children and adults (i.e., herd immunity) (4). In our study, we found that the prevalence of VT was significantly reduced in the post-inoculation cultures compared with that in the inoculation-period cultures (9.5% to 2.9%).

Serotype 6B was isolated from both the inoculation-period and post-inoculation cultures. Dagan et al. reported that in subjects carrying VT pneumococci before the first dose of PCV7, the serum IgG response to the carried serotype after 2 or 3 doses was significantly lower than that in noncarriers (9). Furthermore, the prevalence of pneumococcal phenotypes is associated with the structure of the capsular polysaccharide (10,11). Serotypes such as 6B, which have capsules with larger zones of dextran exclusion, were more resistant to neutrophil-mediated killing and more prevalent in carriage (10).

Serotype 6C was highly prevalent in both the inoculation-period and post-inoculation cultures. Increases in the prevalence of serotype 6C have received attention in the United States and Europe as the cause of invasive pneumococcal disease (12–14). According to a report recently released by Nariai (15), an increase in the prevalence of serotype 6C was reported among children with lower respiratory infection in Japan. In our multilocus sequence typing (MLST) analysis, 5 of 11 serotypes, which were identified from these serotype 6C isolates, were confirmed as new serotypes (unpublished data) from the database at http://www.mlst.net. One of the hypotheses was that asymptomatic 6C, which is always prevalent in this area, may have been detected by chance in this study.

The primary limitation of our study was the lack of a non-vaccinated control group, which made it difficult to definitively interpret the effects of PCV7.

In summary, we prospectively investigated changes in *S. pneumoniae* serotypes among Japanese children after PCV7 inoculation. The protection of PCV7 against nasopharyngeal colonization was inferred from the decrease in VT carriage after the completed vaccination. The decrease in VT carriage may be conducive to reducing VT transmission within the study area. Concomitantly with the decrease in colonization with VT, it is necessary to monitor emerging new pneumococcal serotypes not included in PCV7. Thus, it is critical to conduct constant surveillance of serotype replacement by NVT within the study area.

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Conflict of interest None to declare.

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Hyporesponsiveness to the infecting serotype after vaccination of children with seven-valent pneumococcal conjugate vaccine following invasive pneumococcal disease

Kazuyo Tamura[a,b], Kousaku Matsubara[c], Naruhiko Ishiwada[d], Junichiro Nishi[e], Hidenori Ohnishi[f], Shigeru Suga[g], Toshiaki Ihara[g], Bin Chang[h], Yukihiro Akeda[a], Kazunori Oishi[a,i,*], the Japanese IPD Study Group

[a] *Laboratory for Clinical Research on Infectious Disease, International Research Center for Infectious Diseases, Research Institute for Microbial Diseases, Osaka University, Osaka, Japan*
[b] *Department of Respiratory Medicine, Allergy and Rheumatic Disease, Graduate School of Medicine, Osaka University, Osaka, Japan*
[c] *Department of Pediatrics, Nishi-Kobe Medical Center, Kobe, Japan*
[d] *Division of Control and Treatment of Infectious Diseases, Chiba University Hospital, Chiba, Japan*
[e] *Department of Microbiology, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan*
[f] *Department of Pediatrics, Graduate School of Medicine, Gifu University, Gifu, Japan*
[g] *National Mie Hospital, Mie, Japan*
[h] *Department of Bacteriology I, National Institute of Infectious Diseases, Tokyo, Japan*
[i] *Infectious Disease Surveillance Center, National Institute of Infectious Diseases, 1-23-1 Toyama, Shinjyuku, Tokyo 162-8640, Japan*

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ABSTRACT

Antibody responses to the infecting serotype in children who are vaccinated with pneumococcal conjugate vaccine (PCV) after having invasive pneumococcal diseases (IPD) have not been fully investigated. Of 56 children diagnosed with IPD between October 2009 and April 2013 in whom the infecting serotype was confirmed, 17 who were vaccinated with PCV7 following IPD were tested to determine the geometric mean concentration of serotype-specific immunoglobulin G (IgG) and the geometric mean titers of opsonization indices (OIs) using paired sera obtained at the

OI results were available, the OIs for the infecting serotype at the time of IPD onset were <8, although the IgG levels varied between from <0.2 to >5.0 μg/ml. After the last PCV7 dose, the OIs for the infecting serotype remained <8 for six (43%) of 14 children. In these six children, hyporesponsiveness to PCV7 was specific for the infecting serotype. Hyporesponsiveness was found for serotypes 6B ($n=5$) and 23F ($n=1$). No difference was found between the responders ($n=8$) and the hyporesponders ($n=6$) with regard to any clinical characteristics. Our data suggest that hyporesponsiveness to the infecting serotype may occur in children vaccinated with PCV7 following IPD.

1. Introduction

Streptococcus pneumoniae is a major worldwide cause of morbidity and mortality resulting from pneumonia, bacteremia, and meningitis [1]. Antibodies to pneumococcal capsular polysaccharide (CPS) and complement provide protection against pneumococcal strains with homologous or cross-reactive capsular serotypes [2]. The introduction in 2000 of the seven-valent pneumococcal conjugate vaccine (PCV7; Prevenar®, Pfizer) for children in the United States younger than 2 years and children aged 2–4 years in a high-risk category was effective, dramatically reducing the incidence of invasive pneumococcal disease (IPD) [3,4]. The

* Corresponding author. Tel.: +81 3 5285 1111; fax: +81 3 5285 1129.
E-mail address: oishik@nih.go.jp (K. Oishi).

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lowered rate of hospitalization for childhood and adult pneumonia has been sustained during the decade since the introduction of PCV7 [5].

In Japan, PCV7 was licensed in October 2009, the Japanese government began to subsidize it for children less than 5 years of age in November 2010. PCV7 for children under 5 years of age was subsequently included in the routine immunization schedule at public expense in April 2013.

Vaccine-induced protective immunity is currently estimated by measuring the concentrations of serotype-specific immunoglobulin G (IgG) using enzyme-linked immunosorbent assay (ELISA) [6] and the opsonization index (OI) using a multiplex opsonophagocytic assay (MOPA) [7]. The World Health Organization (WHO) working group reported that antibody concentrations of 0.2–0.35 μg/ml measured with the ELISA using serum without serum absorption with 22F polysaccharide, correlated best with an OI of 8, which in turn correlated best with protective efficacy [8]. Henckaerts et al. proposed a protective threshold concentration of 0.20 μg/ml assessed with ELISA using serum absorption with 22F polysaccharide as a measure of the serotype-specific efficacy of the pneumococcal conjugate vaccine against IPD among infants less than 1 year of age [9], with an exception of 19F [10]. We recently reported that the OIs for the infecting serotypes in sera of children with IPD were almost undetectable during acute phase of IPD, although the levels of serotype-specific IgG were higher than 0.20 μg/ml [11]. Based on this finding, it was necessary for us to examine whether children with IPD could develop antibody response to the infecting serotype after vaccination with PCV7.

A previous study demonstrated that most children respond to PCV7 following resolution of IPD, but suggested that IPD caused by particular serotypes in children could result in hyporesponsiveness to the infecting serotype [12]. However, limited information is available in regards to the immune response in children vaccinated with PCV following IPD because the serotype-specific OIs have never been evaluated. We, therefore, conducted the present study to determine antibody response to PCV7 vaccine serotypes by measuring the OIs as well as the IgG levels in children vaccinated with PCV7 following IPD.

