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75 Immunization in the Asia-Pacific Region

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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 nine Gavi (The Vaccine Alliance)–eligible countries, as well as others that meet Gavi low-income, but not other, eligibility criteria.[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 global vaccination programs by countries that also are vaccine exporters. While China, India, Indonesia, and Vietnam are Gavi-graduate or Gavi-eligible countries, eight manufacturers located there and in Korea are among the 12 Developing Country Vaccine Manufacturers Network (DCVMN) suppliers that produce 75% of United Nations (UN) agency-procured vaccine doses.[2] Asian manufacturers have evolved from providers of downstream vaccine processing, to developers of lower-cost production solutions for previously licensed vaccines, such as hepatitis B (HepB), oral polio, diphtheria-tetanus-pertussis (DTP) combination vaccines incorporating *Haemophilus influenzae* type b (Hib) antigen, measles-containing vaccines, and more recently, group A meningococcal glycoconjugate vaccine. At the same time, they have become innovators of novel products such as an oral cholera vaccine, virus-like particle hepatitis E and live-attenuated hepatitis A vaccines, typhoid glycoconjugate vaccine, rotavirus vaccines, and inactivated enterovirus A71 (EV-A71) vaccine—representing, in fact, a continuation of local innovation to meet public health needs to control regionally important diseases such as Japanese encephalitis (JE), hemorrhagic fever with renal syndrome (HFRS), and Kyasanur Forest disease (KFD; see "Kyasanur Forest Disease Vaccine" later).

While investment in biomedical research and development (R&D) from 2007 to 2012 declined in the United States, Canada, and Europe, expenditures by countries in Asia-Oceania increased from 18.2% of the global share to 23.8%, led by China.[3] Interestingly, inflation-adjusted R&D spending by the U.S. public sector remained flat in this interval, while expenditures of U.S. industry declined by US$12.9 billion even as Asia-Oceania regional industry expenditures increased by US$15.1 billion, enlarging its global share from 19.0% to 26.5%. The trend may reflect industry recognition of the greater growth potential of vaccine opportunities in Asia, which as a component of other emerging-country markets, has been projected to exceed that of developed countries by 2020.[2,3] The trends in R&D expenditure also are reflected in growth rates of scientific publications and patents from Asian institutions that now exceed those from the United States and Europe.[4]

Manufacturers are entering the global network of vaccine production and supply, not only by providing basic Expanded Programme on Immunization (EPI) vaccines but also by commercially exporting products to Africa, Latin America, and within the region (e.g., meningococcal polysaccharide vaccine from China to Latin America and Africa; live attenuated and inactivated Vero cell–derived JE vaccines from China, Japan, and Korea, regionally; live attenuated hepatitis A vaccine from China, regionally; live attenuated and inactivated pandemic and seasonal influenza vaccines from India and China, internationally; and oral cholera vaccine from Vietnam, internationally). Previously, Asian manufacturers did not themselves market novel vaccines in Europe or the United States, choosing to distribute their innovative products, such as acellular pertussis and live attenuated varicella vaccines, through multinational companies. However, an increasing global integration is taking place, as multinational companies acquire Asian manufacturers (e.g., Sanofi-Aventis, France, acquired Shantha Biotechnics, India); Asian companies acquire or obtain technologies and distribution rights from European countries (e.g., inactivated polio vaccine by Serum Institute of India Ltd. acquiring Bilthoven Biologicals, Netherlands; Astellas, Japan, acquiring recombinant influenza hemagglutinin from Protein Sciences, U.S.; Thai Government Pharmaceutical Organization acquiring chimeric JE vaccine from Sanofi-Pasteur, France; and Biological Evans, India, acquiring JE vaccine from Intercell AG, Austria); and vaccine codevelopment is agreed between entities in developed and Asian countries (e.g., genetically modified, inactivated HIV vaccine codeveloped by Sumagen, Korea, and the University of Western Ontario, Canada; mycobacterial proteinAg85A candidate tuberculosis vaccine codeveloped by Tianjin CanSino Biotechnology, China, and McMaster University, Canada; universal influenza vaccine codeveloped by Xiamen Wantai and Sanofi-Pasteur, France; and novel pneumococcal conjugate vaccine codeveloped by SK Chemicals, Korea and Sanofi-Pasteur, France).[2,4,5]

The role of Asian companies as developers and providers of neglected and improved vaccines for the region and, for developing countries more generally, is an emerging trend as illustrated by the joint research activity agreement between the National Research Council, Canada, and the Chinese National Biotec Group that covers development of *H. influenzae* type a and Hib bivalent conjugate vaccine, novel mucosal adjuvants and therapeutic vaccines against *Helicobacter pylori* infection, and cell culture manufacturing platforms for viral and vectored vaccines. A Korean-manufactured biosimilar (generic) biological, infliximab, now is licensed in Europe, a step toward commercial expansion of Asian region-manufactured biologicals to developed countries. The emergence of Asia as the base of new multinational vaccine companies with broad development, production, and distribution capabilities is on the horizon, even as consolidation of existing companies occurs elsewhere.[6–8]

