed that no records were missing. The second type was the medical records of 132 patients at the Fifth Japanese Army Garrison Hospital in Russia from March 1919 through April 1920. These records were also bound, and it was again assumed that no records were missing. The third type was the medical records of 419 patients at Tokyo First Army Hospital from January 1918 through May 1920. These records were not associated with time and were partially discontinuous, which indicated that some records (dates) were missing.

Information on the hospitals (e.g., numbers of beds and physicians) was unclear. This research was reviewed and approved by the research review boards at IMCJ

Hospital. Statistical significance of between-group differences was analyzed by using the Mann-Whitney U test. A p value <0.05 was considered statistically significant.

Results

We first investigated hospitalization registries of Tokyo First Army Hospital from January to November 1918. These registries had the names and diagnoses of patients admitted to the hospital on a monthly basis. Numbers of patients admitted for respiratory infectious disease during this period are shown in the Figure. Cases diagnosed as pneumonia, acute bronchitis, and influenza were classified as respiratory infectious diseases. Although records of patients with tuberculosis were found, we excluded them from this study. In the 10-month period from January to October, the mean (± standard deviation) monthly numbers of patients with pneumonia, acute bronchitis, and influenza were 10.9 ± 6.5, 10.0 ± 3.6, and 1.8 ± 4.1, respectively (22.7 ± 9.6 for all 3 illnesses). Death rates from pneumonia, bronchitis, and influenza during this period were 3.4% (4/116), 0% (0/109), and 0% (0/18), respectively. The number of influenza patients suddenly increased to 109 in November, and 9 of them died (8%). Because our information about these 109 patients was found only in the hospitalization registries (the patients' medical records were not found), we could not identify their clinical symptoms. However, it can be assumed that the hospital experienced the first wave of Spanish influenza in November 1918. Because no hospitalization registry before this period was found, comparison with outbreaks in average years was not possible.

We then investigated the medical records of the Fifth Japanese Army Garrison Hospital, which may have been a Japanese military field hospital in Krasnoyarsk, Russia. These records covered 2 years (1919 and 1920), but most cases of clinical influenza were concentrated in May–November 1919. All 132 cases were in infantrymen 19–49 years of age (mean ± standard deviation 22.7 ± 4.1 years); 47% had been farmers before entering the military, and 72% had no recorded medical histories. The initial symptom was sudden fever in 116 patients (94%), headache in 101 (81%), chills in 92 (74%), cough in 86 (69%), general malaise in 60 (48%), appetite loss in 56 (45%), pharyngalgia in 45 (36%), arthralgia/myalgia in 33 (27%), and vomiting/diarrhea in 27 (22%). On admission, reddish pharynx was noted in 105 (85%), coated tongue in 95 (77%), thoracic rale in 71 (57%), facial flush in 24 (19%), and conjunctival congestion in 16 (13%). The period from onset to admission was 4.7 ± 3.9 days (range 0–24 days), the duration of hospitalization was 14.8 ± 12.0 days (range 3–79 days), and the death rate was 6.0% (8/132). A comparison of 124 patients who survived and 8 who died is shown in the Table. In the patients who died, body

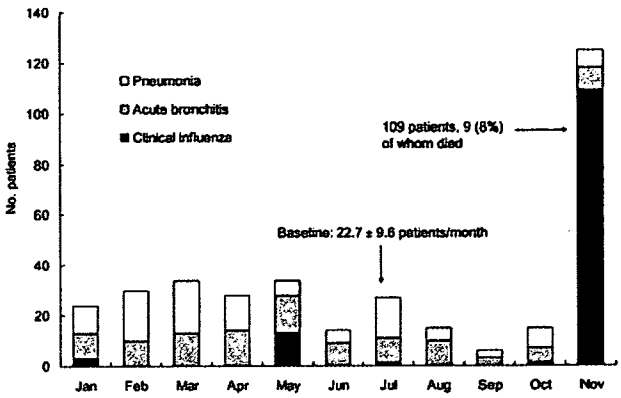

Figure. Number of patients hospitalized for respiratory infection, Tokyo First Army Hospital, 1918.

temperature and pulse rate were higher at the time of hospital admission, and thoracic rale and an "agonized facial expression" (a painful expression as reported by Japanese doctors) were observed in many patients. The death rate was higher in patients who had digestive symptoms, but the difference was not statistically significant. In fatal cases, the patients died an average of 13.9 days after symptom onset and 7.1 days after admission.

Fever patterns in 132 patients were classified as typical (fever resolved in <10 days after onset), prolonged (fever persisted for ≥10 days), biphasic (fever resolved and then recurred), and other (unclassifiable). A total of 77 (58%), 38 (29%), 7 (5%), and 10 (8%) patients, respectively, were classified as these types.

Discussion

Once a pandemic occurs, it may cause large-scale effects worldwide; various countries and organizations, including the World Health Organization, must prepare for such a situation (*5,6*). To take countermeasures against pandemics, past pandemics should be further investigated. Researchers are particularly interested in the biggest pandemic of the 20th century, Spanish influenza in 1918. Influenza A (H1N1) virus was the causative agent of Spanish influenza. However, this pandemic occurred almost 90 years ago, which makes investigation difficult.

