

Prevention of Infectious Diseases due to Immunosuppression and Vaccinations in Asian Patients with Inflammatory Bowel Disease

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Keywords

Immunization coverage · Immunocompromise · Inflammatory bowel disease · Live vaccine · Vaccination

Abstract

Background: Inflammatory bowel disease (IBD) patients with immunocompromise have a high risk of developing complications related to viral infections. Western countries were the first to formulate vaccine guideline. Asian countries developed their national and international vaccine guidelines a little later in order to reduce the risk of mortality from viral infections. However, no studies to date have examined the differences in vaccinations that prevail among Asian countries. **Summary:** This review summarizes the vaccination status and schedules in various Asian countries for immunocompromised IBD patients. Vaccination rates, regardless of the specific vaccine, were high in Japan, South Korea, and China and low in India and the Philippines. Vaccine schedules differed by country, and outbreaks of measles and rubella were seen due to low vaccination rates in Southeast

Asia and South Asia. Live vaccines cannot be administered during immunosuppressive treatment. Infection with measles, mumps, and varicella during immunosuppressive therapy carries a high risk of mortality, and thus confirmation of immunization status is recommended as soon as IBD is diagnosed and, when possible, live vaccines should be administered before the initiation of immunosuppressive treatment. In patients seronegative for hepatitis B, administration of the hepatitis B vaccine is also recommended. **Key Messages:** Physicians, while considering severity of outbreaks, should understand the differences in vaccination status that exist among the various Asian countries and regions.

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Introduction

Inflammatory bowel disease (IBD) causes chronic inflammation in the gastrointestinal tract, which is often difficult to treat, as the etiology is unknown. However, the pathology is thought to be related to an exaggerated im-

immune response. In the past 20 years, treatment for IBD has advanced greatly, and many new therapeutic agents have been developed. Many of these therapies suppress the immune response, and the resultant increase in incidence and severity of infections associated with the use of these medications is a matter of concern. One approach to address these concerns is appropriate immunization for vaccine-preventable diseases (VPD). Vaccines may be inactivated or live, and live vaccines are contraindicated during immunosuppressive therapy. Once immunosuppressive treatment is initiated, live vaccines can no longer be given, and treatment must be halted in some cases to allow vaccination.

Japan experienced a measles outbreak in 2007, and 2018 and a rubella outbreak in 2013, mostly among college students, raising societal concerns. Vaccine schedules, immunization rates, and the endemic status of infections vary by country and region, and so understanding the current situation in each country and region is important. IBD patients have a higher risk of VPD compared with the general population; therefore, childhood vaccine records and seropositivity status must be determined in each patient as soon as possible after IBD is diagnosed [1].

In this article, we evaluate measured titers of rubella, measles, varicella, and mumps viruses in IBD patients in Japan compared with previously reported values and discuss the differences in vaccine guidelines and coverage in various Asian countries and the management of IBD patients.

Immunization Coverage in Japan

Live Vaccines

Of the VPD, vaccines for tuberculosis, rubella, measles, varicella, and mumps are live vaccines, and the timing of vaccination is important in relation to immunosuppressive therapy for IBD. Past medical history of infections and immunization history should be obtained at the first visit, and if the patient does not have a history of infection or vaccination, 2 doses of a live vaccine should be administered [2, 3]. However, according to a study in Japan, about 40% of patients did not remember whether they had previously contracted measles, mumps, rubella (MMR), or varicella, and a third of patients are unsure of their vaccination status, highlighting the insufficiency of history alone and the importance of measuring titer levels [4]. In a study on the seropositivity rate of rubella, measles, varicella, and

mumps in Japan, Naganuma et al. [4] reported in 2013 that the seronegativity rate of IBD patients (defined as anti-rubella Immunoglobulin G (IgG) <10 IU/mL, anti-measles IgG <16 IU/mL, anti-mumps/varicella zoster IgG <4 IU/mL) for measles, mumps, rubella, and varicella were 34, 37, 30, and 5% respectively. There are various methods for measuring titers, including the neutralization method, enzyme immunoassay (EIA), hemagglutination inhibition, enzyme-linked fluorescent immunoassay, latex turbidimetric immunoassay, and chemiluminescent EIA, depending on the target antibody. For the IBD patients at our institution, we measured specific antibody levels for MMR, and varicella using EIA, which has a high sensitivity and high versatility. Measles titers were measured in 246 patients (168 ulcerative colitis [UC] cases, 74 Crohn's disease [CD] cases, 4 Bechet's disease [BD] cases), mumps titers in 193 patients (136 UC cases, 54 CD cases, 3 BD cases), rubella titers in 247 patients (168 UC cases, 75 CD cases, 4 BD cases), and varicella in 254 patients (173 UC cases, 76 CD cases, 5 BD cases).