The broad income range within countries in the region results in large population segments that have sufficient means to pay for vaccines out-of-pocket. Even among countries that otherwise qualify economically for Gavi funding (e.g., India), substantial numbers of families can avail themselves of vaccines not covered by the national EPI, resulting in a two-tiered system of vaccination, paralleling the public–private dichotomy of healthcare delivery in general. Practitioners serving these and expatriate families generally follow current U.S., 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 (e.g., for JE vaccine in southern and Southeast Asia) to a degree of skepticism equal to, if not more deeply and widely held, than vaccine hesitancy in Europe and the United States. Within the last 20 years, Japan discontinued routine childhood vaccine programs for combination measles-mumps-rubella, influenza, and JE, and withdrew recommendations for the human papillomavirus (HPV) vaccine for adolescents, owing in several of instances, to incorrectly thinking that coincidental adverse events were causally related. The requirement for subcutaneous, as opposed to IM administration for all vaccines, exemplifies the misattribution of adverse reactions, arising in this case from an extrapolation of muscle contractures resulting from repeated IM administration of antibiotics, to other intramuscularly administered products, including vaccines.[9,10] The extrapolation has had unintended consequences of impeding the licensure of vaccines with newer adjuvants with mechanisms of action that require IM administration. With the global spread of information, concerns over the thimerosal content of childhood vaccines and vaccine-associated autism have been as active a parental concern among middle-class families in developing countries as elsewhere. Parental refusal of routine JE vaccination in Korea and significant declines in vaccine coverage occurred in a different context after seven cases of temporally related cases of anaphylactic shock and neurological disease, including five deaths, occurred in 1994. The cases could not be excluded as causally related to administration of the mouse-brain–derived vaccine, prompting a national debate and establishment of a vaccine adverse events reporting scheme, a national vaccine injury compensation system, and introduction of a live attenuated JE vaccine derived from a nonneural tissue substrate.[11]

From this mosaic, we 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 (e.g., pandemic influenza and JE vaccines) or vaccination topics common to developing countries (e.g., initiatives surrounding injection safety, measles and neonatal tetanus elimination, and polio eradication, nor financing mechanisms). 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 focus on childhood vaccines and vaccination and on 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 75.1). These include vaccines for JE, Hantaan (HTN)- and Seoul (SEO) virus-related HFRS, Russian spring–summer encephalitis, KFD, cholera, severe acute respiratory syndrome, 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 EV-A71 have potential for broader use internationally, an indicator of the region's transition from a provider of fill-finish and manufacturing capacity to a full-fledged participant in biotechnology research and clinical development.

Japanese Encephalitis 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 or inactivated vaccine (SA14-14-2 strain) grown in primary baby hamster kidney (PHK) cells and in higher-income countries with Vero cell–derived inactivated vaccines (licensed in the United States, Australia, Canada, and Europe, as well as several Asian countries) or a replicating chimeric yellow fever–JE virus recombinant vaccine (manufactured in Thailand). Details are provided in Chapter 33.

Tickborne Encephalitis Vaccine

To control cases and occasional outbreaks of the Far Eastern subtype of tickborne encephalitis 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 59.

Kyasanur Forest Disease Vaccine

The Kyasanur Forest disease virus (KFDV) is a highly pathogenic member of the family Flaviviridae causing a zoonosis, KFD, that is transmitted by the bite of infective ticks (*Haemaphysalis spinigera*) primarily in its nymphal stage, and characterized by acute febrile illness with severe hemorrhagic manifestations.[12] It was first described from outbreaks centered in Karnataka State, India, among herders and villagers with forest exposure and was considered to be localized in the Shimoga district area of the state. However, since first being reported in 1957, the virus has been found in other areas of India including the Kutch and Saurashtra parts of Gujarat state, Andaman Islands and West Bengal. It is estimated that close to 500 cases of KFD occur in India every year and, from 2003 to 2012, among 823 confirmed cases, 28 were fatal.

Following the outbreak in India various vaccines including a formalin inactivated Russian Spring Summer Encephalitis virus, a Russian Spring-Summer Encephalitis virus–based mouse-brain vaccine, and a live attenuated vaccine that was serially passaged in tissue culture were tried but with limited success.[13] Finally, a formalin inactivated vaccine with the KFD virus grown in chicken embryo fibroblasts was tested in a large field trial from 1990 to 1992 among inhabitants of 72 affected villages. The disease attack rates reported were 0.15% (14/9072) among persons receiving one dose and 0.047% (10/21,083) among recipients of two doses, respectively, compared to an attack rate of 0.870% (325/37,373) in unvaccinated persons, for vaccine efficacies of 82.4% and 94.8%, respectively.[14] The vaccine was subsequently commercialized and is produced by the state Institute of Animal Health and Veterinary Biologicals, Hebbal, Bangalore, and has been central to KFD prevention efforts in the state of Karnataka. Annual vaccinations have been done since 1990 in the Shimoga and adjacent districts wherein two doses of the vaccine were administered in individuals 7 to 65 years of age at an interval of 1 month. Periodic boosters were also administered after 6 to 9 months.

