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Immunization in the Asia-Pacific region

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Theodore F. Tsai
Hans Bock
Zhi Yi Xu

The Asia-Pacific region, spanning one third of the globe's circumference and containing more than half of the world's population, is highly diverse, culturally, politically, economically, and in other dimensions that impact vaccine development and implementation. The region includes China and Japan, the second and third largest national economies globally but, at the same time, also encompasses 17 Global Alliance for Vaccines and Immunization (GAVI)-eligible countries.[1] In a region this diverse and experiencing breakneck economic development, all stages of vaccine innovation, production, and consumption are represented, along with paradoxical overlaps of reliance on aid for vaccination programs in countries that also are vaccine exporters. While India, Indonesia, the Philippines, and Vietnam are GAVI-eligible countries, they produce bacille Calmette-Guérin vaccine, oral polio vaccine, and measles vaccine for UNICEF, and India is a growing source for diphtheria-tetanus-pertussis–*Haemophilus influenzae* type b (DTP-Hib)–containing combination vaccines for export and the supplier of a novel meningococcal group A conjugate vaccine for Africa. China, meanwhile, has exported a novel live attenuated hepatitis A vaccine to India, pandemic H1N1 vaccine to Chile, and seasonal influenza, hepatitis B, Japanese encephalitis (JE), rabies, and meningococcal and typhoid polysaccharide vaccines to developing and developed countries.

The broad income range within countries results in large population segments that have sufficient means to pay for vaccines out-of-pocket. So, even among countries that otherwise qualify economically for GAVI funding (eg, India), substantial numbers of families can avail themselves of vaccines not covered by the national Expanded Programme on Immunization (EPI), resulting in a two-tiered system of vaccination, paralleling the public-private dichotomy of health care delivery in general. Practitioners serving these and expatriate families generally follow current US, European, or Australian vaccine recommendations or some modification of those schedules.

Perceptions of the value of vaccines and their risks also range widely, regionally and within individual countries, from largely enthusiastic acceptance and even demand for additional routine vaccinations (eg, for JE vaccine in southern and Southeast Asia) to a degree of skepticism equal to, if not more deeply and widely held, than antivaccine sentiment in Europe and the United States. Within the last 20 years, Japan discontinued all production and use of combination measles, mumps, rubella vaccine and routine childhood influenza and JE vaccination programs, largely owing to vaccine-related adverse events or public perception of their occurrence. Similarly, in Korea, parents have objected to routine JE vaccination because more cases of vaccine-related acute disseminated encephalopathy were suspected than naturally acquired cases of JE.[2] With the global spread of information, the thimerosal content of childhood vaccines has been as active a parental concern among middle-class families in developing countries as elsewhere.[3]

From this mosaic, we have tried to describe some common themes, highlighting representative approaches and unique issues that hold a wider interest. Because they are covered elsewhere in this volume, we have not reviewed specific vaccines of regional concern (eg, pandemic influenza and JE vaccines) or vaccination topics common to developing countries (eg, initiatives surrounding injection safety, hepatitis B, measles and neonatal tetanus elimination, and polio eradication). We concentrate, instead, on other aspects of vaccine development and implementation, organized by the steps of vaccine development, approval, production, recommendation, and delivery. We also restrict our focus to childhood vaccines and vaccination and to selected countries in the region.

Vaccines developed in and for the Asia-Pacific region

Japan is acknowledged as the innovator of several vaccines now used internationally, including acellular pertussis and live attenuated varicella vaccines, but other novel vaccines have been developed by Japan, China, India, Australia, and Vietnam for region-specific needs (Table 69-1). These include vaccines for JE, hemorrhagic fever with renal syndrome (HFRS), Russian spring-summer encephalitis, Kyasanur Forest disease, cholera, severe acute respiratory syndrome (or SARS), and Q fever. In addition, novel attenuated strains of measles, mumps, hepatitis A, rotavirus, and intranasally delivered pandemic H1N1 virus have been derived for products distributed principally within the region. Additional novel vaccines for hepatitis E and enterovirus 71 (EV71) are in development, with potential for broader use internationally, an indicator of the region's transition as a provider of fill-finish and manufacturing capacity to a full-fledged participant in biotechnology research and clinical development.

JE vaccines

Five JE vaccines have been developed and licensed in Asian countries. The widely used first-generation inactivated suckling mouse brain (SMB)-derived vaccine is being replaced rapidly in economically disadvantaged countries by the Chinese developed and manufactured live attenuated vaccine (SA_{14}-14-2 strain) grown in primary baby hamster kidney (PHK) cells and in higher income countries with Vero cell–derived inactivated vaccines (licensed in Japan, China, the United States, Australia,

Table 69-1 Pediatric Immunization Recommendations by Antigen and Jurisdiction, Asia-Pacific Region, 2011*

Jurisdiction	BCG	HBV	DTP combinations	Hib	Polio	PCV/PnPS	Rota
Australia		B, 2, 3, 4, 12 mo; 10-13 y	DTaP, 2, 4, 6 mo; 4y dTaP, 15-17 y	2, 4, 6 mo, 1y	IPV, 2, 4, 6 mo; 4 y	2, 4, 6 mo *PS, 1.5-2 y*	2, 4, 6 mo
Bangladesh	B	6, 10, 14 wk	DTP-Hib-HBV, 6, 10, 14 wk TT, 15 y		OPV, 6, 10, 14, 38 wk		
Brunei Darussalam	B	B, 1, 6 mo	DTP-Hib, 2, 3, 4 mo DT, 5 y		OPV, 2, 3, 4 mo		
Cambodia	B	1-7 d	DTP-HBV, 6, 10, 14 wk		OPV, 6, 10, 14 wk		
China	B	B	DTP, 3, 4, 5m; 1.5-2 y; DT, 6 y		OPV, 2, 3, 4 mo; 4 y		
Democratic People's Republic of Korea	B	B	DTP-HBV, 6, 10, 14 wk TT, 3-4 y		OPV: 6,10,14w		
Hong Kong	B	B	DTaP-IPV, 2, 4, 6 mo, 1.5 y, Primary 1 dTaP, Primary 6			2,4,6m, 1y	
India	B	*6, 10, 14 wk* **B, 6, 10, 14 w**	DPT, 6, 10, 14 wk; 16-24 mo **(15-18 mo); 5 y** DT, 5 y	**6, 10, 14 wk; 15-18 mo**	B, OPV + **IPV**, 6, 10, 14 wk; 16-24 mo **(15-18 mo); 5 y**		
Indonesia	B	B	DTP-HBV, 2, 3, 4 mo; DT, 6 y **DTP, 2, 4, 6 mo; 1.5, 2, 5 y**	**2, 4, 6, 15-18 mo**	*OPV, B, 1, 2, 3 mo;* IPV, 2, 3, 4, 9 mo **IPV, 2, 4, 6 mo; 1.5-2, 5 y**	**2, 4, 6, 15-18 mo**	
Japan	4-5 mo	**B+, ×3**	DTP, 3, 4, 6 mo, 1.5 y	**3, 4, 6 mo, 1.5 y**	OPV, 7, 10 mo	**3, 4, 6 mo, 1.5 y**	
Korea	B-4 wk	B, 1, 6 mo	DTaP, 2, 4, 6 mo; 1.5-1.8, 4-6 y Td, 7-12 y		IPV, 2, 4, 6 mo; 4-6 y	**1, 2, 4, 12-15 mo**	
Lao People's Democratic Republic	B	B	DTP-Hib-HBV, 6, 10, 14 wk		OPV, 6, 10, 14 wk		
Malaysia	B	B, 2, 3, 5 mo	DTP-Hib, 2, 3, 5 mo DTP, 1.5 y DT, Primary 1 T, Form 3		OPV, 2, 3, 5 mo		
Mongolia	B	B	DTP-Hib-HBV, 2, 3, 4 mo DT, 7, 15 y		OPV, B, 2, 3, 4 mo		
Myanmar	6 wk	B, 6, 10, 14 wk	DTP, 6, 10, 14 wk		OPV, 6, 10, 14 wk		
Nepal	B		DTP-Hib-HBV, 6, 10, 14 wk		OPV, 6, 10, 14 wk		
New Zealand			DTaP-IPV-HBV-Hib, 6 wk, 3, 5 mo DTaP-IPV, 4 y dTap, 11 y	15 mo		6 wk, 3, 5, 15 mo	
Pakistan	B	B, 6, 10, 14 wk	DTP, 6,10,14w		OPV, B, 6, 10, 14 wk		