2. Materials and methods

2.1. Patients

Children under 9 years of age, who had infection caused by *S. pneumoniae*, which was isolated from normally sterile body sites such as blood or cerebrospinal fluid, were enrolled in this study when their attending doctors requested the measurement of the antipneumococcal antibodies in their sera. Fifty-six children were enrolled between October 2009 and April 2013 at 41 hospitals in Japan. All of the pneumococcal isolates were serotyped at the Department of Bacteriology I, National Institute of Infectious Diseases, by agglutination tests with rabbit antisera (Statens Serum Institute, Copenhagen, Denmark). Serotype 6C was confirmed by an in-house antiserum [13]. Because the OI for the infecting serotype was assumed to be low after the onset of IPD, we determined the antibody response after vaccination with PCV7 vaccination following the resolution of IPD. Of 56 children with IPD, 21 received PCV7 vaccination following the resolution of IPD (Fig. 1). One child who died of IPD and the other 34 children did not receive PCV7 vaccination. Paired sera collected at the onset of IPD (the first blood sample) and after PCV7 vaccination (the second blood sample) were collected from 17 children of the 21

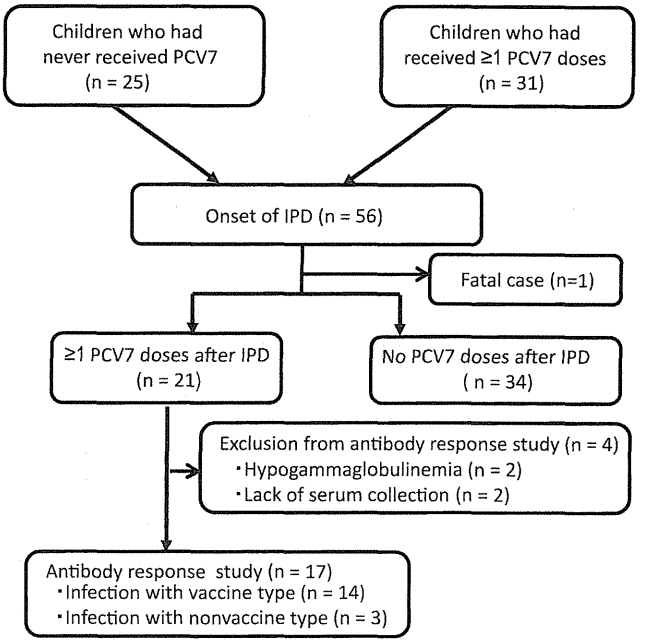


Fig. 1. Flow diagram of this study of children with invasive pneumococcal disease.

children who received PCV7 vaccination following the resolution of IPD. The other four children were excluded from this study was not collected at the time of IPD (two children) or they had comorbid hypogammaglobulinemia (two children). Fourteen of the 17 children were infected with a PCV7 serotype, and three were infected with a non-PCV7 serotype. As children received one to three doses of PCV7 after their episode of IPD, we defined the PCV7 dose before the second blood sampling as the last PCV7 dose. The median number of days (range) from IPD onset to the first blood sampling and from the last PCV7 dose to the second blood sampling was 0 (0–11) and 32 (27–120), respectively. The median number of days (range) from the IPD onset to the last PCV7 dose was 132 (15–633). Sera from children were submitted to the Research Institute for Microbial Diseases (RIMD), Osaka University, Japan, for determination of the IgG levels by ELISA and the OIs by MOPA.

Data collected from these patients included age at illness, clinical manifestations, outcome, comorbid conditions, and vaccination history. Clinical manifestations were divided into two categories: meningitis and non-meningitis. The non-meningitis categories included clinical manifestations of sepsis and sepsis with focal signs other than meningitis. The schedule of immunization with PCV7 was implemented according to a previous guideline [3]. The standard schedule is for infants aged 2–6 months: 3 doses as a primary series and the fourth (booster) dose at age 12–15 months. The catch-up schedules are for children aged ≥7 months: 2 doses as primary series and 1 dose as a booster for infants aged 7–11 months, 2 doses for children aged 12–23 months, and a single-dose for children aged ≥24 months. Furthermore, some of the children received more PCV7 doses than the age-appropriate schedules after treatment for IPD, if the parents or guardians agreed with additional booster doses of PCV7. Breakthrough infection was defined as IPD in a child who had received ≥1 PCV7 dose and for which the pneumococcal isolate was a PCV7 serotype, and vaccine failure was defined as the subset of breakthrough infection in which the patients had completed the vaccine schedule [3,14,15].

This study was reviewed and approved by the Ethics Committee of RIMD, Osaka University, and conducted according to the principles expressed in the Declaration of Helsinki.

2.2. ELISA

Antipneumococcal IgG antibodies were measured with the WHO-approved ELISA using standard reference sera (89-SF and 007sp) and absorptions with C-polysaccharide and 22F polysaccharide, as previously described [6,16]. The cutoff for the assay was 0.05 μg/ml for all serotypes. The levels of serotype-specific IgG for the infecting serotypes, comprising serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, were determined according to the WHO protocol (available at www.vaccine.uab.adu/ELISA protocol).

2.3. MOPA

The MOPA for the infecting serotype, based on antibiotic-resistant target bacteria, was performed as previously described [7].

Table 1
Clinical characteristics including antipneumococcal antibodies of paired serum for infecting serotype in fourteen children.

Case	Sex	Comorbid condition	Clinical category	Infecting serotype	Age (months) at IPD onset	Age (months) at which PCV7 administered		Time (days) from IPD onset to the first blood sampling	Time (days) from the last PCV7 dose to the second blood sampling	IgG concentration and OI for the infecting serotype			
										At the first blood sampling		At the second blood sampling	
						Before IPD	After IPD			IgG (μg/ml)	OI	IgG (μg/ml)	OI
1	F	None	Non-meningitis[a]	23F	11	6,7, and 8	15	0	30	0.34	<4	0.13	<4
2	M	None	Meningitis	6B	21	18	22 and 24[h]	0	46	1.81	7	1.43	<4
3	F	None	Non-meningitis[b]	6B	31	26	35[h]	0	120	1.18	<4	0.39	<4
4	M	None	Non-meningitis[c]	6B	30	28	34[h] and 45[h]	0	30	0.53	<4	0.32	<4
5	F	None	Meningitis	6B	12,13[f]	None	13,14, and 32[h]	0[g]	103	0.78	<4	2.80	<4
6	M	None	Non-meningitis[b]	6B	14	None	16,18, and 20[h]	11	32	0.22	<4	0.15	<4
7	M	None	Non-meningitis[b]	23F	12	None	13	0	27	0.36	<4	2.62	19
8	F	None	Non-meningitis[b]	6B	16	None	18 and 19	0	28	5.62	<4	2.37	562
9	F	None	Non-meningitis[b]	23F	18	None	19 and 22	0	31	0.72	<4	8.27	5491
10	M	None	Non-meningitis[b]	6B	14,17	None	31	3[g]	37	1.78	<4	1.18	17,946
11	M	None	Non-meningitis[b]	19F	35	None	36	0	28	0.68	<4	3.73	85
12	M	None	Non-meningitis[d]	14	13,16	None	16 and 18	0[g]	42	2.09	5	9.61	4040
13	F	None	Non-meningitis[b]	14	15	None	36	0	31	1.75	<4	3.55	5266
14	M	Mondini dysplasia	Meningitis[e]	9V	67	None	68	1	44	0.17	<4	2.65	491

OI, opsonization index; F, female; M, male.

[a] Septic arthritis.

[b] Bacteremia.

[c] Bacteremic pneumonia.

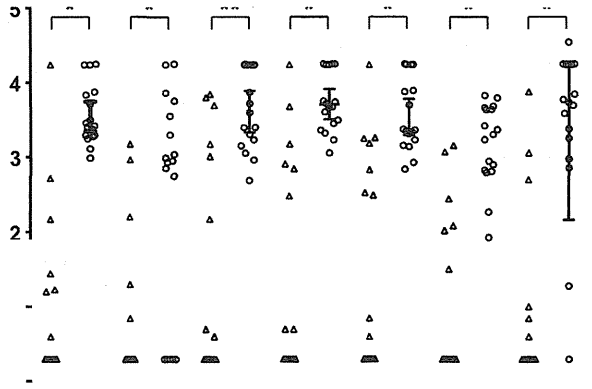
[d] Bacteremia with otitis media.

[e] Meningitis with otitis media.

[f] This patient had IPD at 12.0 and 13.9 months of age after the first dose of PCV7 at 13.0 months of age.

[g] Patient who had two episodes of IPD. Serum was obtained during the first episode of IPD.

[h] Additional booster dose of PCV7.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(OI < 8) to the infecting serotype after the last PCV7 dose, although the other eight children showed variable responses to the infecting serotype based on increased OIs (OI = 19–17,946). We could not identify any clinical characteristic of the six children that was associated with their specific hyporesponsiveness to the infecting serotype after the last PCV7 dose.