Virus genes have been isolated from lung samples of patients who died of Spanish influenza. The nucleotide sequences of these genes have been determined, and the viral characteristics have been reported (*7,8*). However, the only method that can clarify the pathophysiology of Spanish influenza is investigation of the medical records at the time of the pandemic. Thus, the discovery of medical records and hospitalization registries of the Spanish influenza pandemic is useful. Although we studied only patients in Japan, studying patients in the Japanese Army

Table. Characteristics of patients who survived influenza with those who died of influenza, Fifth Japanese Army Garrison Hospital, 1919–1920*

Characteristic	Patients who survived (n = 124)	Patients who died (n = 8)	p value
Age, y	22.7	22.8	>0.9
Medical history	31/116	2/8	>0.9
Body temperature at time of hospitalization, °C	38.7	39.9	0.0005
Heart rate, beats/min	89	106	0.004
Rales	63/116	8/8	0.01
Reddening of throat	98/116	7/8	>0.9
Digestive symptoms	23/116	4/8	0.07
"Agonized facial expression"†	5/116	3/8	0.009
No. days from onset of illness to hospitalization	4.5	6.8	0.14
No. days hospitalized	14.8	7.1	0.04

*Mann-Whitney U test was used to test differences between the 2 groups. Fisher exact test was used to test differences in the ratio of the cross-calculation table. One case (at day 79) was excluded. This patient was admitted to the hospital with flulike symptoms but died of a bacterial infection.
†A painful expression as reported by Japanese doctors.

Garrison hospital in Russia may provide a clue to the conditions of the influenza outbreak in that region.

Many theories exist as to the source of Spanish influenza, but the first reported case in the United States likely occurred in March 1918 (*3*). After that, it spread worldwide through 1920. Of the 1.8–2.0 billion persons in the world at that time, 600 million were affected and 20–40 million died from this disease (*9*). In Japan, 23 million persons were affected, and 390,000 died. The first wave occurred in Japan in August 1918, and many cases were reported in Tokyo in mid-October (*10,11*). Hospitalization registries of the Tokyo First Army Hospital showed a sudden increase in admissions for influenza in November 1918; this outbreak may have been the beginning of the Spanish influenza pandemic in Japan.

Because the patients were all soldiers in the Japanese army, they were essentially healthy men. Medical records indicated that the soldiers did not go home for long periods and lived together in barracks without external contact. Once a virus infection occurred, it may have caused an outbreak among the soldiers within a short time. Initial symptoms were fever, headache, chills, and cough, and their frequency was not different from those of patients with seasonal or ordinary influenza. When cases in patients who survived were compared with those in patients who died (Table), high fever, tachycardia, thoracic rale, and an "agonized facial expression" were associated with poor outcomes. All treatments were antisymptomatic supportive therapy, and none of the drugs used was typical of modern medical care. Thus, most cases may not have been affected by treatments. The duration of hospitalization was shorter for patients who died, perhaps due to rapid exacerbation of symptoms and discharge within a short time.

Frequencies of hemoptysis and bloody sputum were reportedly high in patients with Spanish influenza (*12*), but high frequency of these signs was not observed in these patients, perhaps because of the limitation of our investigation to symptoms at the time of hospital admission. Bloody sputum was noted during hospitalization for some patients, but these episodes were excluded from the analysis because many descriptions of it during hospitalization were difficult to read. Because chest radiographs were not taken, we cannot discuss complications of pneumonia and its characteristics. However, chest auscultation indicated rales in 57% of the patients, which suggests that many patients also had pneumonia. Generally, complication by secondary bacterial pneumonia prolongs fever and leads to relapses (*13*).

To evaluate the presence of complications by bacterial pneumonia, we classified the fever patterns. Fever pattern was prolonged or biphasic in approximately one third of the patients, which suggests that many patients had secondary bacterial infection. The death rate was 6%–8%, and patients died an average of 2 weeks after onset of symptoms. The former Japanese Ministry of the Interior reported that the mean death rate from Spanish influenza in Japan was 1.21%–5.29% (*11*), but the death rate for our study patients was higher. The death rate from influenza is high for patients ≥65 years of age, but the death rate from Spanish influenza was also reported to be high for persons 20–30 years of age (*14,15*). The mean age of the population investigated was 22.7 years. Persons 20–30 years of age had the highest death rate and this may have been the reason for the overall higher death rate. The cause of a high death rate in young persons is unclear, but it may have been related to poor immunity because they had not previously been exposed to influenza virus. It may have also been related to poor conditions in military field hospitals at the end of World War I. Poor conditions in military field hospitals in foreign countries have also been reported (*16,17*).

Our study shows that when a novel influenza virus emerges, a large-scale outbreak can suddenly occur in large groups living together, such as military personnel. However, our data were incomplete because many documents were missing and radiographs were not available. Diagnoses were made solely on the basis of clinical symp-

toms, but this was unavoidable because no definitive virologic diagnostic techniques were available at that time.

