Vaccination for Patients with Inborn Errors of Immunity: a Nationwide Survey in Japan

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Abstract
We conducted a nationwide survey of inborn errors of immunity (IEI) in Japan for the second time in 10 years, focusing on protective measures for IEI patients against infectious diseases. Questionnaires were sent to various medical departments nationwide, and a total of 1307 patients were reported. The prevalence of IEI was 2.2 patients per 100,000 population, which was comparable with the previous nationwide study. The most common disease category was autoinflammatory disorders (25%), followed by antibody deficiencies (24%) and congenital defects of phagocyte number or function (16%). We found that a significant number of patients received contraindicated vaccines, principally because the patients were not diagnosed with IEI by the time of the vaccination. Regarding diseases for which BCG vaccination is contraindicated, 43% of patients had actually received BCG, of which 14% developed BCG-related infections. BCG-related infections were mainly observed among patients with CGD and MSMD. In order to prevent IEI patients from receiving inadequate vaccines, continuous education to parents and physicians is needed, along with the expansion of newborn screening, but efforts to screen IEI at the site of vaccination also remain important.

Keywords Inborn errors of immunity · Epidemiology · Japan · Vaccine · BCG

Introduction
The majority of patients with IEI are susceptible to various types of infections, emphasizing the importance of infection prophylaxis in this population. Vaccines are important for establishing immunity against pathogens, but they may be contraindicated in a subgroup of IEI patients due to potential severe vaccine-related adverse events, especially infections due to live vaccine strains [1]. Since children receive routine vaccine administration beginning as early as several months of age, it is important to diagnose IEI early enough to prevent any serious vaccine strain infections. However, the actual proportion of patients who receive contraindicated vaccines before diagnosis in Japan is unknown. Childhood vaccine protocols vary between countries due to differences in vaccine cost or insurance policies and the epidemic status of pathogens. One example is the Bacille de Calmette et Guérin (BCG) vaccine, which is not routinely administered in many western countries but is part of a routine schedule in Japan, where tuberculosis is an endemic disease [2]. This indicates that Japanese IEI patients are at high risk for BCG-related infections; but although the prevalence of BCG infections has been reported in various countries [3, 4], the situation for Japanese IEI patients is unknown. Furthermore, concerns regarding appropriate immunization for IEI patients are increasing, since the number of newly diagnosed IEI patients is expanding due to advances in diagnostic methods such as next-generation sequencing (NGS) [5]. In 2018, we conducted a nationwide survey of IEI patients, focusing on protective measures against infectious diseases. The present study focuses on results from the survey regarding individual vaccination status.
in Japanese IEI patients, aiming to elucidate the situation of pre-diagnostic vaccination. Regrading BCG, we also analyzed the rate of BCG-related adverse events after inoculation.

**Methods**

This study was conducted according to the nationwide epidemiological survey manual of patients with intractable diseases (3rd edition 2017), as was the previous survey which was published in 2011 [6]. Five clinical departments (pediatrics, internal medicine, hematology, rheumatology, and dermatology) were selected for having a high tendency of attending to IEI patients. A primary questionnaire requesting the number of IEI patients treated between January 1 and December 31, 2018, was sent to 20% of all of the five departments in hospitals nationwide; hospitals were selected randomly after setting selection ratios according to hospital size and academic status (Table 1, Table S1; Online Resource 1). The questionnaire requested patients with a confirmed diagnosis irrespective of clinical severity, but genetic testing was not compulsory. The estimated number of patients was calculated by dividing the number of reported patients by the selection rate and response rate. A secondary survey was performed by sending questionnaires to departments where at least one patient was treated during the observation period. The secondary questionnaire was comprised of the following questions; (1) general information concerning age, sex, and diagnosis, (2) clinical symptoms or signs leading to diagnosis, (3) a description of all treatments (e.g., IgG replacement, antibiotic prophylaxis, stem cell transplantation (SCT), etc.), (4) a description of all previous vaccines, and (5) the vaccination policy of the attending physician. We classified diseases according to the International Union of Immunological Societies (IUIS) 2017 classifications [5]. Statistical analysis was performed using GraphPad Prism software version 8.0 (San Diego, CA, USA). The protocol for this study was approved by the ethics committee at the University of Tsukuba Hospital (H30-208).