A lack of a significant increase in IgG specific for serotype 6B after PCV7 vaccination in 17 children with IPD could partly be explained by the relatively weak immunogenicity of serotype 6B. Previous studies have demonstrated no marked increase in anti-6B IgG in children after one or two doses of PCV [18–20]. As the hyporesponsiveness found in this study in children vaccinated with PCV7 following the resolution of IPD was specific to the infecting serotype, nonspecific immunosuppressing factors or genetic factors of the host are unlikely to contribute to this phenomenon.

Borrow et al. reported that eight of 107 children with IPD failed to develop an IgG response to their infecting serotype [12]. For all of these children, the IgG levels for the infecting serotypes were less than 0.35 μg/ml (range: 0.01–0.34 μg/ml). The authors speculated that this phenomenon could be explained by an immune paralysis because of a large load of pneumococcal polysaccharide during the episode of IPD and/or to a potential genetic basis for hyporesponsiveness to individual serotypes. In contrast, in our study, the IgG levels for the infecting serotypes ranged from 0.13 to 2.80 μg/ml in the six children in our study who were hyporesponsive to the infecting serotype after the last PCV7 dose. Although the IgG levels exceeded 0.35 μg/ml for three of these six children, the OIs for all six were less than 8. Therefore, an OI <8, but not an IgG level <0.35 μg/ml, is a sufficient criterion to define children who are hyporesponsive to PCV7.

Recent studies reported that pneumococcal carriage in the nasopharynx of children resulted in serotype-specific hyporesponsiveness to PCV [21,22]. The hyporesponsiveness following pneumococcal carriage may be attributable to the binding of the circulating pneumococcal polysaccharides to serotype-specific B cells in the marginal zone of the spleen in infants where CD21-expressing cells are scarce [23]. Furthermore, a recent study has demonstrated that B cell receptor crosslinking with a T cell-independent type II antigen (TI-2 Ag) does not activate IgG+ memory B cells, but rather induces tolerance of these cells [24]. This may support the hypothesis of immune paralysis to the infecting serotype proposed by Borrow et al., because a pneumococcal polysaccharide is known to be a TI-2 Ag.

Hyporesponsiveness to serotype 6B after PCV7 immunization lasted for more than 1 year in two children in our study (Cases 4 and 5). Dagan et al. similarly demonstrated that hyporesponsiveness lasted for several months, and was only partially overcome by the 12-month booster [21]. Follow-up of the hyporesponders is necessary to determine whether their hyporesponsiveness can be overcome with time.

Two previous studies demonstrated that children unimmunized against polyribosylribitol phosphate-tetanus protein conjugate vaccine (PRP-T) developed a low or undetectable PRP antibody after invasive *Haemophilus influenzae* type b infection, and that additional doses of PRP-T conjugate vaccine were required to elicit a protective immune response in these children [25,26].

The limitations of our study are the small number of IPD cases examined and the variable periods between the onset of IPD and the last PCV7 dose and between the last PCV7 dose following IPD and the second blood sampling. Another limitation is that children with IPD were enrolled from 41 hospitals when their attending doctors requested the measurement of the antipneumococcal antibodies in their sera, which may have resulted in a selection bias.

In conclusion, a significant increase in the serotype-specific IgG for PCV7 serotypes, except for serotype 6B, and in the OIs for all PCV7 serotypes was found in sera from 17 children who were vaccinated with PCV7 following the resolution of IPD. Of 14 children with IPD caused by PCV7 serotypes, six were identified on the basis of the OI to be specifically hyporesponsive to the infecting serotype after PCV7 vaccination. Although the precise mechanisms of hyporesponsiveness to the infecting serotype remain uncertain, the clinician should be aware of possible hyporesponsiveness to the infecting serotype in children who were vaccinated with PCV following IPD. Because of a small number of IPD cases in the present study further studies for hyporesponsiveness to the infecting serotype after the resolution of IPD are required.

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CONCISE REPORT

Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tocilizumab therapy

Shunsuke Mori,[1] Yukitaka Ueki,[2] Yukihiro Akeda,[3] Naoyuki Hirakata,[2] Motohiro Oribe,[4] Yoshiki Shiohira,[5] Toshihiko Hidaka,[6] Kazunori Oishi[7]

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[1]Department of Rheumatology, Clinical Research Center for Rheumatic Disease, NHO Kumamoto Saishunsou National Hospital, Kohshi, Kumamoto, Japan
[2]Rheumatic and Collagen Disease Center, Sasebo Chuo Hospital, Sasebo, Nagasaki, Japan
[3]Research Institute for Microbial Diseases, Osaka University, Suita, Osaka, Japan
[4]Oribe Rheumachika-Naika Clinic, Oita, Oita, Japan
[5]Department of Internal Medicine, Tomishiro Central Hospital, Tomigusuku, Okinawa, Japan
[6]Institute of Rheumatology, Zenjinkai Shimin-no-Mori Hospital, Miyazaki, Miyazaki, Japan
[7]Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Shinjyuku-ku, Tokyo, Japan

Correspondence to
Shunsuke Mori, Department of Rheumatology, Clinical Research Center for Rheumatic Disease, NHO Kumamoto Saishunsou National Hospital, 2659 Suya, Kohshi, Kumamoto 861-1196, Japan;
moris@saisyunsou1.hosp.go.jp

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ABSTRACT

Objectives We assessed the impact of tocilizumab (TCZ), a humanised monoclonal anti-interleukin-6 receptor antibody, on antibody response following administration of the 23-valent pneumococcal polysaccharide vaccine (PPV23).

Methods A total of 190 patients with rheumatoid arthritis (RA) received PPV23. Patients were classified into TCZ (n=50), TCZ + methotrexate (MTX) (n=54), MTX (n=62) and RA control (n=24) groups. We measured serotype-specific IgG concentrations of pneumococcal serotypes 6B and 23F using ELISA and functional antibody activity using a multiplexed opsonophagocytic killing assay, reported as the opsonisation indices (OIs), before and 4–6 weeks after vaccination. Positive antibody response was defined as a 2-fold or more increase in the IgG concentration or as a ≥10-fold or more increase in the OI.

Results IgG concentrations and OIs were significantly increased in all treatment groups in response to vaccination. The TCZ group antibody response rates were comparable with those of the RA control group for each serotype. MTX had a negative impact on vaccine efficacy. Multivariate logistic analysis confirmed that TCZ is not associated with an inadequate antibody response to either serotype. No severe adverse effect was observed in any treatment group.

Conclusions TCZ does not impair PPV23 immunogenicity in RA patients, whereas antibody responses may be reduced when TCZ is used as a combination therapy with MTX.

INTRODUCTION

Streptococcus pneumoniae (pneumococcus) infection is responsible for substantial mortality and morbidity among adults aged ≥65 years or those with underlying chronic or immunosuppressive conditions. The CDC Advisory Committee on Immunization Practice has recommended the use of the 23-valent pneumococcal polysaccharide vaccine (PPV23) for prevention of invasive pneumococcal disease in at-risk populations.[1] Patients with rheumatoid arthritis (RA) are at an increased risk of contracting infectious diseases because of immunological changes that are intrinsic to RA and that result from immunosuppressive agents, and thus it is likely that pneumococcal vaccination can benefit this patient population.

Tocilizumab (TCZ), a humanised monoclonal antibody against the interleukin-6 (IL-6) receptor, is effective and generally well tolerated when administered either as monotherapy or in combination with methotrexate (MTX) in patients with moderate to severe RA. IL-6 was originally identified as a factor essential for B cell differentiation into antibody-producing plasma cells,[2] and IL-6-deficient mice had reduced antigen-specific IgG following immunisation with a T-cell-dependent antigen.[3] PPV23 induces serotype-specific IgG in a T-cell-independent polysaccharide antigen pathway, which can enhance pneumococcal opsonisation, phagocytosis and killing by phagocytic cells.[4] PPV23 immunogenicity is often impaired in certain groups of immunocompromised patients,[1] but evidence of PPV23 efficacy and safety is lacking in RA patients receiving TCZ.

The objective of the present study was to evaluate the influence of TCZ therapy on antibody response to PPV23 in RA patients. We determined the serum concentrations of serotype-specific IgG using ELISAs and the functional antibody activity using multiplexed opsonophagocytic killing assays (OPAs) in RA patients being treated with TCZ, MTX or TCZ and MTX, and in control RA patients who received neither drug.