However, recent observations suggest a lower field effectiveness than had been reported previously, especially following a single dose, while overall coverage has also been low. Between 2005 and 2010, effectiveness among individuals

Text continued on p. 1472

TABLE 75.1 Pediatric Immunization Recommendations by Antigen and Jurisdiction, Asia-Pacific Region, 2014[a]

Jurisdiction	BCG	HBV	DTP Combinations	Hib	Polio	PCV/PnPS	Rota	Dengue
Australia		B	DTaP-Hib-HBV-IPV 2, 4, 6 mo; DTaP 18 mo; DtaP-IPV 4y; dTap 10–15 y	2, 4, 6 mo; Hib-Men C, 12 mo		PCV 2, 4, 6, mo; *PCV 12-18 mo*; PCV 12 mo (medical risk); PPS 4 y (medical risk)	2, 4, 6 mo	
Bangladesh	B		DTP-Hib- HBV, 6,10,14 wk; TT, 15 y		OPV, 6, 10, 14, 38 wk; IPV 14 wk	6, 10, 18 wk		
Bhutan	B	B	DTP-Hib- HBV, 6, 10, 14 wk; DTP, 24 mo; Td, 6, 12 y		OPV, B, 6, 10, 14 wk IPV, 14 wk			
Brunei Darussalam	B	B, 1, 6 mo	DTP-Hib, HBV, IPV, 2, 4, 6 mo; DTaP, IPV, 5 y	Hib, 1 y	IPV, 2, 3, 4 mo			
Cambodia	B	B	DTP-Hib, HBV, 6, 10, 14 wk		OPV, 6, 10, 14 wk	6,10,14 wk		
China	B	B,1,6 mo	DTaP, 3, 4, 5, 18 mo; DT 6y; *DT 4 y*		OPV 3, 4, mo; 4y IPV 2 mo; *IPV 2, 3 mo*			
Democratic People's Republic of Korea	B	B	DTP-Hib- HBV, 6, 10, 14 wk; TT, 3–4 y		OPV, 6,10,14 wk; IPV, 14 wk			
Hong Kong	B	B, 1, 6 mo	DTaP-IPV, 2, 4, 6 mo, 1.5 y, Primary 1; Primary 6, dTap-IPV			2,4,6 mo, 1.5y, Primary 1		
India	B	B, **6–10 wk, 6 mo**	DTP-Hib-HBV, 6, 10, 14 wk; DPT 16–24 mo, 5 y; TT, 10–16 y; **DTaP, 6, 10, 14 wk, 16–18 mo, 4–6 y; TdaP, 10–12 y**	**6, 10, 14 wk; 16–18 mo**	OPV B, 6, 10, 14 wk, 16–24 mo; *IPV, 14 wk;* **IPV, 6, 10, 14–18 wk, 16–18 mo; OPV 6, 9 mo, 4–6 y**	*6, 10,14 wk; 12–18 mo;* ***PnPS, 2–18 y***	**6, 10, 14 wk**	
Indonesia	1 mo; **B– 2 mo**	0–7 d	DPT-Hib-HBV, 2, 3, 4, 18 mo; Td 7–8, 8–9 y; **DTP, 2, 3, 4, 18 mo, 15–18 mo, 5 y**	**2, 3, 4, 15–18 mo**	OPV, B, 1, 2, 3, 4 mo; *IPV, 2, 3, 4 mo;* **IPV, 2, 4, 6 mo, 1.5–2, 5 y**	**2, 4, 6, 12–15 mo**	**2,4,6 mo**	9 mo + × 3
Japan	7 mo	2, 3, 7 mo	DTaPIPV 3, 4, 5, 18 mo	2, 3, 4, mo 1 y		2, 3, 4, mo, 1 y	**Dose 1, <15 wk × 2 or 3**	
Korea	B	B, 1, 6 mo	DTaP, 2, 4, 6 mo; 15–18 mo, 4–6 y; Td/ Tdap, 11–12 y	2, 4,6, 12–15 mo	IPV, 2, 4, 6 mo; 4–6 y	2, 4, 6, 12–15 mo	**2,4, or 2,4,6 mo**	
Lao People's Democratic Republic	B	B	DTP-Hib-HBV, 6, 10, 14 wk; Td 15 y		OPV, 6, 10, 14 wk IPV 14 wk	4, 10, 14 wk		