In the present study, seronegativity rates for measles, mumps, rubella, and varicella were 32.5, 37.1, 32.0, and 5.1%, respectively, similar to the rates reported by Naganuma et al. [5, 6]. In addition, in a study on healthcare workers in major hospitals in Japan, in which seronegativity was defined as IgG <4 IU/mL by the EIA method, the reported seronegativity rates were 7.4% for measles, 16.1% for mumps, 8.4% for rubella, and 0.8% for varicella [4, 7–11], and when we computed the seronegativity rates of our IBD patients using the same cutoff value, the rate was 3.0% for measles, 37.1% for mumps, 14.1% for rubella, and 5.1% for varicella, indicating higher seronegativity rates for healthcare workers in the general population were for IBD patients, with the exception of measles. Although the difference in assay methods prohibits an accurate comparison, seronegativity rates in Asian countries and 2 European countries are shown in Table 1. In Japan, universities and professional schools are increasingly conducting vaccination programs, and so healthcare workers in Japan likely had a lower seronegativity rate compared with those in our study. If possible, immunization history should be obtained at the time of the IBD diagnosis, and in cases without a history of infection and with inadequate vaccination, the titers for MMR, and varicella should be measured and all patients should be vaccinated [12]. However, for now, not all vaccines are covered by health insurance in Japan; thus, vaccination in all cases is practically difficult and infeasible. Never-

Table 1. Seronegative rates of antibodies against MMR and varicella

Population	Japan		South Korea general	China general	Philippines general	India general	Spain general	Germany general
	general	IBD (our group)						
Measles	7.4	3.0	18.5	–	–	9.5	6.3	8.5
Mumps	16.1	37.1	–	–	–	32.0	9.2	19.7
Rubella	8.4	14.1	–	9.8* 32.4	15.4	16.6	2.5	9.9
Varicella	5.1	5.1	–	–	–	25.8	1.8	3.1

Numbers in the table indicate prevalence as a percentage.

* Chinese woman, Hong Kong.

MMR, measles, mumps, rubella; IBD, inflammatory bowel disease.

theless, knowledge of the different vaccination rates by region and age is beneficial for the diagnosis of infectious diseases.

Measles

Although 88% of countries throughout the world by 2005 had a vaccine program that included 2 doses of the measles vaccine, Japan did not begin 2-dose administration of the vaccine until 2006. The antibody titers of vaccinated individuals increase through repeated contact with the virus, which is known as booster effect, but given the decrease in outbreaks of measles and rubella, antibody levels may decrease after a single administration. Indeed, in 2008, a total of 11,013 cases of measles were reported in Japan, and patient age was mostly in their teens to 30s [13]. Our study on IBD patients showed a 30% seronegativity rate in those aged 10–40 years who had received only 1 dose, but the study did not include patients less than 10 years of age or those who have received 2 doses; it should be noted that their antibody level may decrease further. An increase in measles infection rate and mortality rate in IBD patients has not been reported anywhere in the world. However, a study in France found that none of the 36 measles patients who were admitted to the intensive care unit were vaccinated, and all 3 of those patients (8.3%) who had been undergoing immunosuppressive therapy after renal transplant died after developing acute respiratory distress syndrome [14]. In addition, the mortality rate from measles in immunocompromised patients was high at 20–83.3%. The cause of death was either pneumonia or encephalitis as a complication of measles [15–17]. Also, measles re-infection

has been reported in a rheumatoid arthritis patient receiving an anti-tumor necrosis factor (TNF)- α agent in Japan [15, 18], and the relationship between immunosuppressive treatments/anti-TNF- α agents and severe measles should be examined. It remains unclear whether live vaccines should be administered during treatment with anti-integrin antibodies such as vedolizumab and other biologics. A case has been reported of the MMR vaccine administered during vedolizumab therapy in a patient with ileocolonic CD, in whom antibodies were detected 8 weeks after vaccination and no side effects were seen at the 3-month follow up [19], but further examination of vaccination during biologic treatment other than anti-TNF- α antibodies is necessary.