METHODS

Patients

RA patients who were receiving TCZ therapy (at least the first dose of an intravenous infusion of 8 mg/kg every 4 weeks) and/or MTX (4–18 mg per week) for ≥12 weeks at our rheumatology outpatient clinics were invited to participate in this open-label study. RA patients who had been treated with bucillamine or salazosulfapyridine were also included as RA controls. All participants fulfilled the 1987 American College of Rheumatology criteria for RA diagnosis. Exclusion criteria were current prednisolone use (≥10 mg/day), current use of immunosuppressive antirheumatic drugs other than MTX (such as tacrolimus, cyclosporine, leflunomide, cyclophosphamide and azathioprine), a recent history (within 6 months) of pneumococcal infection and a history of pneumococcal vaccination. Patients who had changed treatments during the follow-up period or those who had received biological agents other than TCZ were also excluded from this study.

Vaccine

We used commercially available PPV23 (Pneumovax NP, Merck Sharp & Dohme Corp., Tokyo, Japan) containing 25 μg each of 23 capsular polysaccharide

types. From October 2011 to March 2012, each patient received a single dose of vaccine (0.5 ml) subcutaneously in the upper arm. For RA patients receiving TCZ, the vaccination was performed on the same day as the TCZ infusion.

ELISAs for serotype-specific IgG and multiplexed OPAs

Sera were collected immediately before and 4–6 weeks after vaccination and stored at −30°C until tested. To measure serotype-specific IgG concentrations and functional antibody activity against pneumococcus serotypes 6B and 23F, we performed ELISAs and multiplexed OPAs, respectively. For detailed protocols, see online supplementary text.

Antibody response

Fold increases relative to pre-vaccination values (post-vaccination value to pre-vaccination value ratios) were determined. Positive antibody response was defined as a 2-fold or more increase in IgG concentrations or as a 10-fold or more increase in opsonisation indices (OIs).[5]

Monitoring adverse effects

Adverse events that occurred during a follow-up period of 4–6 weeks after vaccination were recorded. Systemic adverse effects included fever, headache, myalgia, asthenia and fatigue. Local adverse events included pain/tenderness, swelling/induration and erythema at the injection sites.

Statistical analysis

To access the PPV23 immunogenicity in patients in each treatment group, IgG concentrations and OIs before and after vaccination were transformed into logarithmic values. IgG geometric mean concentrations (GMCs) and geometric mean OIs (GM-OIs) were calculated as the exponential of an arithmetic mean of log-transformed values. For details regarding statistical analysis, see online supplementary text.

RESULTS

Clinical and demographic characteristics

A total of 190 RA patients were divided into four groups according to their ongoing anti-RA therapy. There was one group of 50 patients treated with TCZ as monotherapy (TCZ group), 62 patients treated with MTX alone (MTX group), 54 patients who received a combination therapy consisting of TCZ and MTX (TCZ+MTX group) and 24 patients who did not receive either drug (RA control group). Prior to participating in this study, no patients had received a pneumococcal vaccination. Patients' clinical and demographic characteristics are shown in table 1.

Serotype-specific IgG concentrations

After vaccination, serotype-specific IgG GMCs to pneumococcal serotypes 6B and 23F in all four groups were increased significantly ($p<0.0005$; table 2). For serotype 6B, a significantly higher post-GMC was obtained in the TCZ group compared with that in the TCZ+MTX group ($p=0.004$). The TCZ group also showed a significantly greater fold increase than did the TCZ+MTX group ($p=0.036$). For serotype 23F, the TCZ group also showed a significantly higher post-GMC than did the MTX group ($p=0.027$). Increases were twofold or more in all treatment groups, and there were no statistically significant differences.

Opsonophagocytic killing assays

After vaccination, GM-OIs for the 6B and the 23F serotypes were increased significantly in all four groups ($p<0.0005$; table 2). For serotype 6B, the post-vaccination GM-OI was significantly higher in the TCZ group compared with that in the MTX group ($p=0.001$). The TCZ group also showed a significantly higher post-vaccination GM-OI for serotype 23F compared with the MTX group ($p=0.001$) or with the TCZ+MTX group ($p=0.042$). For either serotype, there were no significant differences in fold increases among the four treatment groups.

Table 1 Clinical and demographic characteristics of RA patients prior to pneumococcal vaccination

	MTX group (n=62)	TCZ+MTX group (n=54)	TCZ group (n=50)	RA control (n=24)	p Values between treatment groups
Male/female	11/51	4/50	7/43	5/19	NS
Age, mean (95% CI) (years)	68.3 (66.6 to 70.1)	65.1 (63.1 to 67.0)	68.3 (65.8 to 70.8)	69.2 (65.3 to 73.1)	NS
RA duration, mean (95% CI) (years)	10.0 (7.8 to 12.1)	9.1 (7.3 to 10.8)	12.5 (9.6 to 15.3)	11.3 (6.0 to 16.6)	NS
MTX dose, median (IQR) (mg/week)	8 (6 to 8)	8 (6 to 8)	–	–	NS
MTX duration, median (IQR) (months)	48 (14.3 to 86.3)	48.5 (26 to 81)	–	–	NS
TCZ duration, median (IQR) (weeks)	–	56 (16 to 95)	58 (15 to 98)	–	NS
Use of prednisolone, number of patients (%)	17 (27.4)	14 (25.9)	12 (24)	1 (4.2)	0.018 (M vs C) 0.029 (T/M vs C) 0.049 (T vs C)
Prednisolone dose, median (IQR) (mg/day)	0 (0 to 2)	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)	NS
Positive RF, number of patients (%)	35 (56.5)	39 (72.2)	31 (62)	8 (33.3)	0.001 (T/M vs C) 0.021 (T vs C)
Positive anti-CCP Abs, number of patients (%)	44 (71.0)	46 (85.2)	41 (82)	11 (45.8)	0.029 (M vs C) 0.0003 (T/M vs C) 0.001 (T vs C)
Lymphocytes, mean (95% CI) (/μl)	1374 (1230 to 1517)	1651 (1420 to 1881)	1717 (1545 to 1890)	1600 (1358 to 1842)	NS
Serum IgG, mean (95% CI) (mg/dl)	1286 (1194 to 1377)	1172 (1075 to 1269)	1196 (1121 to 1271)	1394 (1258 to 1530)	NS

Data were obtained immediately before pneumococcal vaccination. p Values between treatment groups were determined using the Mann–Whitney U test, ANOVA (analysis of variance) with a Tukey's HSD (honesty significant difference) post hoc test, the Kruskal–Wallis test with a Scheffe post hoc test, the χ^2 test or Fisher's exact probability test.
anti-CCP Abs, anti-cyclic citrullinated peptide antibodies; M, MTX group; MTX, methotrexate; NS, not significant; RA, rheumatoid arthritis; RF, rheumatoid factor; T, TCZ group; T/M, TCZ +MTX group; C, RA control; TCZ, tocilizumab.

Table 2 Concentrations of pneumococcal polysaccharide antigen serotype-specific IgG antibodies and opsonisation indices in the RA treatment groups before and after 23-valent pneumococcal polysaccharide vaccination