ANTIGENS									
MCV-rubella	**Varicella**	**Men**	**JE**	**HPV**	**Influenza**	**HepA**	**Typhoid**	**Rabies**	**HFRS**
MMR, 12 mo; MMRV 18 mo	10–15 y in schools	Hib-MenC, 12 mo	*1 y+, × 3; boosters every 3 y*	12–13 y in schools	*6 mo+ (at medical risk); 6 mo–5 y; 15 y+ (at-risk ethnic groups)*	*1–2 y × 2*			
M 15 mo; MR 38 wk, 15 y									
MR, 9, 24 mo				12–18 y × 2 in 6th grade girls					
MMR, 12, 18 mo				13 y × 3	*< 2 y*				
9, 18 mo			SA14-14-2, 9 mo						
MR, 8 mo; MMR, 18 mo; *MMR, 4–5 y, M college entry*		A, 6–18 mo (polysaccharide); AC, 3, 6 y (conjugate)	SA14-14-8 mo, 2 y; *inactivated, 8 mo × 2, 2, 6 y*		6 mo to 8 y, × 2	Live, 18 mo; *inactivated, 18 mo, 2 y*			*16–60 y × 3*
M, 9, 15 mo			*SA14-14-2, 1 y*						
MMR, 1 y; MMRV, Primary1	1 y	1 y			*6 mo, 6 y*				
9, 16–24 mo; **MMR, 9, 15–18 mo, 4–6 y**	**15 mo, 4–6 y**	***2–18 y***	*SA14-14-2, 9, 16–24 mo*	**10–12 y/9–26 y**	***6 mo + annually***	**12, 18 mo, inactivated; 12 mo, live**	**TCV, 9–12 mo, 2–3 y**	***B+ × 3***	
M, 9 mo, 2, 6 y; **M, 9 mo; MMR, 12 mo, 5 y**	**12 mo +**		12 mo, 24–36 mo	**10–18 y × 3**	**6 mo +**	**24 mo+, × 2**	**24 mo + × 3**		
MR, 1 y, 5–7 y; **mumps, 1, 5–6 y**	12, 18 mo		36, 37 mo, 4, 9 y		6 mo–12y, × 2 annually; 13y+, 1 × annually	**1 y+ × 3**			
MMR, 12–15 mo; 4–6 y	12–15 mo		1–3 y × 3, 6 y, 12 y; SA14-14-2, 1–3 y × 2	12 y × 2	6 mo +, IIV, 24 mo + LAIV	1–3 y × 2	PS, 2 y +; oral, 4–6 y × 3–4		10 y + × 2 + 1 booster
MR, 9 mo			live vaccine, 9 mo	*10 y + 6 m girls, 5th grade*					

Continued on following page

TABLE 75.1 Pediatric Immunization Recommendations by Antigen and Jurisdiction, Asia-Pacific Region, 2014[a] *(Continued)*

Jurisdiction	BCG	HBV	DTP Combinations	Hib	Polio	PCV/PnPS	Rota	Dengue
Malaysia	B	B, 1, 6 mo	DTaP-Hib-IPV 2, 3, 5, 18 mo; DT, 7 y; TT, 15 y			**2–6 mo × 1–3, 12 mo**	1.5–5 y × 2 or 3	
Mongolia	B	B	DTP-Hib-HBV, 2, 3, 4 mo; Td, 7, 15 y		OPV, B, 2, 3, 4 mo; IPV, age TBD	TBD		
Myanmar	B– 2 mo	B, 6, 10, 14 wk	DTP-Hib-HBV, 2, 4, 6 mo		OPV, 2, 4, 6 mo; IPV, 4 mo			
Nepal	B		DTP-Hib-HBV, 6, 10, 14 wk		OPV, 6, 10, 14 wk; IPV 14 wk	6, 10 wk, 9 mo		
New Zealand	*B (high risk)*		DTaP-IPV-Hib-HBV, 6 wk, 3, 5 mo; DTaP-IPV, 4 y; dTap, 11 y	15 mo		6 wk, 3, 5, 15 mo; *PPS (high risk)*	6 wk, 3 mo	
Pakistan	B	B, 6, 10, 14 wk	DTP-Hib-HBV, 6, 10, 14 wk		OPV, B, 6, 10, 14 wk; *IPV, 14 wk*	6, 10, 14 wk		
Papua New Guinea	B	B	DTP-Hib-HBV: 1, 2, 3 mo; TT 7, 13 y		IPV, 3 mo; OPV 1, 2, 3 mo	1, 2, 3 mo		
Philippines	B	B	DTP-Hib- HBV, 6, 10, 14 wk; Td, 6, 10 y; **DTaP-Hib-HBV, 6–8, 10–16, 14–24 wk; DTaP-IPV-Hib, 12–18 mo; DTaP-IPV, 4–6 y; Tdap/Td, 7–18 y**		OPV, 6, 10, 14 wk; IPV 14 wk; **OPV/IPV, 6–8, 10–16, 14–24 wk**	*6, 10, 14 wk;* **6–8, 10–16, 14–24 wk, 12–15 mo**	*6–15, 32 wk;* **6–32 wk, 2 or 3**	*9 mo + × 3*
Singapore	B	B, 1, 5–6 mo	DTaP, 3, 4, 5 mo; 1.5 y; TdaP, 10–11 y	3,4,5,mo, 1.5 y	IPV, 3, 4, 5 mo; 1.5 y; OPV 10–11 y	3, 5, 12 mo		
Sri Lanka	B		DTP-Hib-HBV, 2, 4, 6 mo; DTP, 18 mo; DT, 5 y; Td, 12 y		OPV, 2, 4, 6, 18 mo, 5 y; IPV, 4 mo			
Taiwan	5 mo	B, 1, 6 mo	DTaP-Hib-IPV, 2, 4, 6 mo, 1.5 y; Tdap, 5 y			1, 2, 12–15 mo		
Timor-Leste	B		DTP-Hib-HBV, 6, 10, 14 wk		OPV, 6, 10, 14 wk; IPV, 4 mo			
Thailand	B	B, 1 mo	DTP-HBV, 2, 4, 6 mo; DTP 1.5, 4 y; Td, 12 y in 6th grade; **DTaP, 2, 4, 6, 18 mo; TdaP/DTaP, 4–6 y; TdaP/dT11–12 y**	**2, 4, 6, 18 mo**	OPV, 2, 4, 6, 18 mo, 4–6 y; **IPV, 2, 4, 6, 18 mo, 4–6 y;** IPV, age TBD	**2, 4, 6 mo, 1–2 y**	**2, 4, 6 mo;** *2, 4 mo*	**9 y + × 3**
Vietnam[b]	B	B	DTP-Hib-HBV, 2, 3, 4 mo; DTP 18 mo	9 mo	OPV, 2, 3, 4 mo			