Antigens									
MCV-rubella	**Varicella**	**Men**	**JE**	**HPV**	**Influenza**	**Hep A**	**Typhoid**	**Rabies**	**HFRS**
MMR, 1, 4 y	1.5 y	C, 1 y	*1 y+, × 3; boosters every 3 y*	12-13 y		*1-2 y*			
M, 38 wk									
MMR, 1, 3 y									
9-11 mo			*SA_{14}-14-2, 10 mo*						
M or MMR, 8 mo; 1.5-2 y*		*A, 6, 9 mo; AC, 3, 6 y*	*SA_{14}-14-2, 8 mo, 2 y Vero inactivated, 8 mo × 2, 2, 6 y*			Live, 18 mo Inactivated, 1.5-2.5 y × 2			*16-60 y, × 3*
M: 9, 15m			*SA_{14}-14-2:1y*						
MMR: 1y, Primary1									
9-12 mo; **MMR, 15-18 mo, 5 y**			*SA_{14}-14-2, 1-12 y*				**2 y, every 3-4 y**		
M, 9 mo, 6 y **MMR, 15 mo, 5-7 y**	**12 mo +**				**6 mo +**	**24 mo+, × 2**	**24 mo + × 3**		
MR, 1, 5-6, 12-14, 17-18 y **Mumps, 1 y**	**1 y**		3-4 y, × 3, 9 y	**10 y+, × 3**	**6 mo+, × 2**	**16 y+, × 3**			
MMR, 12-15 mo; 4-6y	12-15 mo		1-2 y × 2; 2-3, 6, 12 y **SA_{14}-14-2, 1-2 y; 2-3, 6 y**		**6 mo +**	**1-2; 2-3 y**	PS, 2 y + Oral, 4-6 y × 3-4		10 y + × 2 + 1 booster
M, 9 mo									
MMR, 1 y, Primary 1 *M, 6 mo*			*9, 10 mo; 1.5, 4.5, 8, 11, 15 y*						
MMR, 9 mo, 2 y *R, 10-16 y*		*ACWY, 2-14 y*							
M, 9 mo, 1.5 y									
M, 9 mo			*SA_{14}-14-2, 12 mo*						
MMR, 15 mo, 4 y				12 y × 3					
M, 9 mo									

Table 69-1 Pediatric Immunization Recommendations by Antigen and Jurisdiction, Asia-Pacific Region, 2011*—cont'd

Jurisdiction	BCG	HBV	DTP combinations	Hib	Polio	PCV/PnPS	Rota
Papua New Guinea	B	B	DTPHibHBV: 1,2,3m		OPV, 4, 8, 12 wk		
Philippines	B	B, 1-6 mo × 2	DTP, 6, 10, 14 wk; *DTP-Hib-HBV, 6, 10 14 wk* **DTaP, 6, 10, 14 wk; 1-2, 4-6 y Tdap, 10-18 y**	6, 10, 14 wk; **1-5 y**	OPV, 6, 10, 14 wk **OPV/IPV, 6, 10, 14 wk; 1-2, 4-6 y**	**6-16 wk × 2; 14 w-2 y × 2**	**6-32 wk, 2 or 3**
Singapore	B	B, 1, 5-6 mo	DPT, 3, 4, 5 mo; 1.5 y DT, 10-11 y		OPV, 3, 4, 5 mo; 1.5, 6-7, 10-11 y	3, 4, 5 mo; 1-2 y	
Sri Lanka	B		DTP-Hib-HBV, 2, 4, 6 mo DTP, 18 mo DT, 5 y Td, 12 y		OPV, 2, 4, 6 mo; 1.5, 5 y		
Taiwan	B	2-5 d, 1, 6 mo	DTaP-Hib-IPV, 2, 4, 6 mo 1.5 y Tdap, Primary 1		Primary 1		
Thailand	B	B, 2, (4), 6 mo	DTP, 2, 4, 6 mo; 1.5, 4-6 y **DTaP, 2, 4, 6 mo; 1.5 y TdaP, 4-6, 11-12 y**	**2, 4, 6 mo; 1.5 y**	OPV, 2, 4, 6 mo; 1.5, 4-6 y **IPV, 2, 4, 6 mo; (1.5), 4-6 y**	**2, 4, (6) mo; 1-1.5 y**	**2, 4, 6 mo**
Vietnam	B	B-1, 1-2, 4-6, 15-18 mo; 4-6 y	DTP, 2, 3, 4, 15-18 mo	2, 3, 4, 6-9 mo	OPV, 2, 3, 4, 15-18 mo	PnPS, 2 + × 1	

aP, acellular pertussis; B, birth; BCG, bacille Calmette-Guérin; DTP, diphtheria, tetanus, pertussis; HBV, hepatitis B vaccine; Hep A, hepatitis A; Hib, *Haemophilus influenzae* type b; HPV, human papillomavirus vaccine; IPV, inactivated poliovirus vaccine; JE, Japanese encephalitis; M, measles; MCV, measles-containing vaccine; Men, meningococcal; MMR, measles, mumps, rubella; OPV, oral poliovirus vaccine; PCV, pneumococcal conjugate vaccine; PnPS, pneumococcal polysaccharide; R, rubella; Rota, rotavirus.
*Schedules recommended as of April 2011. Sources: surveys of local governments and academic societies. MMR or various combinations are used as replacement for M in different provinces depending on vaccine availability: Guangxi, MR at 8 and MMR at 18-24 mo; Hebei, MR at 8 moand MM (measles + mumps) at 18-24 mo; Zhejiang, M at 8 mo, MMR at 18-24 mo, and MR at 15 y; Shanghai, M at 8 mo, MMR at 18-24 mo, and MMR at 4 y. Italic type indicates recommendations for certain geographic areas or groups; bold type indicates optional vaccines in national schedule or recommendations of academic or practitioner societies.

Canada, and Europe) or a replicating chimeric yellow fever–JE virus recombinant vaccine. Details are provided in Chapter 19.

Tick-borne encephalitis vaccine

To control cases and occasional outbreaks of the Far Eastern subtype of tick-borne encephalitis (TBE) virus in northeastern China, the Changchun Biologicals Institute developed a formalin-inactivated vaccine, derived from a human isolate, Senzhang strain, and grown in PHK cell cultures. Related vaccines prepared from Central European strains and distributed in Europe are described in Chapter 34.

Kyasanur Forest disease vaccine

The tick-borne flavivirus infection has been a frequent cause of severe hemorrhagic fever outbreaks centered in Karnataka State, India, among herders and villagers with forest exposure. The scale and frequency of outbreaks stimulated the National Institute of Virology to develop an inactivated cell culture–derived vaccine that was manufactured initially by the state government at Shimoga.[4] A large field trial in 1990 to 1992 among inhabitants of 72 affected villages disclosed attack rates of 0.15% (14/9,072) among persons receiving 1 dose and 0.047% (10/21,083) among recipients of 2 doses compared with an attack rate of 0.870% (325/37,373) in unvaccinated persons, for vaccine efficacies of 82.4% and 94.8%, respectively. The commercial vaccine is produced by the state Institute of Animal Health and Veterinary Biologicals.

Hantavirus vaccines

HFRS, a widespread rodent-borne bunyaviral zoonosis in Asia, is a pantropic infection with prominent capillary hemorrhages, interstitial nephritis, and a 3% to 10% case-fatality ratio that, until the last decade, caused more than 1,000 annual cases in the Republic of Korea and more than 100,000 cases in China.[5,6] Although the disease had been well known in parts of Russia and Asia as a sporadic and occasionally epidemic disease among farmers, soldiers, and others exposed to campestral and sylvatic habitats, it was largely unknown in the West until thousands of military cases and deaths occurred during the Korean war, when the disease was described as Korean hemorrhagic fever. The etiologic agent eluded investigators until 1976, when a novel virus (Hantaan virus) was isolated from the striped field mouse, *Apodemus agrarius*, which proved to be the principal viral reservoir in most areas of Asia. Later, a related member of the Bunyaviridae, Seoul virus, was isolated from *Rattus rattus* and *Rattus norvegicus*, explaining the occurrence of sporadic HFRS cases and outbreaks in urban areas. Subsequently, Sin Nombre and related hantaviruses were discovered in the Western hemisphere, where rare encounters with infected rodents lead to small numbers of cases that feature prominent pulmonary involvement. Multitudinous hantaviruses now have been described globally.