Mumps

In developed countries, individuals are vaccinated against rubella, measles, and mumps in early childhood, before the onset of IBD. Thus, the risk of these infections is considered low [20]. In Japan however, although the MMR vaccine was introduced in 1989, the incidence of aseptic meningitis caused by the mumps vaccine was unexpectedly high, so MMR vaccination was stopped in 1993. In 2006, the routine administration of measles and rubella vaccine was introduced, but not the administration of mumps vaccine; as such, many individuals are seronegative for mumps [21]. In IBD patients in Japan aged 10–60 years, the seronegativity rate was around 40% (Fig. 1). In other Asian countries aside from South Korea, mumps vaccination is not routinely administered, and the seronegativity rate is suspected to be higher than in Western countries. In terms of the prog-

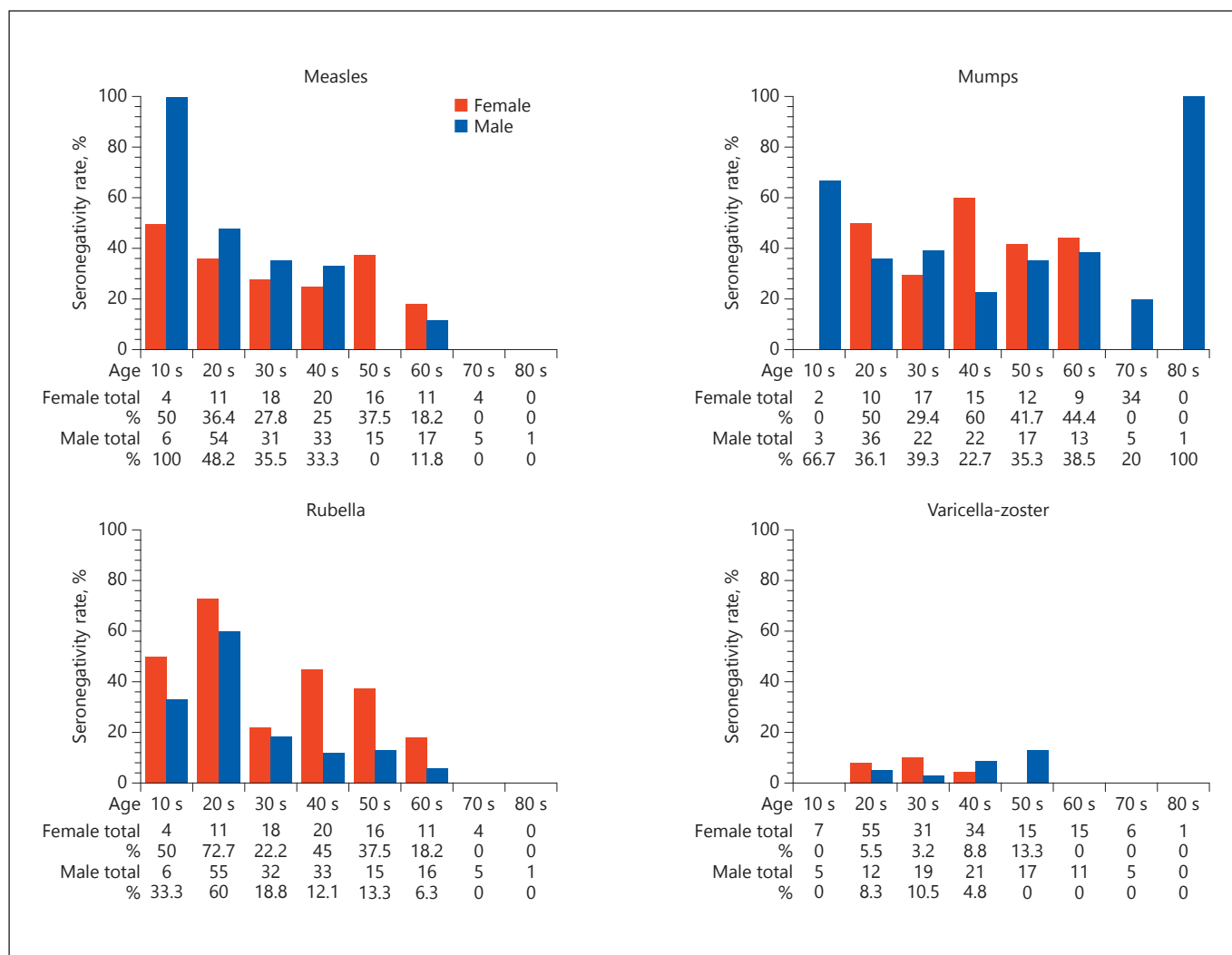


Fig. 1. The seronegativity rates against measles, mumps, rubella, and varicella-zoster viruses in Japanese patients.

nosis of patients who contract mumps during immunosuppressive therapy, there have been no case reports and its effect on disease severity remains unclear. However, it should be noted that cases of fatal mumps meningitis after hematopoietic stem cell transplantation for severe immunodeficiency have been reported in the United States and the United Kingdom [22].

Rubella

In Japan, vaccination against rubella became mandatory for 12-year-old girls in 1977, and in 1994 changed to 12–90-month-old boys and girls and 12–15-year-old unvaccinated boys and girls (until 2003). This was yet

again changed from mandatory to recommended, and consequently many children were not vaccinated. Indeed, in Japanese IBD patients, women aged 40 years and above who did not receive routine vaccination, and men and women in their 20s who were born before 2003 had high seronegativity rates (Fig. 1). Under these conditions, in 2013, there was a mumps outbreak of 14,359 cases, and since many of the cases were women in their 20s, congenital rubella syndrome was noted in as many as 45 patients [23, 24]. Moreover, even in the vaccinated generation, if only a single dose were given without a booster effect, the individual may later become seronegative. With the high seronegativity rate among women of reproductive age, vaccination should be recommended, given the risk of congenital rubella syndrome. No