Serotype	MTX group (n=62)	TCZ+MTX group (n=54)	TCZ group (n=50)	RA control group (n=24)	p Values between treatment groups
IgG GMCs (μg/ml)					
6B					
Before	1.2 (1.0 to 1.5)	1.1 (0.9 to 1.3)	1.3 (1.0 to 1.7)	1.1 (0.8 to 1.6)	NS
After	2.2 (1.7 to 2.7)*	1.7 (1.3 to 2.3)*	6.1 (2.6 to 4.9)*	2.5 (1.5 to 4.4)*	0.004 (T/M vs T)
Fold increase	1.5 (1.1 to 3.0)	1.6 (1.2 to 1.9)	2.8 (1.4 to 4.4)	1.8 (1.3 to 3.7)	0.036 (T/M vs T)
23F					
Before	1.0 (0.8 to 1.2)	0.9 (0.7 to 1.2)	1.3 (1.0 to 1.7)	1.0 (0.6 to 1.5)	NS
After	2.4 (1.8 to 3.3)*	2.5 (1.8 to 3.5)*	4.6 (3.4 to 6.4)*	3.6 (1.8 to 5.7)*	0.027 (M vs T)
Fold increase	2.6 (1.4 to 4.1)	2.9 (1.0 to 6.9)	3.4 (1.5 to 6.8)	3.5 (1.7 to 5.6)	NS
GM-OIs					
6B					
Before	18.8 (18.7 to 32.1)	24.5 (14.7 to 42.1)	43.8 (22.4 to 85.6)	20.70 (7.0 to 61.0)	NS
After	115.6 (64.1 to 206.4)*	232.8 (124.0 to 437.0)*	692.3 (265.1 to 1366)*	262.4 (74.4 to 916.0)*	0.001 (M vs T)
Fold increase	4.5 (1 to 12.5)	6.8 (1.7 to 35.5)	12 (3.5 to 62.4)	8.5 (2.2 to 52.0)	NS
23F					
Before	10.1 (6.6 to 15.3)	15.5 (10.3 to 23.6)	27.9 (15.2 to 51.4)	17.6 (7.5 to 42.1)	0.018 (M vs T)
After	72.2 (39.3 to 133.0)*	124.0 (62.2 to 244.7)*	437.0 (221.4 to 862.6)*	219.2 (82.3 to 578.2)*	0.001 (M vs T) 0.042 (M/T vs T)
Fold increase	7 .0 (2.7 to 15.8)	5.0 (1 to 40)	18.8 (2.7 to 75.1)	11.0 (3.1 to 30.6)	NS

IgG GMCs and GM-OIs are expressed as the mean (95% CI). Fold increases are expressed as the median (IQR). Differences between pre- and post-vaccination GMCs of serotype-specific IgG and those between pre- and post-vaccination GM-OIs were assessed using a paired-sample t test. The four treatment groups were compared using ANOVA (analysis of variance) with a Tukey's HSD (honestly significant difference) post hoc test or the Kruskal–Wallis test with a Scheffe post hoc test.
*p<0.0005 compared with pre-vaccination IgG GMCs or GM-OIs.
GMC, geometric mean concentration; GM-OI, geometric mean opsonisation index; M, MTX group; MTX, methotrexate; NS, not significant; RA, rheumatoid arthritis; T, TCZ group; T/M, TCZ+MTX group; TCZ, tocilizumab.

There was a moderate correlation between IgG concentrations and OIs for the 6B and the 23F serotypes (serotype 6B: r=0.623, p<0.0005; serotype 23F: r=0.601, p<0.0005).

Antibody response rates (percentages of patients with positive antibody response)

The TCZ group antibody response rates were comparable with those of the RA control group for serotypes 6B and 23F (figure 1).

For the IgG concentration specific to serotype 6B, the antibody response rate was significantly higher in the TCZ group (56%) compared with that in the MTX group (37%) and the TCZ+MTX group (24%, p=0.046 and p=0.0009, respectively; figure 1A). For serotype 23F, there was no significant difference in the antibody response rate among the four treatment groups (Control: 67%; MTX: 57%; TCZ+MTX: 56%; TCZ: 72%). The percentage of patients with positive antibody response for both strains were significantly greater in the TCZ group (46%) compared with the TCZ+MTX group (20%, p=0.005) and the RA control group (21%, p=0.044).

For OIs specific to serotype 6B, the TCZ group showed a significantly higher antibody response rate than did the MTX group (56% vs 34%, p=0.019; figure 1B). For serotype 23F, the antibody response rates were significantly higher in the TCZ group (58%) compared with those in the MTX group (37%, p=0.027) and the TCZ+MTX group (35%, p=0.020). For both strains, a higher proportion of patients in the TCZ group responded to pneumococcal vaccination compared with the patients being treated with MTX alone (34% vs 16%, p=0.028).

Predictive factors for antibody response to PPV23

In a multivariate logistic regression analysis, TCZ use was not identified as the predictive factor for antibody response to pneumococcal vaccination for either IgG concentrations or OIs. The negative association of current MTX use with antibody response was confirmed for IgG concentrations specific to serotypes 6B and 23F (for serotype 6B: OR 0.45, 95% CI 0.25 to 0.82, p=0.009; for serotype 23F: OR 0.56, 95% CI 0.31 to 1.04, p=0.007) and OIs for serotype 23F (OR 0.54, 95% CI 0.29 to 0.99, p=0.046).

Vaccination safety

Two patients in the TCZ+MTX group had a fever. Local adverse events were observed in 12 patients (2 in the MTX group, 7 in the TCZ+MTX group and 3 in the TCZ group). All adverse effects were mild.

DISCUSSION

Following immunisation with PPV23, IgG concentrations and OIs for the 6B and the 23F serotypes were significantly increased in all treatment groups. Antibody response rates in the TCZ group were comparable with those of the RA control group for each serotype. Ongoing use of MTX is likely to have affected the antibody response to PPV23.

Results of the present study indicate that TCZ does not diminish T-cell-independent antibody production after PPV23 immunisation. In addition, we recently reported that RA patients receiving TCZ can produce an adequate antibody response to influenza vaccine, which are T-cell-dependent protein antigens.[6] These findings suggest that both T-cell-dependent and T-cell-independent antibody response pathways are conserved in RA patients who are treated with TCZ. There is an increasing awareness of lethal synergism between influenza virus and pneumococcus; influenza virus contributes to secondary pneumococcal pneumonia and can subsequently increase mortality.[7 8] In addition, a large-scale trial suggested that a significant

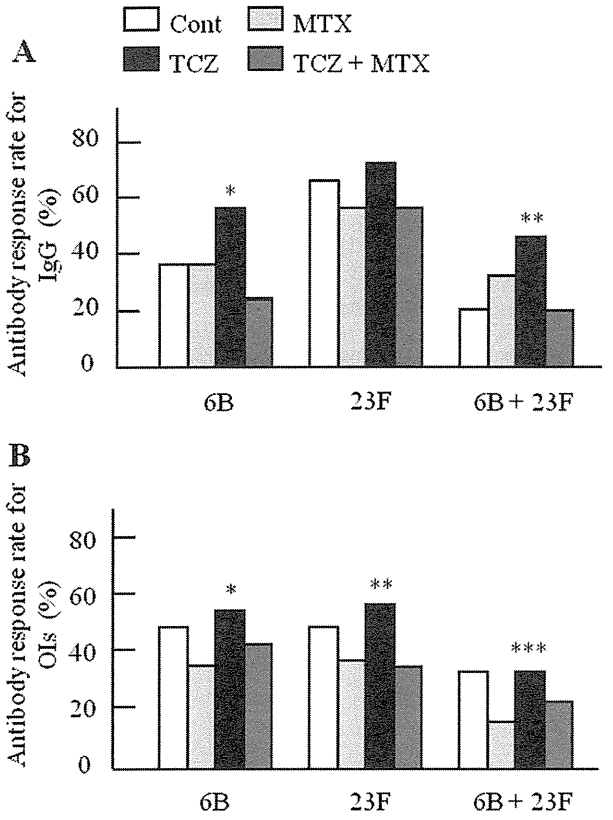

Figure 1 (A) Percentages of patients with twofold or more increases in serotype-specific IgG concentrations for serotypes 6B and 23F in the rheumatoid arthritis (RA) treatment groups. *p=0.046 (TCZ vs MTX) and p=0.0009 (TCZ vs TCZ+MTX). **p=0.005 (TCZ vs TCZ+MTX) and p=0.044 (TCZ vs Cont). (B) Percentages of patients with 10-fold or more increases in OIs for serotypes 6B and 23F in the RA treatment groups. *p=0.019 (TCZ vs MTX). **p=0.027 (TCZ vs MTX) and p=0.020 (TCZ vs TCZ+MTX). ***p=0.028 (TCZ vs MTX). Data were compared using the χ^2 test or Fisher's exact probability test. OIs, opsonisation indices; Cont, RA control group; MTX, methotrexate group; TCZ, tocilizumab group; TCZ+MTX, combination therapy group.

proportion of viral pneumonia, including influenza, is attributable to bacterial co-infection and that this co-infection may be preventable by bacterial vaccination.[9] Immunisation with both influenza and pneumococcal vaccines may, therefore, provide additive benefits for RA patients compared with a single vaccination, even if they are receiving TCZ therapy.