The widespread impact of HFRS in China led public health authorities to pronounce the disease second only to hepatitis B as a public health menace, and, beginning in 1993, vaccines were distributed by several manufacturers. Monovalent or bivalent vaccines against Hantaan and Seoul viruses now are

Antigens									
MCV-rubella	**Varicella**	**Men**	**JE**	**HPV**	**Influenza**	**Hep A**	**Typhoid**	**Rabies**	**HFRS**
M, 6, 9 mo									
M, 9-12 mo MMR, 1-2 y; **4-6 y**	**12-15 mo; 4-6 y**			**10-18 y ×3**	**6 mo +**	**1-2 y ×2**		***5-14 y ×4***	
MMR, 1-2, 6-7 y									
M, 9 mo MR, 3 y R, 13 y			*SA_{14}-14-2, 1 y*						
MMR, 1 y Primary 1	1 y		15 mo × 2; 27 mo Primary 1		6 mo +	*2, 2.5 y*			
MMR, 9 mo-1 y; 4-6 y	**1-1.5 y; 4-6 y**		1-1.5 y × 2 2-2.5 y **SA_{14}-14-2, 9 mo-1 y × 2**	**11-12 + y**	**6 mo +**	**1 y+, × 2**			
M, 9 mo, 6 y MMR, 1-5, 6-8 y	1-5 y	AC, 1.5 y; boosters every 3 y	*9-12 mo × 3, annual boosters until 8 y old*		6 mo +	2-8 y × 2	2 y		

administered for outbreak control in many Chinese provinces. Licensed vaccines use SMB, primary gerbil or baby hamster kidney cells and Vero cell line substrates and have shown efficacies from 85% to more than 95% (Table 69-1).[7–9]

The Chinese-manufactured baby gerbil kidney cell (GKC)-derived vaccine provided 100% and 50% seroconversion by immunofluorescence and neutralization assays, respectively, after three vaccine doses at 0, 7, and 28 days. In a randomized controlled three-armed trial, in which vaccinated subjects received three primary doses and a booster dose 1 year later, 15 HFRS cases were observed in 7,860 control subjects compared with none in 7,872 vaccinees and 20 cases in 10,196 unvaccinated subjects during a 48-month follow-up, for a protective efficacy of 100% with a 95% lower confidence limit of 77.9% ($P = .00003$; cumulative bionomial probability). Efficacy of the primary series alone was shown as, in the year between administration of the primary series and booster dose, 0, 9, and 10 cases occurred in the three groups, respectively. Among 35 cases in the control and unvaccinated groups, 23 were caused by Hantaan virus, 10 by Seoul virus, and 2 by a virus of indeterminate serotype. Thus, the monovalent vaccine was protective against disease caused by the Hantaan and Seoul viral serotypes. No vaccine-related serious adverse event was reported during the trial, and mild local and systemic reactions were reported in 3.78% of subjects. Bivalent GKC-derived vaccine was more immunogenic and induced neutralizing antibody to Hantaan and Seoul viruses in 91.3% and 88.4% of subjects, with geometric mean titers (GMTs) of 18.27 ± 2.21 and 12.47 ± 2.16, respectively. A bivalent Vero cell–derived vaccine with immunogenicity in the same range as the bivalent GKC-derived vaccine was licensed recently.

The efficacies of the PHK and SMB vaccines were similar: in nonrandomized trials, 1 HFRS case was found in 40,757 recipients of PHK cell–derived vaccine compared with 53 in 47,313 unvaccinated subjects, a reduction of 97.81%; for the SMB vaccine, the rates were 3.71 per 100,000 (1/26,942) vs 97.98 per 100,000 (34/34,699) for vaccinees and unvaccinated subjects, respectively, a reduction of 88.45%. Nonsevere adverse reactions were observed in 1.57% of the recipients of the PHK cell–derived and in 3.26% of the SMB-derived vaccine recipients.

In Korea, a monovalent (Hantaan virus strain) SMB-derived vaccine also was licensed, based on immunogenicity and challenge data in mice, accompanied by a controversial field trial in Yugoslavia.[10,11] The vaccine strain, ROK 84-105, was isolated from a human case, serially passaged in brains of suckling mice, purified, and formalin inactivated, following procedures for production of JE vaccine. Immunogenicity of a two-dose primary series in small numbers of human subjects was variable, from 13% to 75% in plaque reduction neutralization tests and 77% to 97% in IgG enzyme-linked immunosorbent assays.[10] Importantly, in one study, plaque reduction neutralization test titers more than 1:10 persisted in only 14% of subjects 1 year after the primary series; booster immunization led to a rise to more than 1:10 in only 50% of the subjects, and the postbooster GMT (138) was lower than the titer after the second primary dose (203). A serologic correlate of protection has not been established, but these observations suggested the need for a booster dose at 12 months to maintain immunity. The vaccine was well-tolerated with principally local reactogenicity. A case-control study showed a dose-related trend, potentially indicating effectiveness, increasing from 25% (95% confidence interval [CI], – 78% to 68%) after one dose, to 46% (95% CI, – 35% to 78%) after two doses, to 75% (95% CI, – 18% to 95%) after three doses.[11] The study evaluated protection through an average of only 7.3 months.

The incidence of HFRS in China and Korea has declined in the last 10 years with the introduction of vaccination and probably, more importantly, because of rural economic development leading to improved (cement) houses, grain harvesting and storage practices, and rapid urbanization, resulting in reduced exposures to the rodent reservoir. This trend has been most evident

in rapidly developing areas of southeastern China and likely will continue in other regions, leading to a diminishing disease incidence and, potentially, discontinuation of routine vaccination in endemic provinces.

Live attenuated hepatitis A vaccines

Two similar live attenuated vaccines, based on the H2 and LA-1 strains, have been licensed in China.[12–14] H2 was attenuated through 15 passages in new monkey kidney cells at 35°C, followed by five passages in the same cell substrate at 32°C. The virus was subsequently adapted to grow in a culture of human diploid fibroblasts (KMB17) at 32°C and was carried through an additional four KMB17 passages at the same temperature. One dose of the vaccine, containing a hepatitis A virus (HAV) titer of more than 6.5 log $TCID_{50}$, is administered subcutaneously; oral administration failed to induce antibody; thus, the attenuated virus is not transmissible from person to person. Genetic stability was demonstrated, with nucleotide identity after two passages through marmosets or eight passages through cell culture at 37°C. After a single dose, vaccine-induced IgG enzyme-linked immunosorbent assay antibody peaked at month 2, resulting in seroconversion of 98.6% of vaccinees (217/220) with a GMT of 287.1 mIU/mL. Specific antibody declined gradually but persisted at protective levels (≥20 mIU/mL) in 81.3% of vaccinees 15 years later.

Field trials of individually randomized children, 2 to 10 years old, disclosed 1 HAV case in 29,376 vaccinees and 22 cases in 32,701 control subjects, for a protective efficacy of 95% ($P < .001$; 95% lower confidence limit, 73.6%; by cumulative bionomial probability) during the 3-year study period.[14] At the same time, the number of acute hepatitis B cases was similar for the same population, one in the vaccine group and two in the control group. Cluster randomized trials among school children, 6 to 18 years old, disclosed no case of HAV in 84,412 vaccinees and 22 cases in 79,254 control subjects, while acute hepatitis B was detected in 9 vaccinees and 10 control subjects. The vaccine was well-tolerated, and no vaccine-related severe adverse event was reported. The frequency of elevation of the alanine aminotransferase level was similar in the vaccine and control groups.