reports of rubella infection in IBD patients or patients undergoing immunosuppressive treatment have been made. Thus, the prognosis in patients receiving immunosuppressive therapy or immunodeficient patients is unclear. A case has been reported in Australia of live mumps vaccine administration in an immunocompromised patient who had been receiving methotrexate and 6-mercaptopurine for acute lymphoid leukemia treatment for 3 months and who developed acute arthritis and arthralgia 1 month after vaccination, with seroconversion of anti-mumps Immunoglobulin M [25]. Administration of the mumps vaccine should be avoided during immunosuppressive therapy, as with other live vaccines.

Varicella

In Japan, the varicella vaccine became part of the routine vaccine schedule in October 2014, and the number of patients in the vaccinated age group has since decreased. Of 20 IBD patients who contracted varicella while immunocompromised, 25% (5/20 cases) were reported to have died [26]. IBD patients who are immunocompromised due to treatment often cannot receive the varicella live vaccine. Improving herd immunity to prevent the spread of varicella zoster virus is effective to protect these patients from the threat of varicella zoster virus. In a study conducted at our institution, there was a wide age range among seronegative individuals, from age 20–50 years (Fig. 1), and of the 13 seronegative patients, 5 had received immunosuppressive treatment (adalimumab 3 cases, tacrolimus 1 case, thiopurine 1 case), highlighting the importance of improving herd immunity [27]. A case has been reported in the United States of a CD patient who contracted varicella after initiating infliximab therapy, developed fulminant hepatitis and disseminated intravascular coagulation, and eventually died [28]. Notably, another study reported a 20% mortality rate among patients who developed disseminated varicella while immunocompromised [29]. As for herpes zoster, an increase in incidence in IBD patients treated with steroids, immunomodulating agents, or anti-TNF- α agents has been reported, with a hazard ratio of 3.7 (95% CI 1.8–7.5) for patients treated with 2 or more agents [30]. An increase in herpes zoster risk is also known with Janus kinase inhibitor use, and its risk has been reported to be particularly high in East Asia [31, 32]. However, there have also been reports of safe vac-

ination during anti-TNF- α agent use [33], and inactivated vaccines are also under development. Thus, immunization during immunosuppressive therapy may become possible in the future.