Previous studies have shown that MTX therapy reduced the antibody response to PPV23,[10–13] which is in agreement with the data obtained in the present study. Although T-cell-dependent protein antigens may be more immunogenic than polysaccharide antigens in immunocompromised patients,[14] MTX was also reported to be a strong predictive factor for an impaired antibody response to protein-conjugate pneumococcal vaccine.[15] Offering PPV23 vaccination before introduction of MTX therapy may be considered in RA patients.[11 16] In contrast, a study by Elkayam *et al*[17] did not demonstrate a detrimental effect of immunosuppressive drugs such as MTX on PPV23 immunogenicity in RA patients. Coulson *et al*[18] have also suggested that a single PPV23 administration offers up to 10 years of protection against the development of pneumococcal pneumonia in RA patients receiving MTX therapy. Determining serotype-specific IgG concentrations after PPV23 vaccination in patients receiving MTX therapy is recommended.[19]

In the present study, no patients were receiving high doses of prednisolone or antirheumatic agents with immunosuppressive effects other than MTX. In addition, there were no differences in the prednisolone dose among the four treatment groups, and the median dose of prednisolone was zero among all groups. The number of prednisolone users was significantly lower in the RA control group; however, there were no significant differences or trends in antibody response to each serotype compared with the other three groups. We can, therefore, say that the influence of such agents on PPV23-induced antibody response was minimal in the present study.

One limitation of this study is the relatively small number of patients in each group and the RA control group in particular. Since most RA patients had already received one or more immunosuppressive antirheumatic drugs, as recommended by the current therapeutic guidelines, it was difficult to recruit a sufficient number of patients who had never received such drugs. Another limitation is that we determined antibody response to only two pneumococcal serotypes. We chose serotypes 6B and 23F because these are the main causative serotypes of pneumococcal pneumonia in Japan and these are representative penicillin-resistant pneumococci.[20] However, the immune response to PPV23 may not be consistent among the 23 serotypes. Lastly, unlike influenza vaccines, antibody levels that are protective against invasive pneumococcal disease in adults have not been clearly defined. We used a 2-fold increase in the IgG concentration or a 10-fold increase in the OI as a measure of positive antibody response to PPV23 in this study, which was also used in previous studies;[5] however, how this threshold may best correlate with protection against invasive pneumococcal disease remains to be determined.

In conclusion, ongoing TCZ therapy does not preclude pneumococcal polysaccharide vaccination in RA patients; however, antibody responses may be reduced when TCZ is administered in combination with MTX.

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Contributors All authors contributed to study conception and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript with regard to important intellectual content.

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Competing interests TH has received lecture fees from Mitsubishi-Tanabe Pharmaceutical Co., Eisai Co. Ltd. and Abbott Japan Co. Ltd. The other authors have no financial relationships that could lead to a conflict of interest.

Patient consent Obtained.

Ethics approval The ethics committees of participating hospitals approved the protocol for this study.

Provenance and peer review Not commissioned; externally peer reviewed.

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Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tocilizumab therapy

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Notes

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
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Nationwide Rubella Epidemic — Japan, 2013

Rubella usually is a mild, febrile rash illness in children and adults; however, infection early in pregnancy, particularly during the first 16 weeks, can result in miscarriage, stillbirth, or an infant born with birth defects (i.e., congenital rubella syndrome [CRS]) (*1*). As of 2013, goals to eliminate rubella have been established in two World Health Organization regions (the Region of the Americas by 2010 and the European Region by 2015), and targets for accelerated rubella control and CRS prevention have been established by the Western Pacific Region (WPR) (*2*). In 1976, Japan introduced single-antigen rubella vaccine in its national immunization program, targeting girls in junior high school. In 1989, a measles-mumps-rubella (MMR) vaccine was introduced, targeting children aged 12–72 months. However, adult males remain susceptible to rubella. From January 1 to May 1, 2013, a total of 5,442 rubella cases were reported through the rubella surveillance system in Japan, with the majority (77%) of cases occurring among adult males. Ten infants with CRS were reported during October 2012–May 1, 2013. Countries and regions establishing a goal of accelerated control or elimination of rubella should review their previous and current immunization policies and strategies to identify and vaccinate susceptible persons and to ensure high population immunity in all cohorts, both male and female.

During 1999–2007, rubella surveillance in Japan consisted of aggregate case reporting to the pediatric sentinel surveillance system. Cases were reported from a representative sample of approximately 3,000 pediatric inpatient and outpatient medical facilities. In January 2008, the sentinel surveillance systems were replaced by nationwide case-based surveillance for rubella, and all physicians were required to report any clinically diagnosed or laboratory-confirmed rubella case* to local health officials. In April 1999, nationwide, case-based surveillance for CRS† had been established.

Until the early 2000s, rubella was endemic in Japan, with periodic epidemics approximately every 5 years and seasonal increases in the spring and summer. The number of reported rubella cases remained at record low levels until 2010, and in 2011, a few outbreaks were reported in the workplace among adult males. In

* Rubella case definition: clinically diagnosed rubella case is a diffuse punctate and maculopapular rash, fever, and lymphadenopathy; laboratory-confirmed rubella case is the presence of all of the mentioned signs and one of the following: 1) isolation of the virus or detection of viral RNA from blood, throat, or cerebrospinal fluid samples by reverse transcription–polymerase chain reaction; or 2) detection of rubella-specific immunoglobulin M antibodies from a serum sample or a significant increase in rubella-specific immunoglobulin G antibody titers in paired serum samples obtained at acute and convalescent phases.

† Laboratory-confirmed CRS case definition: 1) clinically confirmed CRS in an infant who has a positive blood test for rubella-specific immunoglobulin M or hemagglutination inhibition antibody levels sustained or higher than expected from passively transferred maternal antibody; or 2) detection of rubella virus in specimens from throat, saliva, or urine. CRS is clinically confirmed if an infant has 1) at least two of the following complications: cataract, congenital glaucoma, congenital heart disease, hearing impairment, or pigmentary retinopathy; or 2) one of those complications and one of the following complications: purpura, splenomegaly, microcephaly, meningoencephalitis, radiolucent bone disease, or jaundice developed within 24 hours after birth.

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2012, the number of rubella cases sharply increased to 2,392, with the rise in cases continuing into 2013 (Figure 1). From January 1 to May 1, 2013, a total of 5,442 rubella cases were reported (Table). Of these cases, 3,936 (72.3%) were laboratory confirmed. Geographically, over 60% of rubella cases were reported from Kanto area, in the eastern part of Japan comprised of Tokyo and its surrounding prefectures. In recent weeks, the epidemic has expanded from Kanto to other parts of Japan, including Osaka, Hyogo, Aichi, Fukuoka, and Kagoshima. Of the 5,442 cases, males accounted for 4,213 cases (77.4%), of which 3,878 cases (92.0%) were in persons aged >20 years (Figure 2). Of the 4,834 cases in persons aged >20 years, 1,727 (36%) were in persons aged 30–39 years and 1,535 (32%) in persons aged 20–29 years. Among rubella cases, vaccination history was unknown in a majority of cases (3,538 [65%]). For the 1,904 reported rubella cases with known vaccination status, 1,566 (82%) occurred in persons who had not received rubella vaccine (Table). Virus genotypes were determined for 150 cases in 2012; of these, 123 (82.0%) and 26 (17.0%) were genotypes 2B and 1E, respectively (*3*).

During 2008–2011, three cases of CRS were reported nationwide. Since October 2012, 10 CRS cases have been reported from Hyogo (two), Aichi (two), Osaka (two), Tokyo (one), Kagawa (one), Saitama (one), and Kanagawa (one). Six of the mothers of infants with CRS had not received rubella vaccine, and four had unknown vaccination history.

Population immunity is measured by administrative coverage and seroprevalence surveys. In 2011, administrative measles-rubella (MR) vaccine coverage was 95.3% at age 1 year, 92.8% at age 5–6 years, 88.1% at age 12–13 years, and 81.4% at age 17–18 years. Population immunity for eight vaccine-preventable diseases is measured by the National Epidemiological Surveillance of Vaccine Preventable Diseases, an annual, national seroepidemiologic survey conducted among a representative sample of the Japanese population. In 2012, 14 prefectures in Japan joined this serologic survey by measuring rubella hemagglutination inhibition antibody levels in 5,094 healthy persons. Among adults aged 30–50 years, seropositivity for rubella antibody (1:8) was 73%–86% among males and 97%–98% among females (*4*).