Maternal antibody interfered with the live attenuated vaccine in young infants. In a study among 54 infants vaccinated at 2 to 4 months of age, 5 (14%) of 36 whose mothers were anti-HAV positive were seropositive at 3 years of age, compared with 12 (67%) of 18 whose mothers had no detectable anti-HAV. A second dose of 6.5 log $TCID_{50}$ given at 12 months after the first dose of a low HAV concentration vaccine (5.5 log $TCID_{50}$) induced a good booster response: anti-HAV seropositivity increased from 39.3% at 1 month to 100% (27/27) at 13 months. The GMT of 2,036 mIU/mL is comparable to the response induced by two doses of an internationally licensed inactivated HAV vaccine (Havrix, GlaxoSmithKline). However, a single dose of the vaccine is recommended for subjects of any age.

During an outbreak among school children, the vaccine was administered to part of the student body at the peak of the outbreak. At 40 days after immunization, 1 case was detected in 83 vaccinees (1.2%), compared with 2 cases in 156 unvaccinated children (1.3%). Thus, given the very low attack rate in the unvaccinated group, it remains to be proven whether the vaccine can provide postexposure protection.

Measles vaccines

While the majority of all measles vaccines are derived from the Edmonston strain, two attenuated vaccines based on other wild-type viruses and isolated later in time (Shanghai) S-191 and Changchun-47 strains were developed in China.[14–17] Details are available in Chapter 20.

Oral bivalent killed whole-cell cholera vaccine

Toward fulfilling a national goal of self-sufficiency in vaccines, The National Institute of Hygiene and Epidemiology in Vietnam developed an oral bivalent O1-O139 killed whole-cell cholera vaccine that now is produced and distributed by VABIOTECH, Company for Vaccine and Biological Production No.1, in Hanoi. Another oral bivalent O1-O139 vaccine is produced in India. Details can be found in Chapter 11.

Meningococcal group B outer membrane protein complex vaccine

In New Zealand, an outbreak of meningococcal disease due to a specific clone of group B meningococcus (B:4:P1.7b.4) caused a total of 5,635 cases between 1991 and 2004. Because about 80% of all reported meningococcal disease cases in this period were due to this single Por A subtype, it was feasible to commission a tailor-made outer membrane vesicle vaccine that controlled the outbreak. Details are available in Chapter 21.

Enterovirus V71 vaccine

EV71 and related enteroviruses cause principally a self-limited febrile herpangina or syndrome of hand-foot-and-mouth disease that occur sporadically in a cosmopolitan distribution, including the United States, but that since 1997 have emerged in major seasonal epidemics in eastern and Southeast Asia, leading in 2009 and 2010 to more than a million cases, thousands of complicated cases necessitating hospitalization and hundreds of deaths during outbreaks in China.[15,18,19] Although epidemics have had their greatest impact in China, Taiwan, Singapore, and Malaysia, outbreaks also have been a concern in Japan, Korea, Thailand, Hong Kong, and Australia. Their impact is due to the high attack rates resulting in day-care and kindergarten closures and to the cases hospitalized with neurologic and cardiopulmonary complications. Aseptic meningitis, acute flaccid paralysis, pulmonary edema, arrhythmias, cardiac failure, and shock can occur with an incidence as high as 15 to 30 per 100,000 in children younger than 5 years, in whom the case-fatality ratio has ranged from 1% to 20%, depending on the definition of a severe case. Brainstem infection, resulting in autonomic dysregulation, has been implicated in the pathogenesis of pulmonary edema, but systemic inflammatory responses leading to increased pulmonary vascular permeability and direct injury of the myocardium have not been ruled out as contributing causes. Severe psychomotor damage frequently complicates recovery, with central hypoventilation, motor paralysis, and severe cognitive impairment, with developmental delay occurring in half of children younger than 2 years who experienced cardiopulmonary complications during hospitalization.[16] While these rates of death and disability would be significant to parents anywhere, the single child policy in China and similar family structures in Taiwan (having the world's lowest birth rate) and Singapore have focused even more public pressure on governments to control the disease. Rapid vaccine development and priority regulatory approval, analogous to the process for pandemic influenza vaccine, and advance market commitments have been discussed in some countries.

At least five vaccine candidates (from institutes and companies in China, Taiwan, and Singapore) are in advanced stages of development, with field efficacy trials completed in 2012 and expedited licensure expected in 2013.[17,20] All are based on conventional inactivated whole virion antigens, with or without alum, modeled after inactivated poliovirus vaccines. A bottleneck has been the identification of candidate strains that provide adequate yield and stability in production and that also cross-neutralize strains in other genotypes. Proof of principle has been confirmed in vaccinated rhesus monkeys,

challenged by intravenous or respiratory routes or in pups of vaccinated pregnant mice challenged after birth, the recognized animal model established because of the poor susceptibility of older mice to EV71. Although only one EV71 virus serotype has been recognized, the virus has been classified genetically into 4 genotypes, A through D, with subtype C4 strains circulating almost exclusively in China and B subtypes circulating predominantly in Taiwan and Southeast Asia. Regulatory and political considerations may constrain the use of strains based on local molecular epidemiologic patterns.

Hepatitis E vaccine

A Chinese-developed vaccine, approved by the State Food and Drug Administration, is an *Escherichia coli*–expressed, 23-nm, virus-like particle composed of recombinant purified peptide corresponding to aa 376-606 of the hepatitis E virus (HEV) viral capsid protein (660 aa) encoded by ORF2.[21] Three doses of the genotype 1–based vaccine, each containing 20 µg of alum-adjuvanted antigen, given at 0, 1, and 6 months, led to uniform seroconversion in young adults. In a pivotal efficacy field trial conducted jointly by the vaccine developers and the provincial CDC, no case of clinical illness with ALT elevation confirmed as HEV (by IgM plus polymerase chain reaction positivity) was detected in 48,493 HEV-vaccinated healthy adult subjects, while 15 cases (12 due to genotype 4 strains, confirming cross-genotype protection) were observed in hepatitis B–vaccinated control subjects followed up for 12 months, for an efficacy of 100% (95% CI, 72%-100%). However, with a more sensitive case definition of any two of three HEV markers (HEV-RNA, IgM, or IgG anti-HEV antibodies) confirming a case, the vaccine efficacy was 72%. The vaccine was well-tolerated, and no vaccine-related severe adverse events were reported. Further trials in pregnant women, infants, and people with chronic hepatitis are planned. Details are available in Chapter 49.

Clinical development and regulatory approval

Implicit in the region's progress toward novel vaccine development is a maturing capacity to conduct clinical trials and improvements toward more robust regulatory processes and capacity, including pharmacovigilance systems. In addition, multinational companies increasingly have turned to countries in Asia to conduct clinical trials because of lower costs and more streamlined regulatory approvals of clinical trial applications. International contract research organizations operate in many countries, and a growing local infrastructure to conduct clinical trials in compliance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and good clinical practices standards will lead to more clinical research conducted in the region.

Unlike Europe, Asian countries are not unified in a central regulatory approval process. Nor is there a regional public health presence as in Latin America, where the Pan American Health Organization leads regional vaccination programs and also provides central purchasing of certain qualified vaccines. However, the 10-nation Association of Southeast Asian Nations (ASEAN, including Brunei-Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam) in 1992 initiated efforts for a subregional regulatory harmonization scheme to reduce differences in technical requirements and regulatory procedures for pharmaceuticals. The harmonization initiative was undertaken under the association's free trade agreement to remove barriers to regional commerce. A Pharmaceutical Product Working Group, formed in 1999, aims to harmonize pharmaceutical regulations of member countries to eliminate technical barriers to trade without compromising product quality, efficacy, and safety. Eventually, a subregional mutual recognition procedure similar to that of the European Union is envisioned. Importantly, local clinical trials are not required for registration under abbreviated pathways specified by the ASEAN Common Technical Dossier if the vaccine was approved and licensed elsewhere by certain benchmark regulatory agencies, resulting in a certificate of pharmaceutical product. By contrast, the national regulatory authorities (NRAs) of China, India, Japan, Korea, and Taiwan have required local clinical trials before or after registration (not unlike the US Food and Drug Administration requirement for a certain proportion of US study subjects in a new submission).