**Results**

A primary survey was performed by sending questionnaires to 12,517 departments nationwide. Response rates varied between departments, from 18% (internal medicine) to 55% (pediatrics) with an average of 28%. This was comparable to the previous nationwide survey where the response rate for internal medicine and pediatrics was 20% and 55%, respectively [6]. A total of 1307 patients were reported from 706 departments. The estimated number of IEI patients in Japan was 2794 (95% confidence interval 2334–3019) (Table 1). The population of Japan in 2018 was 126 million [7], giving a prevalence of 2.2 IEI patients per 100,000 population. We divided geographical locations into 7 areas: the Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku/Shikoku, and Kyusyu areas, as in the previous nationwide survey [6]. The estimated regional prevalence ranged from 1.3 (Tohoku) to 3.6 (Kyusyu) per 100,000 inhabitants, and no significant differences were observed between areas. Detailed information from secondary questionnaires was obtained for 750 patients (response rate 57%). The rate of any genetic diagnosis was 74%, although the majority of genetically diagnosed patients were reported from pediatric departments (70%). The reported patients are listed in Table 2. The most common IEI category was autoinflammatory disorders (n = 191, 25%), followed by predominantly antibody deficiencies (n = 183, 24%), and congenital defects of phagocyte number or function (n = 121, 16%). Compared to the previous survey in 2011 [6], we observed an increase in autoinflammatory disorders and defects in intrinsic and innate immunity and a relative decrease in other categories. The male to female ratio was 1.46:1 (n = 744, unanswer ed: 6 cases). The patient’s median age at the time of the study was 18.0 years (range: 0 to 85.4 years), and the median age at diagnosis was 2.0 years (range: 0 to 79 years). The distribution of diagnostic age for each disease category is shown in Fig. 1. The median age at diagnosis for patients with autoinflammatory

**Table 1** Results of the primary survey

| Department         | Departments (total) | Departments selected | Selection rate (%) | Response rate (%) | Reported patients | Patients estimated in Japan (95% CI) |
|--------------------|---------------------|----------------------|--------------------|------------------|-------------------|-------------------------------------|
| Pediatrics         | 2053                | 471                  | 22.9               | 54.8             | 1011              | 1491.8 (1258.0–1606.3)              |
| Internal medicine  | 6387                | 1151                 | 18                 | 18               | 47                | 278.4 (107.5–362.1)                 |
| Hematology         | 442                 | 136                  | 30.8               | 23.5             | 38                | 274.2 (136.3–341.8)                 |
| Rheumatology       | 1134                | 248                  | 21.9               | 27.8             | 174               | 665.1 (343.0–822.9)                 |
| Dermatology        | 2501                | 485                  | 19.4               | 28.9             | 37                | 84.6 (15.3–118.5)                   |
| **Total**          | **12,517**          | **2491**             | **19.9**           | **28.3**         | **1307**          | **2794.2 (2334.3–3019.4)**          |
Table 2  Reported number and diagnosis of IEI patients

| IUlS category | Disease | \( n \) | Genetic defect |
|---------------|---------|---------|---------------|
| 1. Immunodeficiencies affecting cellular and humoral immunity (\( n = 52 \)) | | | |
| T-B + severe combined immunodeficiency (SCID) | | | |
| \( \gamma \)C deficiency | 26 | IL2RG |
| JAK3 deficiency | 1 | JAK3 |
| IL-7Ralpha deficiency | 1 | IL7R |
| T-B-SCID | | | |
| RAG1 deficiency | 2 | RAG1 |
| RAG2 deficiency | 1 | RAG2 |
| Artemis deficiency | 3 | DCLRE1C |
| LIG4 deficiency | 1 | LIG4 |
| ADA deficiency | 3 | ADA |
| SCID, undetermined | 1 | (nd) |
| Combined immunodeficiencies less profound than SCID | | | |
| CD40 ligand deficiency | 9 | CD40LG |
| DOCK8 deficiency | 1 | DOCK8 |
| IKBKB deficiency | 1 | IKBKB |
| CID, undetermined | 2 | (nd) |
| 2. Combined immunodeficiencies with associated or syndromic features (\( n = 95 \)) | | | |
| Immunodeficiency with congenital thrombocytopenia | | | |
| Wiskott-Aldrich syndrome (WAS)/X-linked thrombocytopenia | 25 | WAS |
| WAS, undetermined | 3 | (nd) |
| DNA repair defects | | | |
| Ataxia telangiectasia (AT) | 4 | ATM |
| AT, undetermined | 2 | (nd) |
| Immunodeficiency with centromeric instability and facial anomalies (ICF1) | 1 | DNMT3B |
| Thymic defects with additional congenital anomalies | | | |
| DiGeorge syndrome | 6 | 22q11.2 deletion |
| DiGeorge syndrome, undetermined | 3 | (nd) |
| Hyper IgE syndromes (HIES) | | | |
| STAT3 deficiency (Job syndrome, AD-HIES) | 37 | STAT3 |
| Other | 1 | Other |
| Dyskeratosis congenita (DKC) | | | |
| XL-DKC | 1 | DKC1 |
| AR-DKC due to RTEL1 deficiency | 1 | RTEL1 |
| SAMD9L deficiency | 1 | SAMD9L |
| Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) | | | |
| NEMO (IKBKG) deficiency | 6 | NEMO |
| EDA-ID, undetermined | 3 | (nd) |
| Other defects | | | |
| Kabuki syndrome | 1 | KMT2D |
| 3. Predominantly antibody deficiencies (\( n = 183 \)) | | | |
| Agammaglobulinemia | | | |
| BTK deficiency (XLA) | 57 | BTK |
| XLA, undetermined | 5 | (nd) |
| CVID phenotype | | | |
| APDS1 (PIK3CD GOF) | 1 | PIK3CD |
| APDS2 (PIK3R1 LOF) | 2 | PIK3R1 |
| CD19 deficiency | 1 | CD19 |
| NFKB1 deficiency | 3 | NFKB1 |
| NFKB2 deficiency | 2 | NFKB2 |
| IKAROS deficiency | 3 | IKZF1 |
Table 2 (continued)