We now have new tools against influenza, such as antiviral agents, vaccines, and rapid diagnostic methods, that were not available during the Spanish influenza pandemic. However, during the first wave of an outbreak of a new form of influenza, infection would be difficult to avoid and is likely to occur. To prepare for the next pandemic, a surveillance system for early detection of an outbreak (*18*), specific vaccines and rapid diagnostic test kits, and effective treatment strategies must be developed.

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Simultaneous vaccination in Japanese travelers

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KEYWORDS
Pre-travel vaccinations;
Simultaneous administration;
Post-vaccination adverse reactions

Summary
Background: Simultaneous vaccination is not common in Japan because there is little information available on its effects. Some people are quite concerned about the possibility of adverse reactions due to simultaneous vaccination. The objective of this study was to evaluate whether the frequency and severity of adverse effects are increased by simultaneous vaccination in comparison to single vaccination.
Method: A retrospective observational study was conducted in 399 asymptomatic travelers who visited the travel clinic during the period January–July 2005. One hundred forty-two participants were given a single vaccination, 257 participants were given simultaneous vaccination. Travel-specific vaccinations were for hepatitis A, hepatitis B, tetanus, rabies and Japanese encephalitis, and routine vaccines were for diphtheria+tetanus, measles, mumps and oral polio vaccine. To evaluate adverse effects, travelers were asked to complete a prepared questionnaire after vaccination.
Results: Adverse effects were reported by 26.3% of travelers, with 21.8% reporting local reactions and 4.5% reporting systemic reactions. The simultaneous vaccination group reported significantly more frequent adverse effects than those reported by the single vaccination group. Particularly, tetanus vaccination was shown to significantly raise the risk of adverse effects ($P<0.001$). However, no serious adverse effects were reported.
Conclusions: Simultaneous vaccination was feasible for Japanese travelers because most problems were generally minor and related to local reactions at the sites of injections. Provision of a simultaneous vaccination schedule should motivate more Japanese travelers to obtain immunizations and thereby reduce the risk of vaccine-preventable diseases.
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Introduction

The number of Japanese travelers who visit abroad has increased rapidly in recent years. According to data

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reported in Trends in International Tourism,[1] a publication of the Japan Association of Travel Agents, approximately 16.8 million Japanese people traveled to international destinations in 2004. Although pre-travel vaccinations constitute an important part of the preparation for international travel, particularly to developing countries, many Japanese travelers find it difficult to find the time needed for adequate vaccinations before their departure. Therefore, simultaneous vaccination is suggested frequently during pre-travel counseling.[2] However, simultaneous vaccination is still uncommon in Japan, and some travelers are concerned about the adverse effects because data regarding the adverse effects of simultaneous immunization with different vaccines are sparse.

Although, some reports are available in Western countries on the tolerability of vaccines used simultaneously,[3,4] the data cannot be applied directly to Japanese travelers because they can only receive vaccines approved and registered by the Japanese government. We evaluated in this study whether the frequency and severity of adverse effects are increased by simultaneous vaccination in comparison to single vaccination in the Japanese setting.

Methods

A retrospective observational study was undertaken of asymptomatic 959 travelers who visited our clinic to receive vaccination during the period January–July 2005, prior to their departure. The 399 study participants of them who could check their adverse effects on their second visit were able to be grouped as either single or simultaneous vaccine receivers.

Travel-specific vaccinations were for hepatitis A (Aimmugen, Kaketsuken, Japan), hepatitis B (Bimmugen, Kaketsuken), tetanus (Adsorbed Tetanus Toxoid, Seiken, Japan), rabies (Inactivated Tissue Culture Rabies Vaccine, Kaketsuken), and Japanese encephalitis (Beijing strain, Takeda, Japan), and routine vaccines were for diphtheria+tetanus, measles, mumps and oral polio vaccine. Each vaccine, with the exception of the oral polio vaccine, was administered subcutaneously into the outer aspect of the upper arm. Simultaneous injections, when they were given in the same arm, were separated as far as possible.

To evaluate adverse effects, all participants were asked to complete subjectively during their second visit to the clinic a prepared questionnaire, which contained such detailed questions as about the duration and severity of systemic reactions such as fatigue, discomfort, drowsiness and feeling hot and about location and severity of local reactions such as swelling, soreness, itching, lump and numbness.[3] Adverse effects were classified by duration as short, adverse effects persisting for less than 1 day; intermediate, adverse effects persisting for 1–6 days; or long, adverse effects persisting for more than 6 days.[3] Odds ratios and 95% confidence intervals (CI) were computed by means of multiple logistic regression analysis. Association between the number of vaccines and the frequency of adverse events was calculated by χ^2 test. The statistical analyses including Wald method for CI were performed using STATA 8.0 (STATA Corporation, TX, USA).

Results

The participants are those who came to the clinic at least twice for receiving booster or another type of vaccine, who comprised 244 males and 155 females. The total response rate is 399 out of 959 (41.6%). The mean age and standard deviations are 34.2 ± 14.28 years (ranged from 0 to 79, median at 34). One hundred forty-two participants (35.6%) received a single vaccination: for hepatitis A ($n = 63$), hepatitis B ($n = 23$), tetanus ($n = 24$), rabies ($n = 20$), Japanese encephalitis ($n = 1$), or other diseases ($n = 11$). Two hundred fifty-seven participants (64.4%) were given simultaneous vaccination: two vaccines, $n = 123$; three vaccines, $n = 90$; four vaccines, $n = 37$; five vaccines, $n = 7$, (Table 1). The most frequent combination of simultaneous vaccines was hepatitis A+hepatitis B+tetanus (23.7%), followed by hepatitis A+tetanus (18.1%) and hepatitis A+hepatitis B (12.6%).