A rationale for local clinical data to expand the safety and immunogenicity database of previous files has been a concern that local (racial, ethnic, or environmental) differences could affect responses of the local population. Genetically based differences in drug pharmacokinetics and pharmacodynamics, as well as disease risk, increasingly have been recognized, including immune responses to vaccines. Studies of antibody responses to pneumococcal conjugate vaccines (PCV7) in Asia, for example, have found higher prevaccination and postvaccination antibody titers among Philippine and Taiwanese infants compared with European or historical control subjects.[22,23] While the basis for these differences may be an earlier exposure in life to pneumococci or cross-reacting antigens or other regional differences in host microbiomes, the possibility of genetically restricted responses, as has been observed to hepatitis B, measles, vaccinia, rubella, Hib, and other antigens, cannot be discounted, as they are becoming understood in a newly defined field of vaccinomics.[24–28]

Descriptions of individual regulatory requirements for clinical trial applications and new product approvals are beyond the scope of this chapter; see the previous edition for a more detailed introduction.

Vaccine production

Governments have had a greater role in vaccine manufacturing in the region than elsewhere, although devolution toward privatized or state-owned enterprises (SOEs; ie, government-owned corporations) has occurred, eg, Commonwealth Serum Laboratories in Australia was privatized, and the six major government vaccine institutes in China now operate as an SOE (Table 69-2). Although a growing number of private manufacturers have emerged, especially in China and India, in other countries, national and local government manufacturers continue to be important sources of certain vaccines for domestic needs, eg, the Government Pharmaceutical Office in Thailand, Research Institute for Tropical Medicine in the Philippines, Biofarma in Indonesia, the National Institute of Hygiene and Epidemiology in Vietnam, and the Central Research Institute and local government institutes in India. The Thai GPO and the Viet NIHE have also exported JE vaccine to Sri Lanka and to Andra Pradesh, India, respectively. These and other facilities also fill and distribute bulk vaccines supplied by international manufacturers. Several private and SOE manufacturers in the region are members of the Developing Countries Vaccines Manufacturing Network, a consortium that seeks to identify and develop solutions to common challenges faced by manufacturers in developing countries.

A number of manufacturers operate under practices and procedures that have prequalified them to produce certain vaccines for UNICEF purchase (eg, DTP, hepatitis B, and measles vaccines) or that allow them to export vaccine to other countries in the region. World Health Organization (WHO) prequalification requires that the manufacturers and plants must satisfy WHO GMP inspections, but, in addition, that national notifications of adverse events following immunization are captured and analyzed satisfactorily. This last requirement has been the principal impediment to prequalification of products from some countries, and WHO is

Table 69-2 Vaccines and Vaccine Manufacturers in Asia*

Manufacturer	Viral	Bacterial and pediatric combination
Australia		
CSL	Influenza, inactivated split	*Coxiella burnetii,* inactivated
China		
Beijing Huaerdun	Hepatitis B virus (HBV), recombinant Chinese hamster ovary (CHO) cell–derived	
Beijing Lvzhu		Meningococcal A and C, glycoconjugate Meningococcal A, C, Y, W135 polysaccharide (PS)
Changchun Changsheng	Influenza, inactivated split Hepatitis A virus (HAV), live attenuated, 2BS-cell, lyophilized (LA-1) Rabies, inactivated, Vero cell–derived, lyophilized Rabies, inactivated, primary hamster kidney (PHK) cell–derived, lyophilized Varicella, live attenuated, lyophilized (Oka strain)	Diphtheria (D), tetanus (T), acellular pertussis (aP), adsorbed
China National Biotech Corporation comprising Beijing Tiantan Co, Changchun Institute of Biological Products (IBP), Chengdu IBP-Rongsheng, Lanzhou IBP, Shanghai IBP, Wuhan IBP	Oral polio virus (OPV), trivalent, live attenuated Measles, mumps, rubella combined, live attenuated Measles and mumps combined, live attenuated Measles and rubella combined (MR), live attenuated Measles, live attenuated (S-192 or Chang-47 strains) Mumps, live attenuated (S79 strain) Rubella, live attenuated(BRD II strain) Hepatitis B (HBV), recombinant CHO cell-derived HBV, recombinant yeast Hepatitis A (HAV), live attenuated, 2BS cell, lyophilized (H-2 strain) HAV, live attenuated, 2BS cell, lyophilized (La-1 strain) HAV, live attenuated, liquid (H-2) HAV, live attenuated, liquid (La-1) HAV, inactivated Varicella, live attenuated, MRC-5 cell-derived, lyophilized (Oka strain) Japanese encephalitis (JE), live attenuated, PHK cell–derived, (SA_{14}-14-2) JE, inactivated, PHK cell–derived, (SA_{14}-14-2) JE, inactivated, Vero cell–derived Rabies, inactivated, Vero cell–derived Rabies, inactivated, PHK cell–derived Influenza, inactivated whole virion Influenza, inactivated split Hemorrhagic fever with renal syndrome (HFRS), inactivated bivalent, PHK cell–derived, (PS-6 and L99 strains) HFRS, inactivated, PHK cell–derived, (PS-6 strain) Yellow fever, live attenuated, lyophilized (17d strain) Rotavirus, live, newborn calf kidney cell, oral (LLR strain) Tick-borne encephalitis (TBE), inactivated, PHK cell–derived (Senzhang strain)	DT toxoids, aP adsorbed DT pertussis (P), adsorbed dT, adsorbed, for adults dT, adsorbed, for children dP, adsorbed Diphtheria toxoid, adsorbed Tetanus toxoid, adsorbed Acellular pertussis, adsorbed, purified Typhoid, Vi PS Typhoid and paratyphoid A and B, inactivated Meningococcal A PS, lyophilized Meningococcal A and C, PS lyophilized Leptospirosis, inactivated, monovalent and polyvalent, whole cell vaccine of various valencies, up to 24 valent (v) bacille Calmette-Guérin (BCG) Brucellosis, live attenuated, lyophilized Plague, live attenuated, lyophilized Anthrax, live attenuated, lyophilized *Shigella flexneri* 2a/*Shigella sonnei*, live attenuated, bivalent, lyophilized *Haemophilus influenzae* type b-TT (Hib-TT), tetanus toxoid conjugate Pneumococcal PS, 23v BCG, PS, and nucleic acid preparation for therapeutic purposes

Dalian Hissen (Hanxin)	Rabies, inactivated PHK cell–derived HBV, recombinant yeast	
Dalian Aleph	Influenza, inactivated split	
Henan Puxin	Rabies, inactivated, PHK cell–derived	
Huabei	HBV, recombinant CHO cell	
Jiangsu Ealong (Yanshen)	Influenza, inactivated, split	
Jilin Maifeng	Rabies, inactivated, Vero cell–derived	
Jilin Yatai	Rabies, inactivated, PHK cell–derived	
Kunming Medical Biology Institute	OPV, live attenuated HAV, live attenuated, KMB17 cell, liquid (Lv-8 strain) HAV, live attenuated, KMB17 cell, lyophilized (H-2 strain) HAV, inactivated, KMB17 cell, liquid (Lv-8 strain)	
Liaoning Chengda	Rabies, inactivated, Vero cell–derived, (PV2061 strain) JE, inactivated, Vero cell–derived (P3 strain)	
Liaoning Yisheng	Rabies, inactivated, Vero cell–derived	
Ningbo Rongan	Rabies, inactivated, Vero cell–derived, (aGV strain)	
Shanghai United Biotech		Cholera rB subunit-whole cell, oral
Shenzhen Kangtai	HBV, recombinant yeast	
Shenzhen Neptunus (Haiwang)	Influenza, inactivated, split	
Sinovac-Beijing University	Influenza, inactivated split (seasonal) Influenza, split, pandemic H1N1 Influenza, split, avian H5N1, alum adjuvanted [NIBRG-14 A/VietNam/1194/2003(H5N1)RG strain] HAV, inactivated (Hm175 strain) HAV + HBV, inactivated, recombinant	
Tasly Group	Influenza, subunit	
Wuxi Royal (Luoyi)	HFRS, inactivated bivalent, Vero cell–derived	Meningococcal A and C, glycoconjugate, lyophilized
Yunnan Walvax (Wosen)		Hib-TT, conjugate (58534) Meningococcal A and C, glycoconjugate, lyophilized (29201, 29205)
Zhejiang Pukang	HAV, live attenuated	
Zhejiang Tianyuan	Influenza, inactivated split (seasonal and H1N1 pandemic) HFRS, inactivated bivalent, primary Mongolian gerbil kidney cell (Z10,Z37 strains) JE, inactivated, PHK cell (SA_{14}-14-2)	Meningococcal A and C, PS Meningococcal A, C, Y, W135 PS
Zhejiang Vacin (Weixin)	Mumps, live attenuated (S79 strain)	