| IU1S category | Disease | n | Genetic defect |
|---------------|---------|---|----------------|
| Others        |         | 2 | FANCE, RAD50   |
| CVID, undetermined | 59 | (nd) |
| Hyper IgM syndrome (HIMS) | 3 | AICDA |
| Isotype, light chain, or functional deficiencies with generally normal number of B cells | 12 | (nd) |
| Isolated IgG subclass deficiency | 1 | TACI |
| Selective IgA deficiency (SID) | 12 | (nd) |
| SID, undetermined | 20 | (nd) |
| Transient hypogammaglobulinemia of infancy | 47 | |
| 4. Diseases of immune dysregulation (n = 47) | |
| Familial hemophagocytic lymphohistiocytosis (FHL) syndromes | |
| FHL3 | 2 | UNC13D |
| FHL2 | 4 | PRF1 |
| FHL syndromes with hypopigmentation | |
| Chediak–Higashi syndrome (CHS) | 4 | LYST |
| Hermansky–Pudlak syndrome type 2 | 1 | AP3B1 |
| Regulatory T-cell defects | |
| IPEX | 4 | FOXP3 |
| CTLA4 deficiency (ALPSV) | 5 | CTLA4 |
| STAT3 GOF mutation | 1 | STAT3 |
| Autoimmunity with/without lymphoproliferation | |
| ALPS-FAS | 7 | TNFRSF6 |
| ALPS, undetermined | 1 | (nd) |
| Immune dysregulation with colitis | |
| IL-10Ra deficiency | 1 | IL10RA |
| Susceptibility to EBV and lymphoproliferative conditions | |
| SH2D1A deficiency (XLP1) | 3 | SH2D1A |
| XIAP deficiency (XLP2) | 14 | XIAP |
| 5. Congenital defects of phagocyte number or function (n = 121) | |
| Congenital neutropenias | |
| Elastase deficiency (SCN1) | 26 | ELANE |
| HAX1 deficiency (Kostmann disease) | 2 | HAX1 |
| SRP54 deficiency | 2 | SRP54 |
| SCN, undetermined | 6 | (nd) |
| Defects of motility | |
| Shwachman–Diamond syndrome | 3 | SBDS |
| Specific granule deficiency | 1 | CEBPE |
| Defects of respiratory burst | |
| X-CGD, gp91phox | 66 | CYBB |
| AR-CGD, p22phox | 2 | CYBA |
| AR-CGD, p67phox | 5 | NCF2 |
| AR-CGD, p47phox | 1 | NCF1 |
| CGD, undetermined | 6 | (nd) |
| Other non-lymphoid defects | |
| GATA2 deficiency (MonoMAC syndrome) | 1 | GATA2 |
| 6. Defects in intrinsic and innate immunity (n = 25) | |
| Mendelian susceptibility to mycobacterial disease (MSMD) | |
| IFN-γ receptor1 deficiency | 4 | IFNGR1 |
| STAT1 deficiency | 6 | STAT1 |
| Tyk2 deficiency | 1 | TYK2 |
disorders (7.1 years), complement deficiencies (22.3 years), and phenocopies of IEI (21.0 years) was significantly higher than other groups (Fig. 1).