One hundred five participants (26.3%) complained of adverse effects, of which 87 complained of local reactions, and 18 complained of systemic reactions. The most frequent adverse effect was swelling at the injection site in 49 cases, which may have been caused by the tetanus vaccine. Soreness was reported in 23 cases and local itching in 14 cases (Table 2). Age and sex were not associated with frequency of adverse reactions.

Adverse effects were reported as short in 41 cases (39%), intermediate in 49 cases (46.7%) and long in 15 cases (14.3%). However, no serious adverse effects were reported, and all adverse effects resolved without sequelae. Age and sex were not associated with duration of adverse reactions. In comparison to effects reported after a single vaccination, the frequency of adverse effects increased significantly with the number of vaccinations (Table 3). The frequencies of long adverse effects and intermediate adverse effects were also associated with the number of shots. However, the frequency of short adverse effects was not associated with the number of shots (Table 3).

Among the nine types of vaccinations, tetanus vaccination was shown to significantly raise the risk of adverse effects ($P<0.001$) (Table 4), particularly that of intermediate adverse effects ($P<0.001$). Even with adjustment for the number of injections, tetanus vaccination still increased the risk of intermediate adverse effects (Table 5). In addition, the number of injections was significantly related to adverse effects even when adjustment for tetanus was made. When local and systemic adverse effects were analyzed separately, the number of shots and tetanus vaccination were shown to increase the risk of local adverse effects but not of systemic adverse effects.

Discussion

Although some procedures for simultaneous vaccination have been approved by the Japanese government since 1994,[5] they have not been established among clinical practitioners because of the lack of standard protocols for travel-related vaccinations. Another serious issue is that most of the travel vaccines we use are manufactured in Japan. Therefore, data pertaining to Western vaccines in the field of travel medicine cannot be applied directly to Japan.

Table 1 Characteristics of clients receiving single and multiple vaccines.

	Total ($n = 399$)	Single vaccination group ($n = 142$) (%)		Simultaneous vaccination group ($n = 257$) (%)	
Sex					
Male	244	61.2	75	52.9	169	65.8
Female	155	38.8	67	45	88	34.2
Mean age±SD (years)	34.2±14.8		33.4±16.9		34.7±13.5	
Vaccines						
Hepatitis A	272	68.2	63	44.4	209	81.3
Hepatitis B	189	47.4	23	16.2	166	64.6
Tetanus	215	53.9	24	16.9	191	74.3
Rabies	105	26.3	20	14.1	85	33.1
JE	37	9.3	1	0.7	36	14
DT	6	1.5	6	4.2	0	0
Measles	5	1.3	2	1.4	3	1.2
Mumps	2	0.5	0	0	2	0.8
OPV	8	2	1	0.7	7	2.7

SD, standard deviation.
JE, Japanese encephalitis.
DT, diphtheria+tetanus.
OPV, oral polio vaccine.

Table 2 Types of adverse effects with single and simultaneous vaccinations.

Adverse effects	Total ($n = 105$) (%)		Single vaccination ($n = 17$) (%)		Simultaneous vaccination ($n = 88$) (%)	
Local*	87	82.9	11	64.7	76	86.4
Swelling	49	46.7	6	35.3	43	48.9
Soreness	23	21.9	3	17.6	20	22.7
Itching	14	13.3	0	0	14	15.9
Lump	11	10.5	2	11.8	9	10.2
Numbness	2	1.9	0	0	2	2.3
Systemic	18	17.1	6	35.3	12	13.6
Fatigue	8	7.6	2	11.8	6	6.8
Discomfort	4	3.8	1	5.9	3	3.4
Drowsiness	2	1.9	2	11.8	0	0
Feeling hot	2	1.9	1	5.9	1	1.1
Others	2	1.9	0	0	2	2.3

*More than one adverse effect were to be reported.

Table 3 Risk of adverse effects and number of vaccines given.

Number of vaccines	Total AE ($n = 105$)		Long AE ($n = 15$)		Intermediate AE ($n = 49$)		Short AE ($n = 41$)	
	OR (95% CI)*	*P* value	OR (95% CI)*	*P* value	OR (95% CI)*	*P* value	OR (95% CI)*	*P* value
One	1		1		1		1	
Two	3.54 (1.88–6.66)	<0.001	0.77 (0.13–4.66)	NS**	11.2 (3.29–38.3)	<0.001	1.53 (0.67–3.51)	NS
Three or more	4.10 (2.21–7.61)	<0.001	3.74 (1.01–13.9)	0.049	9.10 (2.66–31.2)	<0.001	1.61 (0.72–3.62)	NS

AE, adverse effects.
*Odds ratio and 95% confidence interval (with Wald method) were computed with multiple logistic regression analysis.
**Not significant.

Table 4 Association between the type of vaccine and frequency of adverse effects.