[a]Schedules recommended as of April 2015. 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 months; Hebei, MR at 8 mo and MM (measles + mumps) at 18–24 months; Zhejiang, M at 8 months, MMR at 18–24 months, and MR at 15 years; Shanghai, M at 8 months, MMR at 18–24 months, and MMR at 4 years. *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.

[b]Oral cholera vaccine: 2 doses at 2–5 years in Thua Thien-Hue province.

aP, acellular pertussis; B, birth; BCG, bacille Calmette-Guérin; DTP, diphtheria, tetanus, pertussis; HBV, hepatitis B vaccine; HepA, 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; TBD, to be determined; TCV, typhoid conjugate vaccine.

ANTIGENS									
MCV-rubella	**Varicella**	**Men**	**JE**	**HPV**	**Influenza**	**HepA**	**Typhoid**	**Rabies**	**HFRS**
MMR, 9, 12 mo; MR, 7 y; *M, 6 mo*	**12 mo– 9 y, × 2**	**ACWY 2 mo+ × 1**	*Live, 9, 21 mo*	13 y + 6 mo, girls	**6 mo+ (chronic disease)**	**12 mo+ × 2**			
MMR, 9, 12 mo; MR, 7 y					6 mo– 14 y, chronic illness	14 mo, 2 y			
MR, 9 mo; M, 18 mo									
MR, 9, **15 mo**			*SA14-14-2, 12–23 mo*						
MMR, 15 mo, 4 y	15 mo, 4 y	*C (high risk)*		9–14 y × 2; 15–26 y × 3	*6 mo+ (at risk)*	*× 2 (high risk)*			
M, 9, 15 mo									
MR, 6, 9, 18 mo									
M, 9 MMR 12 mo; MR, 6 y; **M, 9–12 mo; MMR, 12–15, 16–72 mo**	12–15 mo; 18m-6 y		**9 mo, 18 y**	*× 2, age not specified;* **9–18 y × 3**	**6 mo +**	**1–2 y × 2**			
MMR, 12, 15–18 mo				HPV, females 9–26 y × 3					
MMR, 1, 3 y			SA14-14-2, 12 mo						
MMR, 12 mo, 5 y	1 y		15 mo × 2; 27 mo, 5 y		6 mo +	*12, 18 mo*			
MR, 9, 18 mo									
MMR, 9–12 mo, 2.5 y	**MMRV, 1–2, 2.5–6 y**		9–12 mo, × 2, 2.5 y; **9–18 mo × 2, 2–2.5 y**	**9–12 y × 2;** *girls, grade school 5–6 × 2*	**6 mo–12 y**, 6 mo to 2 y	*1–12 y × 2*			
M, 9 mo; MR, 18 mo			12 mo × 2, 2 y				*3 y*		

who received two primary vaccine doses was 62.4% (95% confidence interval [CI], 26.1 to 80.8), and 82.9% (95% CI, 71.3 to 89.8) among those who received two doses followed by a booster.[9] Moreover, vaccination during the months of April and May 2011 did not confer protection in an outbreak in Shimoga during the months of December 2011 to March 2012.[15] The reasons for low vaccine efficacy and coverage rates need to be investigated and the appropriate vaccine regimen for effective control requires further definition. Newer vaccine approaches (e.g.., chimeric or virus protein subunit vaccines) are being investigated to potentially replace the current vaccine.