The actual vaccination history for each patient was acquired and analyzed. Patients were grouped into either of the following: (1) patients who received BCG, (2) patients...
with a positive history of a live vaccine but no BCG, or (3) patients who received inactivated vaccines only. Regarding patients who received SCT, only vaccines that were administered before SCT were counted since these patients are mostly rescheduled for regular vaccines after SCT. We counted pre-SCT vaccines under the assumption that vaccines were administered according to routine schedules in Japan (Figure S2) [8]. Patients with insufficient data concerning vaccination or SCT status were removed (n = 9).

Since one of our objectives was to investigate the rate of pre-diagnostic vaccines, we also excluded patients with autoinflammatory disorders, complement deficiencies, and phenocopies of IEI because they were mostly diagnosed at an age later than the period for routine vaccination in childhood (Fig. 1). The individual vaccination history for several representative diseases within each IUIS category is shown in Fig. 2. While live vaccines are generally contraindicated in patients with severe combined immunodeficiency (SCID) or combined immunodeficiency (CID) [1], we observed that 26% of SCID patients and 54% of CID patients had received some form of live vaccine. Likewise, we saw that live vaccines were administered to 56% of patients with anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) and 36% of patients with familial hemophagocytic lymphohistiocytosis (FHL), for whom live vaccines are thought to be harmful [9, 10]. Regarding patients with the chronic granulomatous disease (CGD) or Mendelian susceptibility for mycobacterial disease (MSMD), for whom BCG is generally contraindicated [11], the rate of patients who actually received BCG was 48% and 82% for CGD and MSMD, respectively. The rate of patients with hyper IgE syndrome (HIES) and chronic mucocutaneous candidiasis (CMC) who received BCG was 39% and 50%, respectively. Of note, 97% of HIES patients were diagnosed with STAT3 deficiency, and 100% of patients with CMC were diagnosed with STAT1 gain of function (GOF) mutations. The vaccination history for patients with other diseases is shown in Figure S1 (Online Resource).
We retrieved information concerning any history of BCG-related infections (BCG-I). We selected diseases for which BCG is generally contraindicated (SCID, CID, CGD, MSMD), or diseases with reports of severe BCG infection (EDA-ID, STAT3 deficiency, STAT1 GOF) [3, 12, 13]. The results for all pooled patients and for each disease are shown in Fig. 3. The number of patients who received BCG for the pooled patients was 83 (43%), of which 27 (14%) had a reported BCG-I. When focusing on individual diseases, we saw that there was no reported BCG-I for SCID and CID, while the prevalence of BCG-I was high among CGD (n = 20, 25%) and MSMD (n = 6, 55%). We also observed one report case of BCG-I among EDA-ID (n = 1, 11%). All cases of BCG-I from the whole survey are summarized in Table 3. Among other diseases, there were cases of BCG-I among patients with WAS/XLT (n = 2) and XLP (n = 1). Other than BCG-I, there were two reported cases of rotavirus-vaccine-related enterocolitis in patients with SCID, and one case of vaccine-derived varicella zoster in a patient with EDA-ID. There were no reports of rubella or oral-polio vaccine strain-related infections, although the oral polio vaccine has been switched to inactivated polio vaccine since 2012.

Regarding vaccination policies for each patient, physicians were questioned whether their policy was to (1) administer all vaccines, (2) administer all vaccines except BCG, (3) allow inactivated vaccines only, or (4) allow no vaccines. For this analysis, we excluded patients who received SCT, since vaccination policy differs greatly with SCT status. There were no cases of SCID for which the policy was to administer live vaccines (Fig. 4). The policy was to avoid all vaccines in 68% of XLA cases, possibly reflecting the fact that most patients were on IgG replacement therapy. Regarding BCG administration, the policy to avoid BCG was seen in 70% and 73% of CGD and MSMD cases, respectively.

**Discussion**

We conducted a nationwide survey of IEI for the second time in 10 years. The prevalence of IEI was 2.2 per 100,000 inhabitants, which was comparable to the previous nationwide study (2.3/100,000) [6]. We observed a marked increase in the percentage of patients with autoinflammatory disorders, which was the most prevalent disease category in this study. This increase possibly reflects advances in genetic
testing and a better understanding for this disease group, since the autoinflammatory disease was introduced into the spectrum of IEI rather recently [14]. Our findings are also in line with a recent report which clarified that familial Mediterranean fever is more frequently observed in Japan than previously recognized [15]. The relative decrease in “classical” IEI such as CID or antibody deficiencies compared to the previous study may be due to a difference in the selection rate of pediatric departments. We set the selection rate to 20% for all medical departments following the epidemiological survey manual [16], which likely shifted our cohort to an older age compared with previous studies which mainly selected pediatric patients [6, 17, 18]. This is supported by the fact that the proportion of patients reported from pediatric departments was 77% (Table 1), compared with 92% from the previous study [6]. The older age of our cohort may also be due to advances in diagnoses and management, as more patients with IEI grow into adulthood, and more adults are newly diagnosed with IEI [19].