Table 69-2 Vaccines and Vaccine Manufacturers in Asia*—cont'd

Manufacturer	Viral	Bacterial and pediatric combination
India		
Bharat *Biological E*	Rabies, Vero cell–derived HBV, recombinant IPV	TT DT DTP DTP-HBV DTP-HBV-Hib-TT glycoconjugate Td
Coonoor, Pasteur Institute of India	Rabies, Vero cell–derived	DPT TT DT
Haffkine	OPV 1 OPV 1, 3 OPV, trivalent, MRC5 or primary monkey kidney cell culture–derived	
Green Signal BioPharma		BCG
Indian Immunologicals Ltd.	MMR, live attenuated (EZ, L-Zagreb, RA27/3 strains) HBV, recombinant Rabies, inactivated, Vero cell–derived	
Panacea Biotech Ltd	OPV 1 OPV 3 OPV, trivalent HBV	DTP DTP-HBV DTP-Hib-CRM197 glycoconjugate DTP-HBV-Hib-CRM197 glycoconjugate
Serum Institute of India	Influenza, live attenuated H1N1 pandemic HBV, recombinant Measles, live attenuated (EZ strain) Rubella, live attenuated (RA27/3 strain) MR, live attenuated (EZ, RA27/3 strains) MMR, live attenuated (EZ, L-Zagreb, RA27/3 strains) Rabies, human diploid cell–derived	BCG TT, adsorbed DT, adsorbed DTP, adsorbed DTP-HBV Dt Hib-TT Meningococcal A-TT glycoconjugate
Shanta Biotech Ltd	HBV, recombinant	TT Hib-TT glycoconjugate DTP-HBV DTP-Hib DTwP-HBV-Hib Oral cholera, whole cell, heat and formalin inactivated (O1 classical and El Tor biotypes and O 139 strains)
Zydus Cadila	Influenza, inactivated H1N1 pandemic Rabies, primary duck embryo cell–derived	

Indonesia		
Biofarma	OPV, trivalent OPV, type 1 OPV, types 1, 3 HBV, recombinant Measles, live attenuated (CAM-70 strain)	Tetanus toxoid, adsorbed
Japan		
Daichi Sankyo-Kitasato	Influenza, inactivated split (seasonal and H1N1 pandemic) Measles, live attenuated (AIK-C strain) Rubella, live attenuated (Takahashi strain) Mumps, live attenuated (Hoshino strain) MR, live attenuated	Tetanus toxoid, adsorbed DTaP, adsorbed
Denka-Saiken	Influenza, inactivated split (seasonal and H1N1 pandemic)	Tetanus toxoid, adsorbed Leptospirosis polyvalent
Handai-Biken	Influenza, inactivated split (seasonal and H1N1 pandemic) Measles, live attenuated strain Rubella, live attenuated strain Mumps, live attenuated strain Varicella, live attenuated (Oka strain) JE, inactivated Vero cell–derived (Beijing strain)	Tetanus toxoid, adsorbed Diphtheria toxoid, adsorbed DTaP, adsorbed
Japan BCG		BCG
Japan Polio Institute	OPV, trivalent	
Kaketsuken	Influenza, inactivated split (seasonal and H1N1 pandemic) HBV, recombinant, yeast-derived HAV, inactivated Rabies inactivated, cell culture–derived JE, inactivated Vero cell–derived (Beijing strain)	Tetanus toxoid, adsorbed DT toxoids, adsorbed DPT, adsorbed DTaP, Adsorbed
Takeda	Measles, live attenuated Rubella, live attenuated Mumps, live attenuated MR, live attenuated	Tetanus toxoid, adsorbed DTaP, adsorbed
Korea		
Berna Biotech, Korea	Influenza, inactivated split HBV, recombinant	
Boryung Biopharma	Influenza, inactivated subunit HBV, recombinant JE, inactivated suckling mouse brain (SMB)-derived	DTP, adsorbed
CJ Cheil Jedang	Influenza, inactivated subunit	

Table 69-2 Vaccines and Vaccine Manufacturers in Asia*—cont'd

Manufacturer	Viral	Bacterial and pediatric combination
Daewoong	IPV	DTP, adsorbed
Green Cross	Influenza, inactivated split (seasonal and H1N1 pandemic) Influenza, inactivated split, MF59-adjuvanted H1N1 pandemic HBV, recombinant HFRS, inactivated SMB-derived (ROK84-105 strain) Varicella, live attenuated (MAV/06 strain)	
LG Life Sciences	Influenza, inactivated split HBV, recombinant	DTaP
SK Chemical	Influenza, inactivated subunit HBV, recombinant	
Myanmar		
Department of Medical Research	HBV, recombinant	
Pakistan		
CIRIN	Rabies, Vero cell–derived	
Taiwan		
Adimmune	Influenza vaccine, inactivated split (seasonal and H1N1 pandemic) JE, inactivated, SMB (Nakayama strain)	Tetanus toxoid, adsorbed
CDC		BCG Tetanus toxoid, adsorbed Diphtheria toxoid, adsorbed dt, adsorbed
Thailand		
Government Pharmaceutical Organization	JE, inactivated, SMB-derived (Nakayama strain)	
Queen Saovabha Memorial Institute		BCG
Vietnam		
IVAC	SARS virus, inactivated	BCG Tetanus toxoid, adsorbed Td, adsorbed DTP, adsorbed
POLYVAC	OPV Measles	
Vabiotech	JE, inactivated, SMB-derived (Beijing-1 and Nakayama strains) HBV, recombinant yeast-derived HAV, inactivated	Oral cholera, whole cell, heat and formalin inactivated including toxin coregulated pilus (O1 classical and El Tor biotypes and O 139 strains)

*Information obtained through surveys of local governments and manufacturers, through April 2011.

working toward a clearer definition of basic requirements (a blueprint) for a pharmacovigilance system for developing countries.

To a growing extent, multinational companies are acquiring or partnering with local companies in the region, with the result that manufacturing standards and their regulation should improve toward meeting international specifications.[29]

Table 69-2 lists the region's principal vaccine manufacturers and their licensed products, but, with the rapid turnover of private companies, no claim is implied that the list is comprehensive. Vaccines that are manufactured elsewhere and refilled and distributed by local manufacturers are not listed.

Vaccine policy and schedules

Countries in the region can be divided broadly into countries with a single national schedule and countries in which a basic schedule of free EPI vaccines is supplemented by recommendations of a professional organization (such as the national pediatric society) for additional antigens that are paid for out-of-pocket. Countries in the first group include, on the one hand, mainly developing countries offering a basic EPI schedule and, on the other, countries like Australia, New Zealand, and Taiwan that provide a universal vaccination program that includes an array of antigens or combination vaccines paralleling those of European and US schedules.

The continued introduction of new and frequently expensive vaccines is an ongoing tension for vaccine recommending and funding entities that must weigh the relative value of such innovations against other preventive and therapeutic health expenditures. For some countries in the region, the total per capita expenditure for all health care may be less than the cost of a full course of the most expensive novel vaccine. On the other hand, national schedules in the region can be as comprehensive as to include the human papillomavirus vaccine (Australia) and influenza and varicella vaccines (eg, Korea, Taiwan). At the same time, Hib vaccine still is not recommended in some jurisdictions with high per capita income (Hong Kong, Singapore). To some degree, the seemingly paradoxical recommendations of relatively high income countries in the region reflect different social expectations of personal responsibility in health care purchases (see subsequent text). As shown in Table 69-1, some national schedules provide optional recommendations for some antigens. The availability of inexpensive DTwP-Hib-HepB combination vaccines cannot be highlighted enough, as they have made possible the introduction of Hib antigen into schedules of economically disadvantaged countries that otherwise would not have adopted the monovalent vaccine. As shown in Table 69-1, in many countries where government tenders choose specific manufacturer products, specific combinations are recommended in the national schedule. In addition, for some antigens, provincial-specific recommendations address regional differences in risk (eg, for routine group AC meningococcal vaccine in China; for JE vaccine in Sarawak, Malaysia and for the Torres Straits, Australia; and for rabies vaccine [preexposure] in areas of the Philippines).