		Total AE	Long AE	Intermediate AE	Short AE	P value*
Hepatitis A	$n = 272$ (68%)	74 (27%)	12	32	30	NS
Hepatitis B	$n = 189$ (42%)	54 (29%)	8	24	22	NS
Tetanus	$n = 215$ (54%)	81 (38%)	11	43	27	<0.001
Rabies	$n = 105$ (26%)	32 (39%)	6	17	9	NS
JE	$n = 37$ (9%)	15 (41%)	3	7	5	NS
DT	$n = 6$ (1.5%)	1 (17%)	0	0	1	NS
Measles	$n = 5$ (1.3%)	0 (0%)	0	0	0	NS
Mumps	$n = 2$ (0.5%)	0 (0%)	0	0	0	NS
OPV	$n = 8$ (2.0%)	2 (25%)	0	0	2	NS

*P value was calculated by χ^2 tests.
AE, adverse effects.
JE, Japanese encephalitis.
DT, diphtheria+tetanus.
OPV, oral polio vaccine.
NS, not significant.

Table 5 Risk of adverse effects for tetanus vaccine and number of vaccines given.

Number of vaccines	Total AE ($n = 105$)		Long AE ($n = 15$)		Intermediate AE ($n = 49$)		Short AE ($n = 41$)	
	OR (95% CI)*	P value	OR (95% CI)*	P value	OR (95% CI)*	P value	OR (95% CI)*	P value
Tetanus	2.85 (1.58–5.16)	0.001	2.85 (1.58–5.16)	0.001	4.64 (1.79–12.0)	0.002	1.60 (0.71–3.62)	NS
One	1		1		1		1	
Two	2.29 (1.15–4.54)	0.018	2.29 (1.15–4.54)	0.018	6.04 (1.67–21.8)	0.006	1.24 (0.50–3.08)	NS
Three or more	2.09 (1.02–4.30)	0.044	2.09 (1.02–4.30)	0.044	3.63 (0.97–13.6)	0.056	1.18 (0.45–3.11)	NS

Number of vaccines	Total AE ($n = 105$)		Local AE ($n = 87$)		Systemic AE ($n = 18$)	
	OR (95% CI)*	P value	OR (95% CI)*	P value	OR (95% CI)*	P value
Tetanus	2.85 (1.58–5.16)	0.001	3.27 (1.70–6.29)	<0.001	1.17 (0.34–4.02)	NS
One	1		1		1	
Two	2.29 (1.15–4.54)	0.018	3.15 (1.45–6.88)	0.004	0.53 (0.12–2.40)	NS
Three or more	2.09 (1.02–4.30)	0.044	2.32 (1.02–5.25)	0.044	1.47 (0.38–5.68)	NS

AE, adverse effects.
NS, not significant.
*Odds ratio and 95% confidence interval (with Wald method) were computed with multiple logistic regression analysis.

Most reports discuss the association between two different vaccines such as hepatitis A and hepatitis B,[6,7] hepatitis A and typhoid,[8,9] hepatitis A and yellow fever[10] or pneumococcal and influenza vaccines,[11,12] on immunogenicity, reactogenicity and tolerability. However, reports on adverse effects of simultaneous vaccines against more than three diseases are sparse. In the present study, adverse effects increased with increases in the number of vaccines, and in particular, local adverse effects increased significantly with the number of vaccines. Multiple logistic regression analysis revealed that tetanus vaccine was responsible for intermediate adverse effects; however, there was no significant relation between tetanus vaccine and short adverse effects.

In a German study[3] and American study,[4] adverse effects after simultaneous vaccination occurred more frequently than in the present study. This may be partly because most travel vaccines used in Japan are administered subcutaneously and partly because some vaccines for hepatitis A, rabies and Japanese encephalitis do not contain aluminum salts as adjuvants to enhance immune response. Antibody titers and seroconversion rates in each participant were not measured in this study, but cross-interference is reported to be significantly slight even when vaccines are used simultaneously in Japanese travelers.[2]

Regardless of the differences in vaccinations between Western countries and Japan, the present study showed a convincingly low level of adverse effects due to

simultaneous vaccination in Japanese travelers. Although adverse effects increased with increases in the number of vaccines, there were no unusual adverse events; that is, there were no reactions not already listed in the printed materials provided with each vaccine made in Japan. However, there were some limitations in the present study; although the number of vaccine combinations were large, study population was relatively small to address the issue of whether specific combinations are more likely to lead to increased toxicity; adverse effects were subjectively described on the questionnaire according to the patients' complaints or inconvenience, so that the side effects are not confirmed by trained observers or doctors.

In conclusion, simultaneous vaccination was feasible for the majority of Japanese travelers because most problems were related to local reactions at the sites of injections. Although the frequencies of adverse effects were associated with the number of vaccines, the reactions are generally minor or tolerable. Provision of a simultaneous vaccination schedule should motivate more Japanese travelers to obtain immunizations and thereby reduce the risk of vaccine-preventable diseases. This should also have a positive influence on travelers' compliance.