A genetic diagnosis was made in 74% of patients, which is relatively high compared to other studies [20] and is again reported BCG infection, or (3) patients who did not receive BCG. The percentage of each group is shown by bar graphs; the actual number of patients for each group is labeled inside the bars.

### Table 3  BCG infections from the whole survey

| Disease                               | n  |
|---------------------------------------|----|
| WAS/XLT                               | 2  |
| EDA-ID                                | 1  |
| CVID                                  | 1  |
| XLP                                   | 1  |
| CGD                                   | 20 |
| MSMD                                  | 6  |
| STAT1 deficiency (AR-LOF)             | 1  |

WAS, Wiskott-Aldrich syndrome; XLT, X-linked thrombocytopenia; EDA-ID, anhidrotic ectodermal dysplasia with immunodeficiency; CVID, common variable immunodeficiency; XLP, X-linked lymphoproliferative disease; CGD, chronic granulomatous disease; MSMD, Mendelian susceptibility to mycobacterial disease; AR-LOF, autosomal recessive loss-of-function
attributable to advances in diagnostic methods, such as the use of next-generation sequencing. However, the majority (70%) of genetically diagnosed patients were reported from pediatric departments, which may suggest that many adult IEI patients remain to be diagnosed. We also believe that this is because pediatricians are generally accustomed to genetic testing since they attend to various congenital disorders including those other than IEI. We observed a difference in diagnostic age between disease groups (Fig. 1), which is in line with previous studies [21, 22]. Another interesting finding was the disease distribution within antibody deficiencies; compared with the previous study, we observed an increase in CVID which outnumbered XLA. Although CVID is a heterogeneous disease and many patients lack a genetic diagnosis, our results may reflect a growing recognition of IEI among non-pediatric physicians, since many patients with CVID are diagnosed in adulthood [23]. However, the number of CVID patients was still smaller than those reported from Europe [24] or the USA [25]. This may be due to the low questionnaire response rate from non-pediatric departments since the majority of CVID patients in this study were reported from pediatric departments. It may also mean that CVID is underdiagnosed in adulthood, although there remains the possibility that the true prevalence is lower in Japan.

One of the objectives of this survey was to understand the current status of vaccination in patients with IEI in Japan. We observed that a significant percentage of patients received a contraindicated vaccine, presumably before the diagnosis of the disease. For example, 26% of SCID and 54% of CID patients had received a live vaccine (Fig. 2), which is contraindicated in this setting. We should assume that these patients may have developed serious adverse events because patients with these diseases are known to have an increased risk when receiving live vaccines [26]. Likewise, the proportion of patients with SCID, CGD, and MSMD patients who received BCG was 23%, 48%, and 82%, respectively. The age at diagnosis for SCID, CGD, and MSMD was 3.5 months, 6 months, and 3 years, respectively. Therefore, the rate of contraindicated BCG vaccines was likely related to whether patients were diagnosed before or after the age recommended for BCG vaccination (Figure S2).

Regarding the issue of BCG vaccination, physicians were asked to report any history of BCG-related infections since they could be important signs of IEI. We saw that within the 195 patients who received an “undesirable” BCG, 27 patients suffered from BCG-related infections, which may be
fetal in patients with IEI [27, 28] (Fig. 3). When focusing on individual diseases, we saw that most of the reported BCG infections were from patients with CGD or MSMD and that there were no reports from patients with SCID or CID. This is in contrast with a previously published review of BCG vaccination in SCID patients, where 51% of patients developed BCG complications [28]. However, most of the patients described in the review received BCG during the first month of life, whereas Japanese patients typically receive BCG during 5 to 7 months of age (Figure S2). Since most SCID patients receive SCT, the patients from our cohort may have been cured before any severe manifestations of BCG infection. Another interesting finding was the report of BCG infection in XLP (Table 3), since there have been no previous reports of BCG infection with this disease, and XLP is rather known for overproduction of interferon-gamma, which is important for the eradication of mycobacterium species.