Elsewhere, a nearly identical strain to the KFDV was isolated from a patient suffering from acute febrile illness from Yunnan province, China in 1985. Seroprevalence studies indicate that KFDV (or the Nanjianyin virus or a related tickborne flavivirus) may be present in various parts of southwestern China.[16] In 1995 a virus similar to KFDV called Alkhurma hemorrhagic fever virus was isolated from patients with febrile illness in Saudi Arabia.[17] Overall, 10 cases with two deaths occurred in sheep and camel handlers exposed to a tick *Ornithodoros savignyi*. The disease has now been confirmed to be more widespread in the country than previously considered.[12]

As tickborne diseases are "diseases of place," KFD virus itself, if it spreads, is likely to disseminate locally. Nevertheless, the discovery of antigenically related viruses elsewhere, such as Alkhurma hemorrhagic fever virus, suggests a potential for more widespread use of KFD vaccine, depending on public health needs.

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 1000 annual cases in the Republic of Korea and more than 100,000 cases in China.[18] 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 bunyavirus, HTN virus was isolated from the striped field mouse, *Apodemus agrarius*, which proved to be the principal viral reservoir in most areas of Asia. Later, antigenically related SEO 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. A multitude of hantaviruses now have been described globally.

The widespread impact of HFRS in China led public health authorities in the 1980s and 1990s to pronounce the disease second only to HepB as a public health menace, and, beginning in 1991, several Chinese vaccine manufacturers used SMB, primary baby gerbil kidney cells (GKCs) or PHK cells to produce inactivated, monovalent vaccines against HTN or SEO viruses. The GKC vaccine was inactivated by β-propiolactone and the other two by formalin. Subsequently, Vero cell line-derived vaccines have been developed. These vaccines were evaluated in nine Chinese provinces hyperendemic for HFRS during 1994 to 2000.

The GKC-derived vaccine against HTN virus produced seroconversions to putatively protective titers of neutralizing antibody in 70.0% of subjects after three primary doses at 0, 7, and 28 days, the proportion rising to 91.2% after a booster at 1 year, and declining to 59.0% at 2 years and 38.9% at 3 years.[1] Similar immunogenicity results were reported for the PHK-derived vaccine and the purified SMB vaccine.[19]

In a randomized, controlled, three-arm trial of GKC vaccine in which vaccinated subjects received three primary doses and a booster at 1 year, 18 HFRS cases were observed in the 7866 age-, sex-, and residence- matched controls, and 23 cases in the 10,196 unvaccinated subjects of similar age (16 to 60 years), compared with none in 7866 vaccinees during 76 months of follow-up, for a protective efficacy of 100% (95% lower confidence limit of 81.94%, $P = .00003$, cumulative binomial probability).[20] Efficacy of the three primary doses alone was shown in the year between administration of the three primary dose series and the booster dose: with zero cases in the vaccinated, and nine and 10 cases in the unvaccinated and control groups respectively. Among 41 cases in the control and unvaccinated groups, 24 were caused by HTN virus, 13 were caused by SEO virus, and four by a virus of indeterminate serotype. Thus, the monovalent GKC-derived HTN virus vaccine was protective not only against the homologous virus, but also cross-protective against SEO virus. No vaccine-related serious adverse event was reported during the trial, and mild local and systematic reactions were reported in 3.78% of vaccinees.

The efficacies of the PHK vaccine and the purified SMB vaccine were similar: in nonrandomized trials, one HFRS case was found in 40,757 recipients of PHK vaccine, compared with 53 in 47,313 unvaccinated subjects, a reduction of 97.81%; for the purified SMB vaccine, the rates were 3.71 per 100,000 (1/26,942) versus 97.98 per 100,000 (34/34,699) for vaccinees and unvaccinated subjects, respectively, a reduction of 88.45%. The observed reductions were maintained through 6 years of follow-up. Nonsevere reactions were found in 1.57% of PHK vaccine recipients and in 3.26% of SMB vaccine recipients.[21,22]

Bivalent HTN and SEO GKC- and PHK-derived vaccines were developed and improved by purification procedures through gradient density ultracentrifugation or chromatography to be more immunogenic and less reactogenic. The purified bivalent GKC vaccine induced neutralizing antibody seroconversion against HTN virus and SEO viruses in 95.4% (83/87) and 93.1% (81/87) of volunteers, respectively, after two doses with an interval of 14 days, and 96.3% (78/81) and 95.1% (77/81), respectively, after a booster dose at 6 months. Only mild reactions were observed; local reactions in 1.72% (14/812) and systemic reactions in 2.83% (23/812) of the vaccinees.[23] The purified bivalent PHK vaccine induced neutralizing antibody seroconversion against HTN virus and SEO virus in 87.4% (90/103) and 89.3% (92/103) of subjects, respectively, after two doses separated by 14 days, and 93.3% (84/90) and 92.2% (83/90), respectively, after a booster dose at 6 months. No systemic reaction was found among 396 vaccinees and mild local reactions were observed in two (0.5%).[24]

The purified, bivalent GKC vaccine was tested for protective efficacy in a nonrandomized trial among 225,576 subjects, 16 to 60 years of age; 112,143 persons received the two primary doses with an interval of 14 days and a booster dose at 6 months; 113,433 persons were unvaccinated. The two groups were similar in age distribution. During 3 years of follow-up, 22 HFRS cases were found in 337,812 person-years among the unvaccinated, a rate of 6.51 per 100,000, compared with none in the vaccinated 334,086 person-years, a reduction of 100%.[25]