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CASE REPORT

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Molecular epidemiology of outbreaks and containment of drug-resistant *Pseudomonas aeruginosa* in a Tokyo hospital

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Abstract We witnessed outbreaks of multidrug-resistant (MDR) and drug-resistant *Pseudomonas aeruginosa* at a hospital in Tokyo, Japan, during the period September 2004 through May 2005. The first outbreak occurred in September and October 2004. Three isolates of MDR *P. aeruginosa* were identified from urine samples obtained from three nonambulatory immunodeficient patients in one ward. After 3 weeks, another outbreak of *P. aeruginosa* occurred in the hematology ward on the same floor of the hospital. During the outbreaks, environmental surveys were conducted twice in each of the two wards, at 2-week intervals, to identify the sources of the pathogens. A total of 23 *P. aeruginosa* isolates, including 11 from environmental sources, were analyzed for chromosomal DNA typing by pulsed-field gel electrophoresis, for O-antigen serotyping, and for other typing. Results revealed two causative clones, as well as environmental contamination by *P. aeruginosa* clones on the surfaces of urine volume-measuring devices in rooms where urine is handled, which may have been sources of the pathogens during the outbreaks. To prevent further outbreaks, we performed the following: (a) environmental surface monitoring for drug-resistant *P. aeruginosa*, (b) active surveillance of specimens, (c) strict isolation of infected patients or carriers of MDR *P. aeruginosa*, (d) rigorous contact precautions, and (e) disinfection with 70% alcohol on the surfaces of apparatuses contaminated by MDR or drug-resistant *P. aeruginosa* and in the rooms where urine is handled. As a result, the outbreaks were contained.

Key words Multidrug resistant · *Pseudomonas aeruginosa* · Environment · Survey · Infection control

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Introduction

Nosocomial infection caused by *Pseudomonas aeruginosa* has been recognized as an important problem in hospitals in recent years because of the danger posed to immunocompromised patients.[1] Nosocomial *P. aeruginosa* is usually multidrug-resistant (MDR), which is not well-defined internationally,[2] but is defined in Japan as resistance to imipenem (IPM; minimum inhibitory concentration [MIC], ≥16 μg/ml), amikacin (AMK; MIC, ≥32 μg/ml), and ciprofloxacin (CPFX; MIC, ≥4 μg/ml).[3]

Recently, we experienced outbreaks of *P. aeruginosa* at the 925-bed International Medical Center Hospital in Tokyo. We successfully controlled these outbreaks within several months. Here, we report how we controlled the outbreaks and determined the cause, the method of transmission, the patterns of drug resistance, and genotyping by pulsed-field gel electrophoresis (PFGE) of the causative *P. aeruginosa* isolates from clinical and environmental sources in the hospital.

Methods

The first outbreak occurred in one ward (5S, the south part of the fifth floor) in September and October 2004. Three isolates of MDR *P. aeruginosa* were obtained from urine taken from three nonambulatory immunodeficient patients. The three patients were hospitalized during overlapping periods (Fig. 1). After 3 weeks, another outbreak of *P. aeruginosa* occurred in the hematology ward (5N, the north part of the fifth floor) on the same floor in the hospital. The

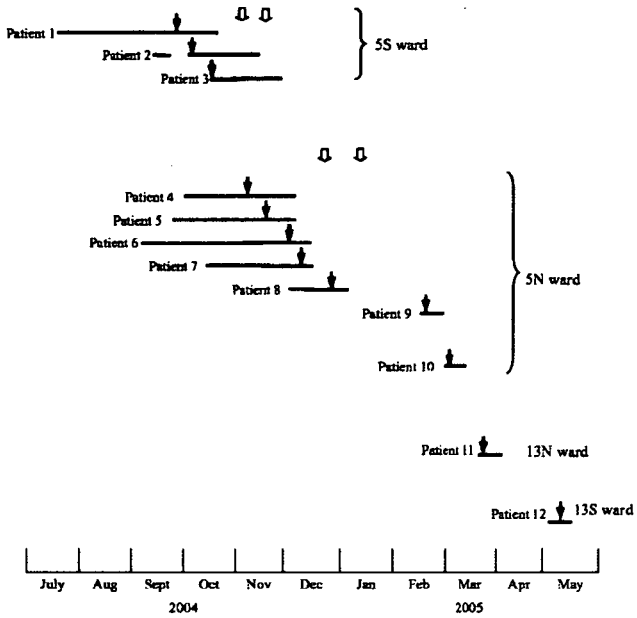

Fig. 1. Time course of *Pseudomonas aeruginosa* O11 detection in the hospital. The *parallel lines* indicate the periods of hospitalization. *Black arrows*, day of *P. aeruginosa* O11 detection; *white arrows*, day of environmental investigation for multidrug-resistant *P. aeruginosa*

causative isolates were not MDR *P. aeruginosa*, but they were AMK-sensitive and IPM- and CPFX-resistant. *P. aeruginosa* was consecutively isolated from three urine samples, one sputum sample, and one pharynx swab from five different patients in the ward. Each of these five patients had a serious underlying disease but was ambulatory. Two more patients were infected with *P. aeruginosa* 1 month later (Fig. 1). Two patients in other wards (13S and 13N, the south and north parts of the thirteenth floor, respectively) were found to have sporadic infections with *P. aeruginosa* during the same period or several weeks later (Fig. 1). The infections were contained by May 2005.