In response to the current outbreak, Japan's Ministry of Health, Labor, and Welfare provided guidance to health-care authorities (*5*). The guidance is to provide information on rubella disease and CRS for pregnant women and their households and encouraged vaccination of the family members of pregnant women (because rubella vaccine is contraindicated in pregnant women) and vaccination for women who plan to get pregnant. The local governments in approximately 100 cities, including several districts in the Tokyo metropolitan area that had high numbers of reported rubella cases, have provided partial funding to help with the cost of MR vaccine or a single rubella vaccine for women planning pregnancy and for men who are living with a pregnant woman. In addition, mass media agencies in Japan have provided information about the rubella epidemic, including rubella disease and CRS, which has helped increase awareness about the importance of rubella vaccination.

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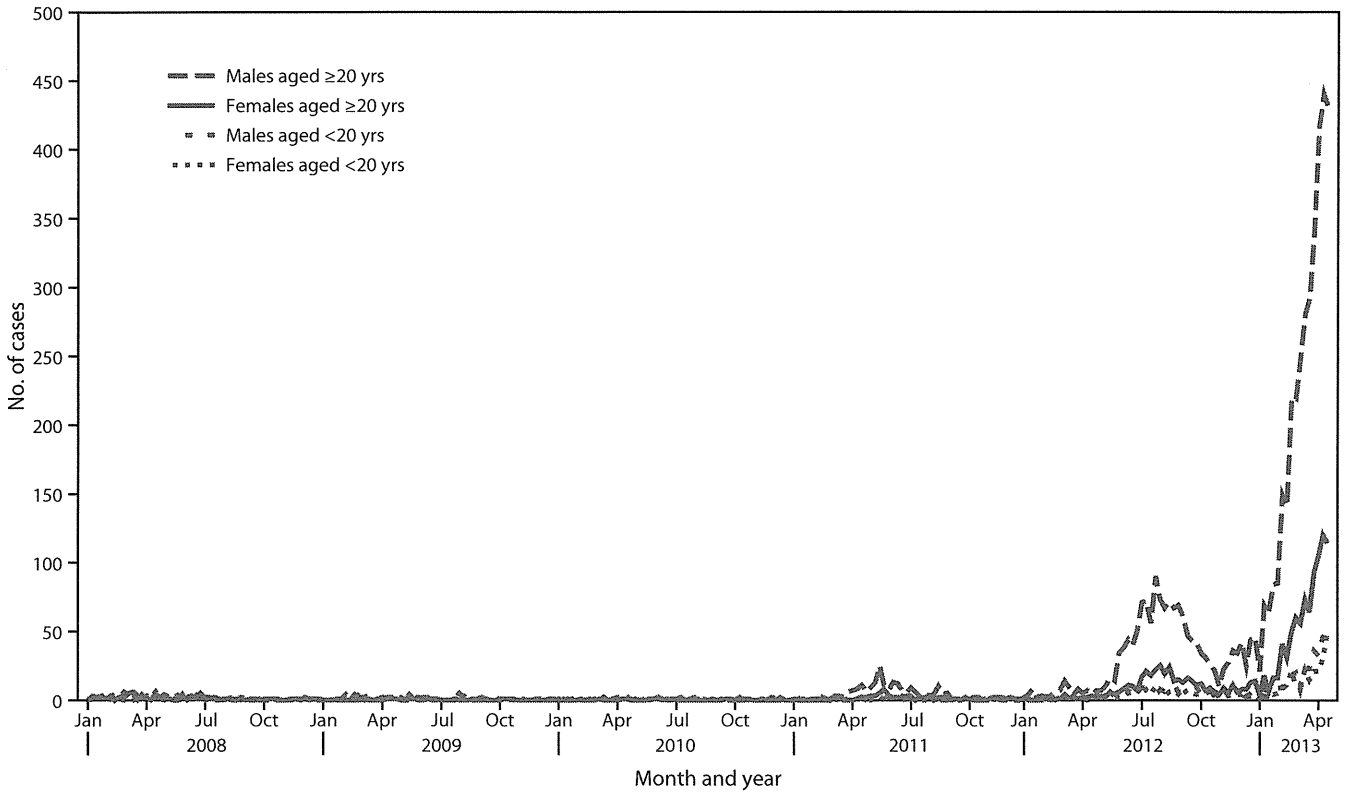
FIGURE 1. Number of rubella cases, by sex and age group — Japan, 2009–2013*



* As of April 24, 2013.

Reported by

Keiko Tanaka-Taya, MD, PhD, Hiroshi Satoh, DVM, PhD, Satoru Arai, DVM, PhD, Takuya Yamagishi, MD, PhD, Yuichiro Yahata, PhD, Kazutoshi Nakashima, MD, PhD, Tamie Sugawara, PhD, Yasushi Ohkusa, PhD, Tamano Matsui, MD, PhD, Takehito Saito, MSc, Kazuhiko Kanou, PhD, Tomoe Shimada, MD, Hitomi Kinoshita, DVM, PhD, Kazuyo Yamashita, PhD, Yoshinori Yasui, MD, PhD, Yuki Tada, MD, PhD, Yoshio Mori, DVM, PhD, Makoto Takeda, MD, PhD, Tomimasa Sunagawa, MD, PhD, Kazunori Oishi, MD, PhD, National Institute of Infectious Diseases, Japan. Peter Strebel, MD, Accelerated Control and Elimination of Vaccine Preventable Diseases, World Health Organization, Geneva, Switzerland. W. William Schluter, MD, Western Pacific Regional Office, World Health Organization, Manila, Phillipines. Hajime Kamiya, MD, PhD, Div of Bacterial Diseases, National Center for Immunizations and Respiratory Diseases; Susan E. Reef, MD, Susan Y. Chu, PhD, Rebecca Martin, PhD, Global Immunization Div, Center for Global Health, CDC. ***Corresponding contributor:*** *Susan E. Reef, sreef@cdc.gov, 404-639-8982.*

Editorial Note

The primary purpose of rubella vaccination is to prevent congenital rubella virus infection, including CRS. In WPR, the Immunization Technical Advisory Group endorsed a regional accelerated rubella control and CRS prevention goal to decrease rubella incidence to <10 cases per million population and CRS incidence to <10 cases per million live births each year by 2015 (*6*). In 2012, Japan reported 18.7 rubella cases per million population, a rate higher than the WPR annual incidence target. As of May 2013 (4 months into the year), the number of reported rubella cases is already double the total number of cases in 2012.

In 1976, Japan established a goal to prevent CRS and introduced single-antigen rubella vaccine in its national immunization program, targeting girls in junior high school. In 1989, an MMR vaccine was introduced, targeting children aged 12–72 months, but this combination vaccine was withdrawn in 1993 after reports of aseptic meningitis related to the mumps component. In 1995, vaccination policy was changed to make all vaccines strongly recommended but not mandatory, and in 2006, the MR combined vaccine was introduced, with a 2-dose schedule administered at 1–2 years and 5–7 years.

TABLE. Number and percentage of rubella cases, by year and selected characteristics — Japan, 2009–2013