In most countries, public health authorities draw on external advisors to help formulate national vaccine recommendations. The Advisory Committee on Immunization Practices (ACIP) in Taiwan and Korea, Expert Committee on Immunization in Singapore, Chinese Expert Committee on EPI, Hong Kong Scientific Committee on Vaccine Preventable Diseases, Immunization Committee of the Indonesian Pediatric Society, and the Australian Technical Advisory Group on Immunization are examples of such medical advisory groups. Japan is in the process of revamping its vaccine approval and recommendations process and will soon establish an ACIP-like body. The Malaysian Pediatric Association and The Pediatric Society of Thailand advise their respective ministries and ACIP in formulating national recommendations.

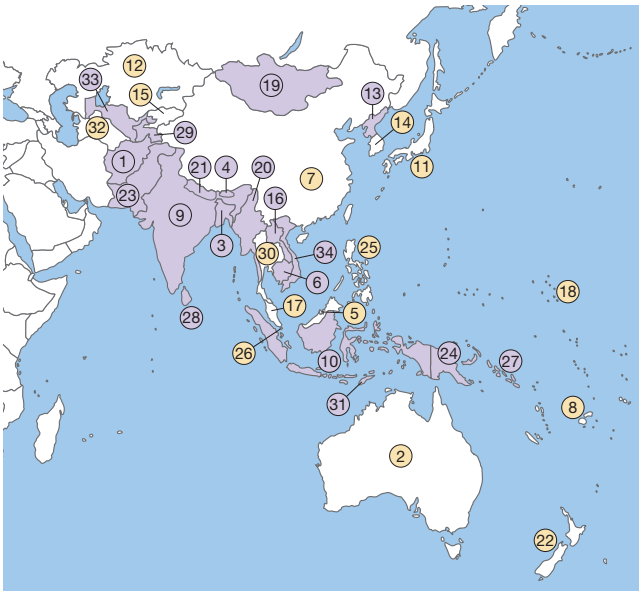
In India, Indonesia, Pakistan, the Philippines, and Thailand where national schedules include the basic EPI antigens, academic pediatric societies and other nongovernmental coalitions or organizations promulgate schedules that include a broader range of vaccines, reflecting closely those recommended in the United States, Europe, and Australia. Schedules of these bodies are shown with their respective national EPI schedules in Table 69-1.

Vaccine delivery and coverage

Vaccines are delivered in varying proportions through public or private channels, depending mainly on local income levels and accessibility to private practitioners. In general, vaccines on national schedules are available at no cost in primary health centers or their equivalent (eg, puskesmas in Indonesia; polyclinics or government hospital clinics in Singapore, Malaysia, and Thailand; village and county level Centers for Disease Control in China; village communes in Vietnam; public health centers and clinics in India and Japan; and at general practitioner [GP] offices in Australia). As a rule, the cost of vaccines is not reimbursed while they are available free in public clinics, so even in affluent countries, families may attend government clinics or hospitals to obtain routine vaccinations and well-child care (eg, in Singapore, ≈ 60% of families obtain vaccines through the government system of polyclinics and hospitals). However, to avoid long waiting times and rotating staff at public clinics, many families opt to obtain these otherwise free vaccines privately and to pay out-of-pocket at pediatric, GP, or other private clinics. In addition, as newer vaccines may be delayed in their introduction to the national reimbursed scheme, it is common for parents to pay for these vaccines out-of-pocket; for example, in Korea, about 90% of children in Seoul are vaccinated with PCV7 through private purchases. As might be expected from the distribution of income, the proportion of children vaccinated in government primary health centers is higher in rural areas. Overall, approximately 90% of children in Thailand and 70% in Malaysia are vaccinated through public channels. In China, all vaccinations are under control of CDCs; therefore, nearly all Chinese children receive free EPI, as well as payable optional vaccines (eg, Hib, PCV7, varicella, rotavirus, and others) at public clinics. Coverage for EPI vaccines for selected countries is summarized in Figure 69-1.[30]

Future trends and challenges

Economic growth and development in Asia and secular trends in population structure and the evolution of health care systems are forces that inevitably will change various aspects of immunization in the region, if in as-yet unforeseeable ways.[31,32] The population of Asia, as in other regions, is aging and shifting toward a structure with a larger proportion of adults and elderly persons. Between 2005 and 2025, the birth cohort of Asia will decrease slightly from 76.1 to 72.2 million, and the population of children 0 to 4 years old will hold nearly constant while the number and proportion of adults from 15 to 64 years will increase dramatically, and the number of people older than 65 years will nearly double, from 250.6 to 480.6 million. A demographic crossover point with more adults 60 + years than children younger than 15 years, was reached in Europe in the 1990s and will occur within another generation in Asia (Figure 69-2).[33] With the exception of almost universal EPI programs of tetanus toxoid vaccination of pregnant women, adult vaccination has been viewed mainly in the context of travel, as in group A meningococcal vaccine for the Hajj, and in tropical Asia, influenza vaccine as appropriate only for travelers to temperate locations. However, the SARS and pandemic H1N1 outbreaks and the regional threat of H5N1 influenza have focused attention on routine seasonal influenza vaccination for the first time in many countries, beginning with elderly populations.[34] As a result of high pediatric vaccination coverage in developed countries in the region, JE has become almost exclusively a disease of adults older than 45 years, reflecting the intrinsic biological



	Country	Esimated coverage (%)			
		DTP3	HepB3	MCV	Pol3
1	Afghanistan	66	66	62	66
2	Australia	92	92	94	92
3	Bangladesh	95	96	94	95
4	Bhutan	91	91	95	92
5	Brunei Darussalam	95	96	94	99
6	Cambodia	92	92	93	92
7	China	99	99	99	99
8	Fiji	99	99	94	99
9	India	72	37	74	70
10	Indonesia	83	83	89	93
11	Japan	98	–	94	98
12	Kazakhstan	99	99	99	98
13	Korea, DPR	93	93	99	99
14	Korea, Republic of	94	94	98	95
15	Kyrgystan	96	96	99	88
16	Lao, PDR	74	74	64	76
17	Malaysia	94	95	96	94
18	Marshall Islands	94	97	97	95
19	Mongolia	96	96	97	96
20	Myanmar	90	90	88	90
21	Nepal	82	82	86	83
22	New Zealand	93	90	91	93
23	Pakistan	88	88	86	88
24	Papua New Guinea	56	56	55	61
25	Philippines	87	85	88	86
26	Singapore	97	96	95	97
27	Solomon Islands	79	79	68	99
28	Sri Lanka	99	99	99	99
29	Tajikistan	93	93	94	95
30	Thailand	99	98	98	99
31	Timor Leste	72	72	66	72
32	Turkmenistan	96	96	99	96
33	Uzbekistan	99	99	98	99
34	Vietnam	93	88	98	94

Figure 69-1 Estimated coverage of basic childhood vaccines by country, 2010. DPT3, at least 3 doses of DPT vaccine; Hep3, at least 3 doses of hepatitis B vaccine; MCV, at least one dose of a measles-containing vaccine; Pol3, at least 3 doses of polio vaccine. Many Global Alliance for Vaccines and Immunization–eligible countries (shaded) have similar coverage rates of basic vaccines as countries at higher levels of economic development, illustrating the success of Expanded Programme on Immunization.