Several manufacturers have adapted their processes from primary gerbil or hamster cells to continuous Vero cells. The purified, bivalent Vero cell–derived vaccine administered in two doses separated by 14 days, induced neutralizing antibody against HTN virus and SEO viruses in 90.12% (73/81) and

91.35% (74/81) adult volunteers, respectively.[7] Mild systemic reactions were observed in 3.66% (12/328) and mild local reactions in 1.83% (6/328) of vaccine recipients.[26] The immunogenicity and safety profiles of the Vero cell–derived, purified bivalent vaccine were similar in children and older adults.[27]

Based on the above data, a schedule of two primary doses with an interval of 14 days, plus a booster at 6 months, has been recommended for the purified bivalent GKC-, PHK-, and Vero-cell–derived vaccines.

A postlicensure, retrospective study was conducted to measure the long-term effectiveness of the GKC vaccine among 24,556 adults 16 to 60 years of age, in 21 villages located in a hyperendemic area of Shaanxi Province.[28] HFRS incidence rates were compared between the vaccinated and the unvaccinated adults: 0.06% (4/6828) versus 3.09% (27/875), respectively, for the first 5 years after vaccination; 0.18% (10/5707) versus 1.53% (28/1827) in years 6 to 10; 0.11% (5/4673) versus 0.96% (26/2719) for years 11 to 14; and 0.29% (5/1713) versus 2.80% (6/214) at 15 to 17 years. The vaccine's effectiveness was thus estimated at 98.06%, 88.24%, 88.54%, and 89.64%, respectively, for the four study periods. The effectiveness was underestimated because the year of onset of HFRS was unknown for 36 cases, all of whom belonged to the unvaccinated group and were not included for analysis.[10] The overall HFRS attack rate was 0.13% (24/18921) in the vaccinees and 2.18% (123/5635) in the unvaccinated subjects, a reduction of 94.04%.[28]

A long-term study of the monovalent PHK-derived SEO virus vaccine also was conducted among adults 15 to 60 years old in a SEO virus-predominating area, from 1995 through 2005.[11] Only three primary doses were given at 0, 7, and 28 days without a booster. Seven HFRS cases were found in 1,467,188 subjects in the vaccine group, a rate of 0.48 per 100,000, and 412 cases were found in 6,379,278 controls, a rate of 6.46 per 100,000, with an overall reduction of 92.61% (95% CI, 87.09% to 98.13%) during the 11 years of the study. The vaccine's effectiveness was estimated at 100% for the first year, 95.56% for the second year, and 92.61% for the 11th year. The rate reductions in other years were approximately 92%.[29]

A SMB-derived HTN virus vaccine also was developed in the Republic of Korea and is available for at-risk individuals. 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 urbanization, rural economic development leading to improved (cement) houses, and grain harvesting and storage practices, 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 diminution of disease incidence and, potentially, discontinuation of routine vaccination in endemic provinces.

Other Novel Vaccines Developed in the Asia-Pacific Region

See Table 75.2.

Two similar live attenuated hepatitis A vaccines, based on the H2 and LA-1 strains, and measles vaccines, based on the Shanghai S-191 and Changchun-47 strains, have been licensed in China and are used domestically and exported. 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 based on the VABIOTEC vaccine but with improved production design is produced in India by Shantha (Sanofi, France). Both vaccines are used domestically and also exported. Similarly, live rotavirus vaccines based on local strains have been developed in India and China for local use. EV-A71 and related enteroviruses have emerged in major seasonal epidemics in Asia and Australia, leading to millions of cases and extensive social disruption as daycares and schools are closed. The extent and impact of seasonal outbreaks stimulated vaccine development in China, Taiwan, Malaysia, Singapore, and Japan, with government prioritization and support in some countries, analogous to mechanisms that facilitated pandemic influenza vaccine development. An *Escherichia coli*–expressed capsid peptide virus-like particle hepatitis E vaccine, approved by the China Food and Drug Administration, is the first novel recombinant vaccine developed and licensed in Asia. Its potential use in Africa, South Asia and, possibly, even in developed countries in immunocompromised or other risk groups could be envisioned.