To determine the cause of the outbreaks and to prevent additional cases, an epidemiologic investigation was initiated by the hospital's infection-control team. Environmental surveys were conducted twice in each of the two wards (5S and 5N), at 2-week intervals, to identify the source(s) of the pathogens. Multiple samples from environmental surfaces were tested to detect *P. aeruginosa* on NAC agar medium (Nissui Pharmaceutical, Tokyo, Japan) supplemented with or without ceftazidime at a final concentration of 16 μg/ml. A total of 23 *P. aeruginosa* isolates, including 11 from environmental sources, were analyzed for chromosomal DNA typing with a counter-clamped homogeneous electric field system (CHEF Mapper; Bio-Rad Laboratories, Hercules, CA, USA), for O-antigen serotyping with control serum (Denka Seiken, Tokyo, Japan), and for antibiotic resistance by a microdilution method according to the guidelines of the Clinical Laboratory Standards Institute.[4] DNA sequences of the quinolone resistance-determining regions (QRDRs) of the *gyrA*, *gyrB*, *parC*, and *parE* genes were determined as described previously.[5] Resistance genes other than quinolone-resistance genes were detected by polymerase chain reaction with three primer pairs designed to amplify the sequences of the metallo β-lactamase bla_{IMP-1} gene,[6] aminoglycoside 6′-acetyltransferase *aac(6′)-Iae* gene,[5] and the aminoglycoside 2″-adenylyltransferase *aadB* gene.[7]

The minimum inhibitory concentrations (MICs) of eight antibiotics tested against *P. aeruginosa* isolates are shown in Table 1. Five of the 12 clinical isolates and 3 of the 11 environmental isolates were MDR *P. aeruginosa* and were resistant to all antibiotics tested, except for gentamicin (GM) and polymixin B (PL-B). Six clinical isolates and 3 environmental isolates were resistant to IPM and CPFX but sensitive to AMK (Table 1). The remaining 6 isolates (IMCJ nos. 333, 262, 264, 268, 326, and 330) were each sensitive to four to eight antibiotics tested.

The five clinical and three environmental isolates of MDR *P. aeruginosa* carried the bla_{IMP-1} and *aac(6′)-Iae* genes, and showed mutations in T83I and S87L in the QRDRs of *gyrA* and *parC*, respectively (Table 1). Among these eight MDR isolates, two (IMCJ nos. 335 and 361) had an additional D87G mutation in the QRDR of *gyrA*. Six other clinical and two other environmental isolates carried the bla_{IMP-1} and *aadB* genes, and showed mutations in T83I, E468D, and S87W in the QRDRs of *gyrA*, *gyrB*, and *parC*, respectively (Table 1). The presence of these genes and their alterations in the QRDRs in *gyrA*, *gyrB*, and *parC* are consistent with their resistance phenotypes. These genetic analyses of drug-resistant genes in MDR *P. aeruginosa* could provide useful information about the evolution of nosocomial pathogens.

Of the total 23 isolates, 18 expressed the O11 antigen, 4 expressed the O1 antigen, and 1 expressed the O6 antigen (Table 1). Notably, all clinical isolates and 6 environmental isolates expressed the O11 antigen (Table 1).

The PFGE patterns of the isolates are shown in Fig. 2. Among the 23 *P. aeruginosa* isolates, 13 different PFGE patterns were detected. Three clinical isolates (IMCJ nos. 254–256) and 3 environmental isolates (IMCJ nos. 260, 261, and 267) from the 5S ward were of the same pattern (PA1; Fig. 2 and Table 1). Six clinical isolates (IMCJ nos., 257, 270, 321–323, and 332) and 2 environmental isolates (IMCJ nos. 324 and 331) in the hematology ward (5N) were of the same pattern (PE). Taken together, the data indicate that the first outbreak was caused by one strain of MDR *P. aeruginosa*, but that the second outbreak was caused by a separate strain of drug-resistant *P. aeruginosa*. Three other MDR *P. aeruginosa* isolates, obtained from patients 10 (ward 5N), 11 (ward 13N), and 12 (ward 13S), had PFGE patterns (shown in lanes 8, 10, and 9, respectively, in Fig. 2) that differed from those of isolates obtained from patients 1, 2, and 3 (ward 5S) and from the isolates obtained from patients 4, 5, 6, 7, 8, and 9 (ward 5N), indicating that the infections in patients 10, 11, and 12 were sporadic.