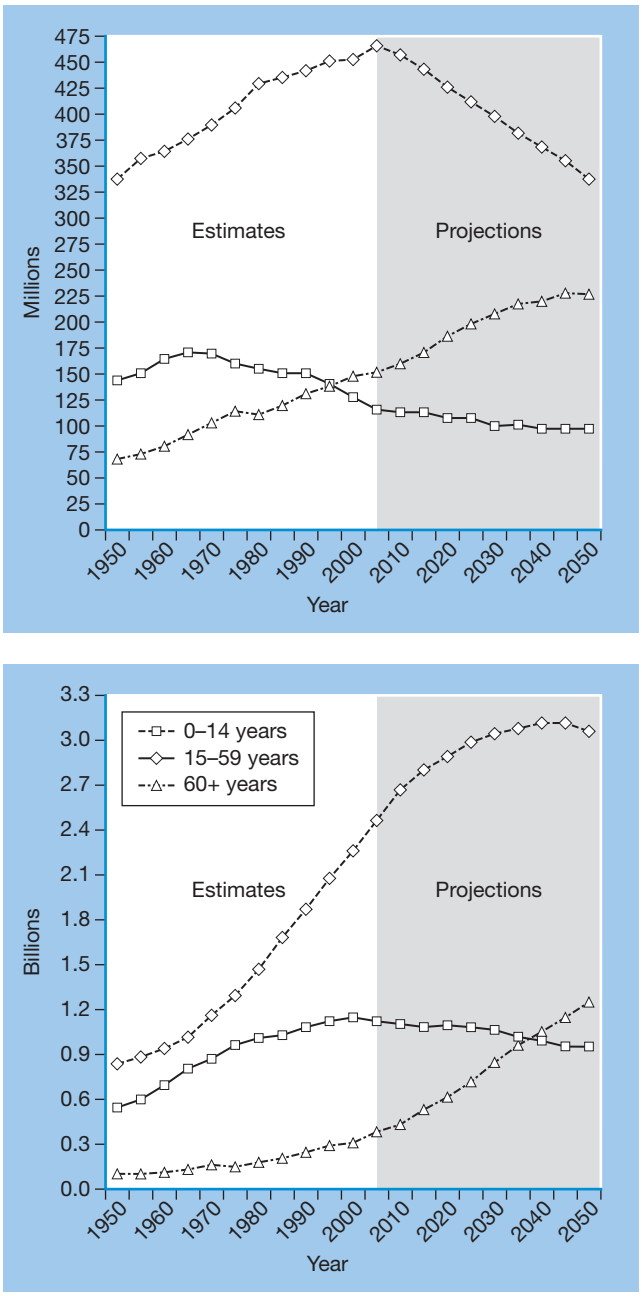


Figure 69-2 Population strata by age in Europe (upper) and Asia (lower), 1950-2050 (projected). The crossover point when the population of adults older than 60 years exceeded the population of children younger than 14 years was crossed in Europe around 1995; that crossover is projected to occur in Asia around 2037, within a generation from now.

susceptibility of older adults to neurotropic flaviviruses and suggesting a future need for adult vaccination.[35] Hepatitis A, interestingly, is now principally a risk in the cohort of young adults who were raised in an era of economic development and improved sanitation and who therefore lack natural immunity but were born before routine childhood vaccination was implemented.[36] A catch-up program to fill this demographic "hole" has been recognized by adult vaccination recommendations in some countries. In China, adult measles vaccination is under discussion, as more than 100,000 cases have occurred annually in the last 5 years, 26% in adults older than 20 years and 28% in infants who had not received their first vaccine dose; respective proportions in the more economically developed Eastern provinces are 40% and 25%. The growing awareness of adult vaccination is reflected in an increasing number of countries with adult vaccination recommendations (Table 69-3).

Table 69-3 Adult Immunization Recommendations by Antigen and Jurisdiction, Asia-Pacific Region*

Jurisdiction	Tdap variations†	Seasonal influenza	Pneumococcal 23-valent	MMR	Varicella	Hepatitis B	Hepatitis A	JE	Meningococcal	HPV	Typhoid	Rabies
Australia		65 y+, 50 y+, aboriginal and Torres Strait islanders	65 y + 50 y+, aboriginal and Torres Strait islanders					Travelers to endemic areas of Australia				
Hong Kong		65 y+, 6 mo-64 y with risk conditions, pregnant women, health care workers, poultry workers, pig farmers, and abattoir workers	65 y +									
Korea	**Tdap × 1 Td every 10 y**	**50 y+, pregnant women, high-risk groups**	**65 y + and high-risk groups, 1 dose**	**Unvaccinated high-risk groups**	**Unvaccinated and seronegative**	**Seronegative**	**30- to 39-y-olds**		**Military recruits; dormitory residents**	**Unvaccinated up to 29 y old**		
New Zealand	TD, 45, 65 y	65 y +		Rubella-susceptible women of childbearing age		Contacts of hepatitis B surface antigen carriers						
Philippines	**dT, primary vaccination for susceptible persons, every 10 y**	**50 y+, high-risk groups, health care workers and workers in essential services, all wanting to reduce risk, including travelers**	**60 y+, high-risk groups**	**All, particularly high-risk groups**	**All, particularly high-risk groups**	**All, particularly high-risk groups**					**Food handlers, health care workers and trainees, laboratorians, contacts of case**	**Health care workers, veterinarians and trainees, laboratorians, field workers**
Sri Lanka				Rubella, 15-44 y not previously vaccinated								

*Bold type indicates recommendations of academic or practitioner societies.
†Tetanus toxoid vaccine for pregnant women is recommended in nearly all Expanded Program of Immunizations schedules within the region.

Two other population trends that will influence the demand for vaccines and channels for their delivery are urbanization and income disparity.[37] The urban-dwelling population in Asia is projected to increase by almost a billion persons between 2005 and 2025, from 1.5 billion to 2.4 billion, while the rural population will decline only slightly. Urban crowding is likely to affect the transmission patterns of certain person-to-person transmitted diseases and even of infections acquired from environmental sources. Dengue, for example, is transmitted by mosquito vectors that are more prevalent in urban environments; the already great need for a dengue vaccine will almost certainly increase with the growth of urban centers.[38] While the growing size and number of large cities may increase transmission of certain infections, delivery of vaccine and of health care in general is better organized in cities than in rural areas. Specific interventions are needed to ensure that the existing disparity in access to health care between urban and rural dwellers does not widen.

Associated with urbanization is the increasing income gap in many countries that, in the health arena, has translated into a two-tiered system of health care, including preventive medicine. While vaccines are regarded by many as a public good to be provided as a government service, as mentioned, access to the increasing number of new vaccines is likely to be stratified by income level and ability to pay, as governments must choose among increasingly costly vaccines and other health interventions. As shown in Table 69-1, pediatric societies in a number of countries promulgate recommendations emulating those of the US ACIP, and it is likely that these schedules, aimed at practitioners serving private-paying families, will diverge increasingly from the national EPI schedules benefiting the majority of children in those countries. How the public and governments will respond to an increasing disparity of what has been perceived as a basic medical service remains to be seen.

In coming years, more novel vaccines are likely to be developed in Asia or licensed first in Asia for a regional, developing world, or international market. These trends and the accompanying need to strengthen regulatory agencies in the region have been recognized by the WHO and NRAs. Revising and harmonizing guidelines and procedures to international standards and enforcing procedures in a consistent and predictable manner will improve the timely introduction to the region of vaccines developed internationally. As important, compliance with international standards will be required of regional manufacturers hoping to license locally developed vaccines more broadly. As many countries still rely on a certificate of pharmaceutical product, considerable investment in infrastructure and training will be needed for their NRAs to provide full regulatory reviews of new applications. Chinese manufacturers currently export a limited number of vaccines, mainly to African and Latin American countries, but their horizons undoubtedly will expand. Similarly, while nonconformity with international intellectual property conventions has been an obstacle to introducing internationally developed products to some countries in the region, governments and local manufacturers may find themselves taking a stricter view as they themselves develop novel vaccines.

A specific area of regulatory control needing particular attention is the strengthening of national control laboratories. Many countries lack the laboratory capacity to test samples for lot release, and because manufacturing and testing technologies change rapidly, keeping up with new procedures and purchasing needed equipment are ongoing challenges. Continuous support also is needed to produce working quantities of reference standards, validation of new assays, staff training, and proficiency testing. As resources are unavailable in many countries to establish and maintain a fully functioning national control laboratory, a regional network has been proposed as an approach to share expertise and to divide workload, while at the same time standardizing methods and criteria. Field surveillance of adverse events following immunization is another area of pharmacovigilance requiring strengthening in many countries.

Regulatory oversight of clinical trials and human subjects protection are other areas that are under growing pressure for improvement. Multinational companies have increased the number of clinical trials in Asian countries to reduce costs and to obtain local registration of products. Their activities are serving an important role in strengthening compliance with good clinical practices, as many groups conducting trials in the region have limited experience with these precepts and procedures. Countries in the region have an interest to establish and enforce clear guidelines, not only as hosts to an increasing number of trials but also because their manufacturers, as future sponsors of new products, will be accountable internationally to uphold recognized standards.

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