Bacille Calmette-Guérin

The prevalence of tuberculosis in Japan was 17 per 100,000 population as of 2015, which was lower than that in other Asian countries, such as 322 in the Philippines, 217 in India, 80 in South Korea, and 67 in China, yet was still higher than the low-prevalence standard of 10, as is the case in many developed countries [34]. Therefore, in many Asian countries including Japan, Bacille Calmette-Guérin (BCG) is generally administered during infancy. BCG is preventive against severe miliary and pulmonary tuberculosis [35], but its efficacy in preventing tuberculosis in immunocompromised patients is unclear. Since the live pathogen remains in the body for several months after vaccination [36], immunization of IBD patients who may undergo immunosuppressive therapy is not recommended. In the United Kingdom, an infant born to a mother with severe CD who continued infliximab therapy during pregnancy developed disseminated mycobacterial infection after receiving BCG at 3 months of age and died. Thus, care must be taken in deciding when to administer BCG in a patient with a mother receiving anti-TNF- α antibodies [37]. In addition, BCG may lead to a false positive tuberculin skin test, so the interferon- γ release assay (IGRA; QuantiFERON-TB Gold In-Tube and T-SPOT.TB) is widely used for diagnosis of latent tuberculosis in countries and regions where BCG is administered [38]. However, IGRA may become negative when performed during steroid or immunosuppressive therapy, so results must be evaluated cautiously [39]. Particularly in Asia, where tuberculosis is endemic and the risk of new infection is higher than that in Western countries, if an IBD patient undergoing immunosuppressive treatment such as anti-TNF- α antibody develops respiratory symptoms, even in the absence of history or radiographic findings of tuberculosis and with a negative tuberculin skin test or IGRA, tuberculosis must be excluded [40].

Inactivated Vaccines

Inactivated vaccines can be administered, regardless of immunosuppressive treatment [2]. Hepatitis B virus (HBV), the prevalence of which differs between Japan

and Western countries will be discussed in detail below. However, the prevalence of influenza virus, *Streptococcus pneumoniae*, rotavirus, *Neisseria meningitidis*, tetanus, diphtheria, pertussis, human papillomavirus, and hepatitis A in Japan is similar to that in Europe and the United States. We therefore do not address these infections in this article.

Hepatitis B Virus

According to the World Health Organization (WHO), 257 million people are infected with HBV worldwide, about 900,000 people die of HBV-related diseases annually (including cirrhosis and hepatocellular carcinoma), and high-prevalence countries where the HBV carrier rate in the population is 6% or higher are concentrated in the Pan Pacific region including Asia, and Africa [41, 42]. Although the HBV prevalence in Japan is relatively low at 1%, the rates in China, Vietnam, and Mongolia are very high at 5–11%. Thus, it is extremely important to distinguish this situation from that prevailing in Western countries [43]. With the goal of controlling HBV infection worldwide, the WHO released a recommendation in 1991 for worldwide universal vaccination against HBV for all children. As a result, 184 countries introduced HBV vaccination for young children by 2014 [44]. In Taiwan, in the 10 years after universal vaccination was introduced, the hepatitis B surface antigen positivity rate in 6-year-old children decreased from 10.5 to 1.7% [45]. In China also, where universal vaccination was introduced early, after 14 years of universal vaccination, the hepatitis B surface antigen positivity rate successfully decreased from 19.86 to 4.91% [46]. As of 2007, among developed countries, only 7 European countries (Denmark, Finland, Iceland, the Netherlands, Norway, Sweden, and the United Kingdom) and Japan did not follow the WHO recommendations but implemented selective vaccination, in which only children born to HBV carriers are immunized [47]. The hepatitis B surface antibody positivity rate in specimens obtained from the lifestyle-related disease health checkup for 10-year-olds conducted from 2013 to 2015 was 1.0–1.5%. Japan started routine HBV vaccination in 2016, which included universal vaccination in addition to selective vaccination [48]. However, because the HBV serum antibody seronegativity rate is high at 75–80% [49], in contrast to European countries and the United States, HBV vaccination of all IBD patients is generally desirable.