In the environmental survey, three isolates of MDR *P. aeruginosa* (IMCJ260, IMCJ267, and IMCJ261; see Table 1) were obtained from wet surfaces in ward 5S; from a rack for urinals, from a urine volume-measuring device in a room for the handling of urine, and from a bath drain in a bathing room, respectively. Three *P. aeruginosa* isolates,

Table 1. Origins and characteristics of the *Pseudomonas aeruginosa* isolates from clinical and environmental sources

Strain	Source (specimen)	Date isolated	Ward	O sero-type	MICs against[a]:								PCR for resistance genes			Mutations in QRDRs[b]			PFGE type (lane in Fig. 2)
					PIPC	CAZ	IPM	AMK	GM	TOB	CPFX	PL-B	bla_{IMP-1}	*aac(b')-Iae*	*aadB*	GyrA	GyrB	ParC	
IMCJ254	Patient 1 (urine)	30-Sept	5S	O11	256	>256	16	128	8	256	>32	4	+	+	−	T83I		S87L	PA1 (2)
IMCJ255	Patient 2 (urine)	30-Sept	5S	O11	>256	>256	32	64	8	256	>32	4	+	+	−	T83I		S87L	PA1 (3)
IMCJ256	Patient 3 (urine)	18-Oct	5S	O11	>256	256	16	64	4	128	>32	4	+	+	−	T83I		S87L	PA1 (4)
IMCJ257	Patient 4 (urine)	8-Nov	5N	O11	>256	>256	>64	2	32	4	>32	4	+	−	+	T83I	E468D	S87W	PE (14)
IMCJ270	Patient 5 (sputum)	12-Nov	5N	O11	>256	>256	>64	1	32	2	>32	4	+	−	+	T83I	E468D	S87W	PE (15)
IMCJ321	Patient 6 (urine)	24-Nov	5N	O11	256	>256	>64	1	32	2	>32	4	+	−	+	T83I	E468D	S87W	PE (16)
IMCJ322	Patient 7 (pharynx)	8-Dec	5N	O11	>256	>256	>64	4	128	16	>32	4	+	−	+	T83I	E468D	S87W	PE (17)
IMCJ323	Patient 8 (urine)	16-Dec	5N	O11	>256	>256	>64	8	256	16	>32	4	+	−	+	T83I	E468D	S87W	PE (18)
IMCJ332	Patient 9 (urine)	2-Feb	5N	O11	>256	>256	>64	2	128	8	>32	4	+	−	+	T83I	E468D	S87W	PE (21)
IMCJ333	Patient 10 (pharynx)	28-Feb	5N	O11	>256	>256	16	2	4	8	>32	4	−	−	−	T83I		S87L	PA2 (8)
IMCJ335	Patient 11 (urine)	23-Mar	13N	O11	>256	>256	>64	64	8	128	>32	4	+	+	−	T83I + D87G		S87L	PA4 (10)
IMCJ361	Patient 12 (urine)	11-May	13S	O11	>256	>256	>64	64	8	64	>32	4	+	+	−	T83I + D87G		S87L	PA3 (9)
	Environmental																		
IMCJ260	Rack for urinal	28-Oct	5S	O11	256	>256	64	64	8	256	>32	4	+	+	−	T83I		S87L	PA1 (5)
IMCJ261	Bath drain	28-Oct	5S	O11	>256	>256	>64	64	8	256	>32	4	+	+	−	T83I		S87L	PA1 (6)
IMCJ264	Sink in P1 room	28-Oct	5S	O1	8	2	4	16	8	2	0.5	4	−	−	−				PD (13)
IMCJ262	Sink in staff room	28-Oct	5S	O1	2	0.5	1	1	0.5	0.5	0.064	2	−	−	−				PG (23)
IMCJ267	Urine volume-measuring device	12-Nov	5S	O11	256	>256	32	64	>256	>256	>32	4	+	+	−	T83I		S87L	PA1 (7)
IMCJ268	Sink in staff room	12-Nov	5S	O1	1	1	1	2	0.5	0.25	0.064	2	−	−	−				PH (24)
IMCJ324	Sink in lavatory	21-Dec	5N	O11	>256	>256	>64	4	256	16	>32	4	+	−	+	T83I	E468D	S87W	PE (19)
IMCJ325	Urine volume-measuring device	21-Dec	5N	O11	>256	>256	>64	4	64	16	>32	4	+	−	−	T83I		S87L	PF (22)
IMCJ326	Sink in staff room	21-Dec	5N	O6	>256	32	8	16	128	128	0.19	4	−	−	−				PB (11)
IMCJ330	Sink in lavatory	11-Jan	5N	O1	>256	>256	>64	4	2	2	0.064	4	−	−	−				PC (12)
IMCJ331	Urine volume-measuring device	11-Jan	5N	O11	>256	>256	>64	4	>256	16	>32	4	+	−	+	T83I	E468D	S87W	PE (20)
IMCJ2.S1[c]				O11	>128	>28	128	128	16	64	32	2	+	+	−	T83I		S87L	PA (1)

[a] PIPC, piperacillin; CAZ, ceftazidime; IPM, imipenem; AMK, amikacin; GM, gentamicin; TOB, tobramycin; CPFX, ciprofloxacin; PL-B, polymixin B

[b] T83I, Thr at position 83 of GyrA changed to Ile (ACC→ATC); S87L, Ser at position 87 of ParC changed to Leu (TCG→TTG); E468D, Glu at position at 468 changed to Asp (GAG→GAT); S87W, Ser at position 87 of ParC changed to Trp (TCG→TGG); D87G, Asp at position 87 changed to Gly (GAC→GGC). The numbering of the amino acids is based on that of *P. aeruginosa* PAO1 (Genbank accession no. NC_002516)

[c] Nosocomial strain that caused outbreaks among hospitals in an area of Japan[3]