The role of BCG vaccines in preventing tuberculosis is unquestionable, especially for the prevention of meningitis and miliary tuberculosis in infants [29]. However, like other vaccines, the policy of vaccination depends on the prevalence of the pathogen. In Western Europe or the USA, where the prevalence of tuberculosis is low, BCG vaccination is reserved for special high-risk groups [2]. The incidence of tuberculosis in Japan has decreased greatly since the 1950s [30]. However, the incidence among young-aged people shows a slight increase during the recent period [31], and Japan is still considered a moderately tuberculosis endemic country. This suggests the continuous need for universal BCG vaccination in Japan, along with the need of diagnosing at-risk patients before BCG.

Newborn screening (NBS) for SCID has proven efficacy in detecting immunodeficient patients before clinical manifestation and is adopted as a universal program in several countries such as the USA [32], Israel [33], and Spain [34]. Although SCID-NBS is only available in limited areas in Japan [35], if it can be applied on a national scale, it may become one solution to the problem of inappropriate vaccination in pre-diagnosed patients. In addition, efforts should be focused on screening patients with CGD and MSMD at the site of vaccination, until novel NBS methods become available [12, 36]. For example, physicians, especially pediatricians, should ask specific questions about the patient’s condition and family history; asking about any family history of IEI may be insufficient, and a more specific interview regarding a family history of severe BCG-I or childhood disseminated tuberculosis infection may be necessary [37, 38].

One limitation of this study is that it was based on physician-directed questionnaires making it subject to reporting bias; an absence of documented adverse events may not necessarily mean there were no actual events. Another important fact is that this was a cross-sectional study, and included patients diagnosed at various ages, some of whom were diagnosed more than 50 years ago. Although we assessed vaccine indications using present guidelines for this study, evidence surrounding IEI has obviously changed over the past years. For example, patients with chronic mucocutaneous candidiasis (CMC) were generally thought to have immunity against pathogens other than candida species, but there is emerging evidence that patients with STAT1 GOF mutations, the most common form of CMC, display susceptibility against various pathogens including the BCG strain [39]. Therefore, patients who received seemingly inappropriate vaccines in the past according to present guidelines may have been vaccinated following up-to-date evidence at that time. Nevertheless, no registry concerning vaccination status and diagnosis exists in Japan, so we believe the results of this study serve as valuable evidence in this field currently available.

For this study, we categorized patients according to recent classifications [5], but one must note that immunological profiles may differ even among patients with the same disease. For example, defects in the IL2RG gene typically lead to T+B-SCID, but there are increasing reports of hypomorphic IL2RG mutations leading to a less severe or “leaky” phenotype, making early diagnosis difficult [40]. Therefore, a thorough immunological survey of each patient is important, and physicians are recommended to consult a clinical immunologist before considering immunization for atypical cases [41].

Conclusions

In summary, we conducted a national survey of IEI in Japan for the second time in 10 years and observed an increase in diseases that are well diagnosed in adulthood. A significant number of patients had received contraindicated vaccines before diagnosis, underscoring the need for continuous education to parents and physicians. The expansion of NBS is expected, but efforts to screen IEI at the site of vaccination continue to be important.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10875-021-01160-x.

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Author Contribution Sho Hosaka and Takahiro Kido contributed to the analysis of the results and to the writing of the manuscript. Takahiro Kido and Hidetoshi Takada designed the study and performed
the survey. Kazuo Imagawa, Hiroko Fukushima, Tomohiro Morio, Shigeaki Nonoyama, and Hidetoshi Takada revised the manuscript for important intellectual content. All authors commented on the paper and approved the final manuscript as submitted.

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**Availability of Data and Material** The data analyzed in the current study is available from the corresponding author on reasonable request.

**Code Availability** Not applicable.

**Declarations**

**Ethics Approval** The protocol for this study was approved by the ethics committee at the University of Tsukuba Hospital (H30-208).

**Consent to Participate** Informed consent was obtained from the parents or their legal guardians in the form of opt-out on the website.

**Consent for Publication** Informed consent was obtained from the parents or their legal guardians in the form of opt-out on the website.

**Conflict of Interest** The authors declare no competing interests.

**References**

1. Pöyhönen L, Bustamante J, Casanova JL, Jouanguy E, Zhang Q. Life-threatening infections due to live-attenuated vaccines: early manifestations of inborn errors of immunity. J Clin Immunol. 2019;39(4):376–90.

2. Public Health Agency of Canada. The BCG World Atlas 3rd edition, updated in 2020. http://www.bcgatlas.org/index.php 2020. Accessed 15th May 2021.