Regional Differences within Asia

East Asia

As discussed above, this region characteristically has a high HBV infection rate [50]. China and South Korea have a higher vaccination rate than Japan (Table 2), and the number of HBV-infected individuals decreased dramatically after the introduction of universal HBV vaccination [43]. Vaccination against *Haemophilus influenzae* type B (Hib) is optional in China, and the immunization rate is unknown, but the current Hib immunization rate is greater than 95% in Japan and South Korea (Table 2). The Hib vaccine became available in Japan on December 19, 2008 and was initially elective. Routine vaccination was initiated on April 1, 2013.

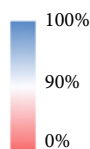
Southeast Asia

Japanese encephalitis is among the highly prevalent diseases in this region. The Japanese encephalitis vaccine was introduced early in Japan, Taiwan, South Korea, and Thailand, and therefore, the disease has been controlled in these countries. However, in some countries such as the Philippines, the vaccine has not been introduced despite some of these countries being endemic areas (Tables 2, 3) [51]. Severe cases of Japanese encephalitis in immunocompromised patients have not been reported, but vaccination prior to travel to an endemic area is recommended in guidelines [52, 53], and administration of the vaccine should therefore be considered in endemic countries such as the Philippines. For measles also, infants in the Philippines have been receiving 1 dose of the measles-containing vaccine (MCV) as part of their routine vaccination program, but since 2010, 2 doses of the MMR vaccine are included in their routine vaccination program. However, as of 2013, the immunization rate of the initial MCV dose was 87.0%, and that of the second MMR was very low at 54%. Consequently, measles has not been eliminated (Table 2). From 2011 to 2014, supplementary immunization activities of the MCV have been conducted, yet the virus continues to spread in this region.

South Asia

The immunization program in India is still in the development phase, and the vaccination rate of the routine vaccines – BCG, diphtheria-tetanus-pertussis, oral poliomyelitis, hepatitis B, and measles vaccines – is at 81% and the immunization rates of elective vaccines are even

Table 2. Percentage of target population vaccinated by antigen in various Asian countries



Vaccine	Country name	2016	2014	2012	2010	2008	2006	2004	2002	2000
BCG vaccine	Japan	98	93	95	99	90			96	96
	South Korea	97	99	99	96	96	98	93	89	73
	China	99	99	99	99	97	92	99	98	85
	Philippines	76	79	89	83	93	91	91	85	81
	India	89		90	89	86	86	80	75	74
1st DTP vaccine	Japan	99	99	99	99	99	99	99	99	99
	South Korea	98	99	99	96	95	98	95	97	97
	China	99	99	99	99	99	94	99	98	
	Philippines	87	78	91	81	94	90	92	84	81
	India	91		89	86	81	81	77	75	74
Hepatitis B vaccine	Japan									
	South Korea	93	92		95	94	98	96	92	93
	China	96	94	96	92	91	88	76		
	Philippines	59	51	39	37	21				
	India	47		30		3				
Haemophilus influenzae type B vaccine	Japan	99								
	South Korea	98	97							
	China									
	Philippines	91	96	88	1					
	India	80								
Oral polio virus (OPV) vaccine or inactivated PV (IPV) vaccine	Japan	99	99	99	98	95	95	97	99	99
	South Korea	98	99	99	95	92	98	90	99	99
	China	99	99	99	99	99	94	99	98	90
	Philippines	72	77	88	78	91	88	85	77	75
	India	86		79	76	69	66	58	58	57
Japanese encephalitis vaccine	Japan	99	99	99	22	4				
	South Korea	97	99	99	89	84	88			
	China	99	99	99	99					
	Philippines									
	India	59		65	37					
1st measles vaccine	Japan	96	98	96	94	97	97	99	99	96
	South Korea	98	99	99	98	92	99	99	97	95
	China	99	99	99	99		93	98	98	98
	Philippines	80	79	87	80	92	92	92	82	80
	India	88		83	82	72	69	64	56	56
Pneumococcal conjugate vaccine	Japan	99								
	South Korea	99								
	China									
	Philippines	64	42							
	India									

lower. In terms of infection susceptibility, no studies have compared seroprevalence between countries. However, in a cross-sectional study of 790 students in India, the serological susceptibility of measles, mumps, rubella, and varicella was 9.5, 32.0, 16.6, and 25.8% respectively

(Table 1) [54]. When considering the addition of immunosuppressive therapy, some cases require consideration of administration of live vaccines, as is the case in Japan.