Characteristic	2009		2010		2011		2012		2013*	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Total	**147**	**(100)**	**87**	**(100)**	**378**	**(100)**	**2,392**	**(100)**	**5,442**	**(100)**
Rubella cases per 1,000,000 population	1.2		0.7		3.0		18.7		42.5	
Sex										
Male	98	(66.7)	54	(62.1)	278	(73.5)	1,797	(75.1)	4,213	(77.4)
Female	49	(33.3)	33	(37.9)	100	(26.5)	595	(24.9)	1,229	(22.6)
Age group (yrs)										
<1	4	(2.7)	1	(1.1)	2	(0.5)	16	(0.7)	24	(0.4)
1–4	22	(15.0)	11	(12.6)	23	(6.1)	69	(2.9)	94	(1.7)
5–9	13	(8.8)	10	(11.5)	10	(2.6)	37	(1.5)	68	(1.2)
10–14	17	(11.6)	8	(9.2)	18	(4.8)	56	(2.3)	118	(2.2)
15–19	19	(12.9)	5	(5.7)	29	(7.7)	217	(9.1)	304	(5.6)
20–29	22	(15.0)	20	(23.0)	114	(30.2)	741	(31.0)	1,535	(28.2)
30–39	30	(20.4)	16	(18.4)	94	(24.9)	681	(28.5)	1,727	(31.7)
40–49	13	(8.8)	14	(16.1)	59	(15.6)	430	(18.0)	1,103	(20.3)
50–59	4	(2.7)	1	(1.1)	22	(5.8)	124	(5.2)	396	(7.3)
>59	3	(2.0)	1	(1.1)	7	(1.9)	21	(0.9)	73	(1.3)
Diagnosis										
Clinically diagnosed	63	(42.9)	26	(29.9)	83	(22.0)	599	(25.0)	1,506	(27.7)
Laboratory confirmed	84	(57.1)	61	(70.1)	295	(78.0)	1,793	(75.0)	3,936	(72.3)
Vaccination status										
Unvaccinated	46	(31.3)	17	(19.5)	96	(25.4)	605	(25.3)	1,566	(28.8)
Once	41	(27.9)	14	(16.1)	29	(7.7)	180	(7.5)	263	(4.8)
Twice	4	(2.7)	4	(4.6)	9	(2.4)	49	(2.0)	75	(1.4)
Uncertain	56	(38.1)	52	(59.8)	244	(64.6)	1,558	(65.1)	3,538	(65.0)
Total CRS* cases	**2**	**(100)**	**0**	**—**	**1**	**(100)**	**5**	**(100)**	**5**	**(100)**
CRS cases per 1,000,000 live births	2.0		0.0		1.0		4.8		4.8	

Abbreviation: CRS = congenital rubella syndrome.
* As of May 1, 2013.

What is already known about this topic?

Congenital rubella syndrome (CRS) is caused by fetal infection with rubella virus from the mother and is characterized by birth defects such as hearing impairment, heart defects, and cataracts. Several countries that initially vaccinated only adolescent or adult women, then later introduced rubella vaccine into their routine programs or conducted mass campaigns in adolescent and adult females, have experienced large rubella outbreaks among adolescent and young adult males, with a concomitant increase in infants with CRS.

What is added by this report?

In 2012, the number of rubella cases in Japan sharply increased to 2,392, with the rise in cases continuing into 2013 and resulting in a cumulative total of 5,442 cases from January 1 to May 1, 2013. Of these cases, 72% were laboratory confirmed, and 23% were in females. Since October 2012, 10 CRS cases have been reported.

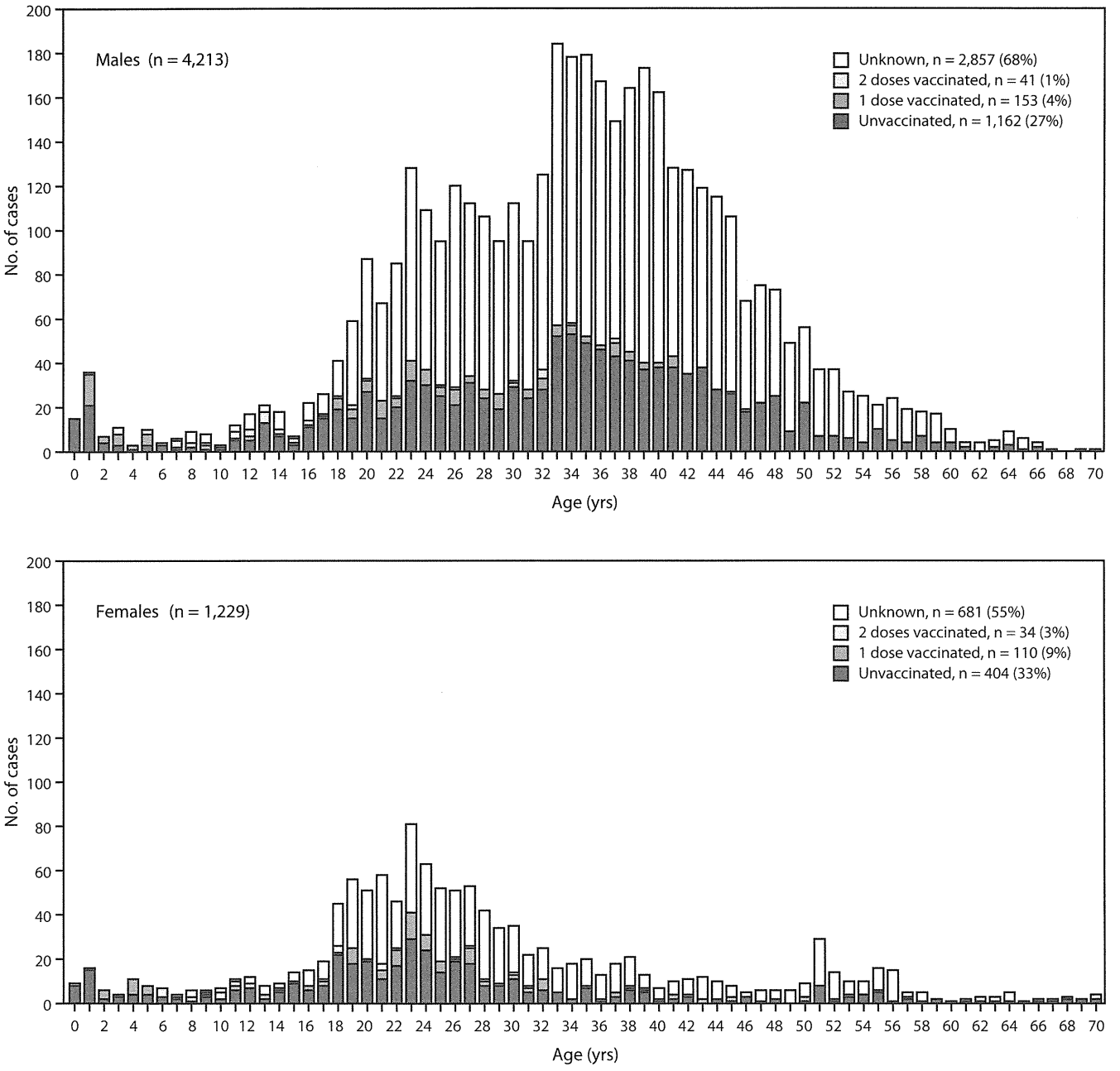
What are the implications for public health practice?

Countries using rubella vaccine should aim to prevent rubella outbreaks (i.e., achieve and maintain interruption of rubella virus transmission) by ensuring high rubella immunity across all age groups (both males and females). In cohorts born since the introduction of rubella vaccine, this immunity is achieved primarily through uniformly high vaccination coverage.

After a large measles outbreak in 2007 and 2008, a catch-up MR vaccination program was implemented, targeting two age cohorts (those aged 12 years and those aged 17 years) each year during 2008–2013 to ensure high population immunity among persons aged 12–22 years in 2013.

In the current outbreak, males aged 20–39 years, who were not included in the initial rubella vaccination program, accounted for 68% of the reported cases. However, with the introduction of 2 doses of MR vaccine into the national vaccination schedule in 2006 for both boys and girls and the successful catch-up vaccination program, children who currently are aged <15 years account for only 5.6% of the cases. In other countries (e.g., Brazil, Chile, and Argentina), where only adolescent or adult females have been targeted through national immunization programs or as part of mass vaccination campaigns, similar large outbreaks have occurred among adolescent and adult males, with a concomitant increase in CRS cases. These types of outbreaks emphasize that national immunization programs should ensure high levels of immunity in all cohorts born since the introduction of rubella vaccine (both males and females) either through the routine program or high-quality mass campaigns that are sufficient to interrupt rubella virus transmission

FIGURE 2. Number of rubella cases among males and females, by age and vaccination history — Japan, surveillance week 1 to 17, 2013*



* As of May 1, 2013.

and prevent CRS cases. In addition, programs should implement high-quality, case-based rubella and CRS surveillance and respond promptly and rapidly to outbreaks.

The effects of this outbreak have been wide-ranging, both within Japan and internationally. In the Region of the Americas, where endemic rubella virus transmission has been interrupted, importations have occurred in the United States and Canada in 2013. The international spread of rubella virus from Japan provides a reminder that countries in regions that have eliminated rubella need to maintain high levels of vaccination coverage and high-quality surveillance to limit the spread and detect imported rubella virus.