3. Nunes-Santos CDeJ, Rosenzweig SD. Bacille Calmette–Guérin complications in newly described primary immunodeficiency diseases: 2010–2017. Front Immunol 2018;9(1423).

4. Yadav RM, Dalvi A, Gupta M, Bargir UA, Aluri J, et al. Spectrum of inborn errors of immunity in a cohort of 90 patients presenting with complications to BCG vaccination in India. Scand J Immunol. 2021;93(5):e13010.

5. Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova J-L, Chatila T, et al. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. J Clin Immunol. 2018;38(1):96–128.

6. Ishimura M, Takada H, Doi T, Imai K, Sasahara Y, Kanegane H, et al. Nationwide survey of patients with primary immunodeficiency diseases in Japan. J Clin Immunol. 2011;31(6):968–76.

7. Statistics Bureau of Japan. Current population estimates as of October 1, 2018. http://www.stat.go.jp/data/jinsui/2018np/index.html. Accessed 15th May 2021.

8. Immunization Schedule Recommended by the Japan Pediatric Society. Japan Pediatric Society. http://www.jpeds.or.jp. Accessed 1st Sep 2021.

9. Bonilla FA, Khan DA, Ballas ZK, Chinen J, Frank MM, Hsu JT, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015;136(5):1186–205.e1-78.

10. Gholam C, Grigoriadou S, Gilmour KC, Gaspar HB. Familial haemophagocytic lymphohistiocytosis: advances in the genetic basis, diagnosis and management. Clin Exp Immunol. 2011;163(3):271–83.

11. Principi N, Esposito S. Vaccine use in primary immunodeficiency disorders. Vaccine. 2014;32(30):3725–31.

12. Fekvand S, Yazdani R, Olbrich P, Genery A, Rosenzweig SD, Condino-Neto A, et al. Primary immunodeficiency diseases and Bacillus Calmette-Guérin (BCG)-vaccine-derived complications: a systematic review. J Allergy Clin Immunol In Practice. 2020;8(4):1371–86.

13. Tsilifis C, Freeman AF, Genery AR. STAT3 Hyper-IgE syndrome—an update and unanswered questions. J. Clin. Immunol. 2021 May 1. https://doi.org/10.1007/s10875-021-01051-1, Online ahead of print.

14. Notarangelo L, Casanova J-L, Fischer A, Puck J, Rosen F, Seger R, et al. Primary immunodeficiency diseases: an update. J Allergy Clin Immunol. 2004;114(3):677–87.

15. Migita K, Izumi Y, Jiuchi Y, Iwanaga N, Kawahara C, Agematsu K, et al. Familial Mediterranean fever is no longer a rare disease in Japan. Arthritis Res Ther. 2016;18:175.

16. Nakamura Y. Nationwide Epidemiological Survey Manual of Patients with Intractable Diseases, 3rd ed. Research Committee on Epidemiology of Intractable Disease; 2017. http://www.jichi.ac.jp/dhp/nanbyou/manual_2017.pdf. Accessed 15th May 2021.

17. Kobrynski L, Powell RW, Bowen S. Prevalence and morbidity of primary immunodeficiency diseases, United States 2001–2007. J Clin Immunol. 2014;34(8):954–61.

18. Rhim JW, Kim KH, Kim DS, Kim BS, Kim JS, Kim CH, et al. Prevalence of primary immunodeficiency in Korea. J Korean Med Sci. 2012;27(7):788–93.

19. Rosenberg E, Dent PB, Denburg JA. Primary immune deficiencies in the adult: a previously underrecognized common condition. J Allergy Clin Immunol In Pract. 2016;4(6):1101–7.

20. Abolhassani H, Azizi G, Sharifi L, Yazdani R, Mohsenzadegan M, Delavari S, et al. Global systematic review of primary immunodeficiency registries. Expert Rev Clin Immunol. 2020;16(7):717–32.

21. Mahlaoui N, Picard C, Bach P, Costes L, Courteille V, Ranohavimirany A, et al. Genetic diagnosis of primary immunodeficiencies: a survey of the French national registry. J Allergy Clin Immunol. 2019;143(4):1646-9.e10.

22. Kallinich T, Gattorno M, Grattan CE, de Koning HD, Traidl-Hoffmann C, Feist E, et al. Unexplained recurrent fever: is it autoinflammation the explanation? Allergy. 2013;68(3):285–96.

23. Frileauf K, Krüger R, Steiner S, Hanitsch LG, Büchel S, Wahn V, et al. A pathogenic missense variant in NFKB1 causes common variable immunodeficiency due to detrimental protein damage. Front Immunol. 2021;12(1327).