Table 3. Vaccine schedule in various Asian countries

	Japan	South Korea	China	Philippines	India
BCG vaccine	1 years	Birth-1 months	Birth	Birth	Birth
Tetanus and diphtheria toxoid	11 years	11–12 years	6 years	6, 10 years	10, 16 years ¹
DTP vaccine	2, 3, 4 months, 1 years ²	2, 4, 6, 15–18 months, 4–6 years 11–12 years ²	3, 4, 5 months ²	6, 10, 14 weeks ³	6, 10, 14 weeks, 16–24 months, 5 years ³
Hepatitis B vaccine	–	Birth 1, 6 months	Birth 1, 6 months	Birth, 6, 10, 14 weeks	Birth, 6, 10, 14 weeks
Oral polio vaccine (or IPV)	3, 4.5, 6, 18 months (inactivated)	2, 4, 6 months 4–6 years (inactivated)	3, 4 months, 4 years	6, 10, 14 weeks	Birth 6, 10, 14 weeks 16–24 months
Haemophilus influenzae type b vaccine	2, 3, 4 months 1 years	2, 4, 6, 12–15 months	–	6, 10, 14 weeks	6, 10, 14 weeks
Japanese encephalitis live vaccine (or inactivated)	36, 37 months 4, 9 years (inactivated)	12–23 months, 6, 12 years (inactivated)	8 months 2 years	–	9, 16–24 months ⁴
Measles vaccine	–	–	–	9 months	9–12, 16–24 months
Measles mumps and rubella vaccine	1, 5 years ⁵	12–15 months, 4–6 years	8 months ⁵	6, 10, 12 months	9 months – 2 years ^{4, 5}
Pneumococcal conjugate vaccine	2, 3, 4 months, 1 years	2, 4, 6, 12–15 months	–	6, 10, 14 weeks ⁴	Up to 1 years ⁴
Pneumococcal polysaccharide vaccine	≥65 years	≥65 years	–	≥60 years	–
Varicella vaccine	12, 18 months	12–15 months	–	12–15 months, 4–6 years	–

¹ Only tetanus toxoid; ² diphtheria and tetanus toxoid with acellular pertussis vaccine (DTaP); ³ diphtheria and tetanus toxoid with whole cell pertussis vaccine (DTwP); ⁴ Not entire country; ⁵ Measles and rubella vaccine.

BCG, Bacille Calmette-Guerin; DTP, diphtheria and tetanus toxoid with pertussis; IPV, inactivated polio vaccine.

Conclusions

Individuals seronegative for VPD were found in various Asian countries, and early vaccination is desirable as soon as IBD is diagnosed for patients with diseases that have a high risk of becoming severe during immunosuppressive therapy.

Given the differences among the various Asian countries and regions in vaccination schedules based on age and sex, as well as in vaccination rates, seronegativity rates, and severity of outbreaks, and given the high prevalence of tuberculosis and HBV compared with European countries and the United States, immunization guidelines for IBD patients should be established that reflect the situation in each country.

Ethics Statement

This study was approved by the Research Ethics Committee of the Kitasato Institute Hospital.

Disclosure Statement

T.K. and T.H. received lecture fees from AbbVie Inc., Kyorin Pharmaceutical Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Co., Ltd., EA Pharma Co., Ltd., JIMRO Co., Ltd., and ZERIA Pharmaceutical Co., Ltd. T.K. received lecture fees from Janssen, Ajinomoto Pharma, Astellas, Mochida Pharmaceutical, Asahi Kasei Medical, Takeda Pharmaceutical, Gilead Sciences, Celltrion, Nippon Kayaku, Alfresa Pharma. T.K. received consulting fees from Janssen, Pfizer, Kyorin Pharmaceutical, Mochida Pharmaceutical, Takeda Pharmaceutical, Eli Lilly, Ferring Pharmaceuticals, Nippon Kayaku, Thermo Scientific, Covidien, Alfresa Pharma. (No funding was received for this work from any of these organizations.)

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