24. Gathmann B, Grimbach B, Beuté J, Dudoit Y, Mahlaoui N, Fischer A, et al. The European Internet-based patient and research database for primary immunodeficiencies: results 2006–2008. Clin Exp Immunol. 2009;157(Suppl 1):3–11.

25. Boyle JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. J Clin Immunol. 2007;27(5):497–502.

26. Sarmento JD, Villada F, Orrego JC, Franco JL, Trujillo-Vargas CM. Adverse events following immunization in patients with primary immunodeficiencies. Vaccine. 2016;34(13):1611–6.

27. Sohani M, Habibi S, Delavari S, Shahkarami S, Yazdani R, Shirmast P, et al. Evaluation of patients with primary immunodeficiency associated with Bacille Calmette-Guérin (BCG)-vaccine-derived complications. Allergol Immunopathol (Madr). 2020;48(6):729–37.

28. Marciano BE, Huang CY, Joshi G, Rezaei N, Carvalho BC, Allwood Z, et al. BCG vaccination in patients with severe combined immune deficiency — a systematic review and meta-analysis. J Allergy Clin Immunol. 2021 May 1. https://doi.org/10.1007/s10875-021-01051-1. Online ahead of print.
immunodeficiency: complications, risks, and vaccination policies. J Allergy Clin Immunol. 2014;133(4):1134–41.

29. Colditz GA, Brewer TF, Berkey CS, Wilson ME, Burdick E, Fineberg HV, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. JAMA. 1994;271(9):698–702.

30. Ohmori M, Ishikawa N, Yoshiyama T, Uchimura K, Aoki M, Mori T. Current epidemiological trend of tuberculosis in Japan. Int J Tuberc Lung Dis. 2002;6(5):415–23.

31. Hagiya H, Koyama T, Zamami Y, Minato Y, Tatebe Y, Mikami N, et al. Trends in incidence and mortality of tuberculosis in Japan: a population-based study, 1997–2016. Epidemiol Infect. 2018;147:e38.

32. Puck JM. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia. Immunol Rev. 2019;287(1):241–52.

33. Rechavi E, Lev A, Simon AJ, Stauber T, Daas S, Saraf-Levy T, et al. First year of Israeli newborn screening for severe combined immunodeficiency-clinical achievements and insights. Front Immunol. 2017:8:1448.

34. Argudo-Ramírez A, Martín-Nalda A, Marín-Soria JL, López-Galera RM, Pajares-García S, González de Aledo-Castillo JM, et al. First universal newborn screening program for severe combined immunodeficiency in Europe. Two-Years’ Experience in Catalonia (Spain). Front Immunol. 2019;10:2406.

35. Muramatsu H, Kojima D, Okuno Y, Kataoka S, Nakajima Y, Ito T, et al. Combination of TREC measurement and next-generation sequencing in newborn screening for severe combined immunodeficiency: a pilot program in Japan. Blood. 2018;132(Supplement 1):3717.

36. Collins CJ, Yi F, Dayuha R, Whiteaker JR, Ochs HD, Freeman A, et al. Multiplexed proteomic analysis for diagnosis and screening of five primary immunodeficiency disorders from dried blood spots. Front Immunol. 2020;11(464).

37. Boisson-Dupuis S, Bustamante J, El-Baghdadi J, Camcioglu Y, Parvaneh N, El Azbaoui S, et al. Inherited and acquired immunodeficiencies underlying tuberculosis in childhood. Immunol Rev. 2015;264(1):103–20.

38. Kulkarni M, Desai M, Gupta M, Dalvi A, Taur P, Terrance A, et al. Clinical, immunological, and molecular findings of patients with p47(phox) defect chronic granulomatous disease (CGD) in Indian Families. J Clin Immunol. 2016;36(8):774–84.

39. Toubiana J, Okada S, Hiller J, Oleastro M, Lagos Gomez M, Aldave Becerra JC, et al. Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype. Blood. 2016;127(25):3154.

40. Lim CK, Abolhassani H, Appelberg SK, Sundin M, Hammarström L. IL2RG hypomorphic mutation: identification of a novel pathogenic mutation in exon 8 and a review of the literature. Allergy Asthma Clin Immunol. 2019;15:2.

41. Shearer WT, Fleisher TA, Buckley RH, Ballas Z, Ballow M, Blaese RM, et al. Recommendations for live viral and bacterial vaccines in immunodeficient patients and their close contacts. J Allergy Clin Immunol. 2014;133(4):961–6.

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