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 Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use and good clinical practices standards will improve 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 (PAHO) leads regional vaccination programs and also provides central purchasing of certain qualified vaccines. However, the 10-nation Association of Southeast Asian Nations (ASEAN; includes 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.[30] A 1999 harmonization initiative, under auspices of a Pharmaceutical Product Working Group, aimed to remove barriers to regional commerce and to eliminate technical barriers to trade without compromising product quality, efficacy, and safety. Eventually, a subregional central or mutual-recognition procedure similar to that of the European Union could be 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 by a benchmark regulatory agency, resulting in a certificate of pharmaceutical product. By contrast, the national regulatory authorities of China, India, Japan, Korea, and Taiwan have required local clinical trials before or after registration, and in other countries, while data in local populations may not be required for registration, those data are important in deliberations on a vaccine's inclusion in the national schedule. For dengue, a disease of special public health urgency regionally, the global debut of candidate vaccines in the region is being considered, with individual country vaccine registrations ahead of approval by a benchmark agency and provision of a certificate of pharmaceutical product. The

Text continued on p. 1478

TABLE 75.2 Vaccines and Selected Vaccine Manufacturers in Asia[a]

Manufacturer	Viral	Bacterial and Pediatric Combination
AUSTRALIA		
Seqirus	Influenza, inactivated split	*Coxiella burnetii,* inactivated
CHINA		
Beijing Minhai	Inactivated poliovirus vaccine (Sabin strains)	*Haemophilus influenzae* (Hib)-tetanus toxin (TT) glycoconjugate Diphtheria, tetanus, and acellular pertussis (DTaP)-Hib
Beijing Lvzhu		Meningococcal (Men) A and C, glycoconjugate Men A, C, Y, W135 polysaccharide (PS); Men A, C + Hib glycoconjugate
Beijing Sanroad (Xiangrui)		Men AC glycoconjugate
Changchun Baike (BCHT)	Varicella, live attenuated (Oka strain) Rabies, Vero cell-derived	
Changchun Changsheng	Influenza, inactivated seasonal split H1N1 inactivated pandemic Hepatitis A virus (HAV), live attenuated, 2BS-cell, lyophilized (LA-1) Rabies, inactivated, Vero cell–derived, lyophilized Varicella, live attenuated, lyophilized (Oka strain)	DTaP, adsorbed; Men AC PS Men ACWY PS
China National Biotech Corporation comprising Beijing Tiantan Co, Changchun Institute of Biological Products (IBP), Changchun Keygen Co, Chengdu IBP-Rongsheng, Lanzhou IBP, Shanghai IBP, Wuhan IBP	Oral polio virus (OPV), trivalent, live attenuated Inactivated poliovirus vaccine (Sabin strains) Influenza, inactivated seasonal Influenza H1N1 pandemic inactivated Measles, mumps, rubella (MMR) combined, live attenuated Measles and mumps (MM) combined, live attenuated Measles and rubella (MR) combined, live attenuated Measles (M), live attenuated (S-192 or Chang-47 strains) Mumps, live attenuated (S79 strain) Rubella, live attenuated (BRD II strain) Hepatitis B (HBV), recombinant yeast 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, (SA14-14-2) Rotavirus, live, newborn calf kidney cell, oral (LLR strain) Tickborne encephalitis (TBE), inactivated, PHK cell–derived (Senzhang strain)	Diphtheria toxoid (DT), adsorbed TT, adsorbed DTaP, adsorbed Diphtheria and tetanus toxoids combined with whole-cell pertussis (DTwP), adsorbed DT, adsorbed Typhoid, Vi PS Meningococcal A PS, lyophilized Meningococcal A and C, PS lyophilized Leptospirosis, inactivated, bacille Calmette-Guérin (BCG) Brucellosis, live attenuated, lyophilized BCG PS + nucleic acid–therapeutic use Plague, live attenuated, lyophilized Anthrax, live attenuated, lyophilized Hib tetanus toxoid conjugate Pneumococcal PS, 23v
Chengdu Kanghua	Rabies, inactivated	Men ACWY PS
Chongquing Zhife		Hib glyconjugate Men AC PS Men AC glycoconjugate Men AC+ Hib glycoconjugate
Dalian Hissen (Hanxin)	Influenza seasonal inactivated HBV, recombinant yeast	
Dalian Aleph	Influenza, seasonal inactivated Influenza H1N1 pandemic, inactivated	
Guangzhou Promise (Nuocheng)	Rabies, inactivated, Vero cell-derived	
Huabei Jintan	HBV, recombinant Chinese hamster ovary (CHO) cell	
Hualan Bio	Influenza seasonal inactivated Influenza pandemic H1N1, inactivated HBV, recombinant, yeast	Men ACWY PS
Jiangsu Simcere Vaxtec	Influenza seasonal inactivated	
Jilin Maifeng	Rabies, inactivated, Vero cell–derived	
Jilin Yatai	Rabies, inactivated, PHK cell–derived	
Kunming Medical Biology Institute	Oral polio vaccine (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)	

TABLE 75.2 Vaccines and Selected Vaccine Manufacturers in Asia[a] *(Continued)*

Manufacturer	Viral	Bacterial and Pediatric Combination
Liaoning Chengda	Rabies, inactivated, Vero cell–derived, (PV2061 strain) JE, inactivated, Vero cell–derived (P3 strain)	
Ningbo Rongan	Rabies, inactivated, Vero cell–derived (aGV strain)	
Shanghai United Biotech		Cholera rB subunit-whole cell, oral
Shenzhen Kangtai	HBV, recombinant yeast	
Shenzhen sanofi-pasteur[b]	Influenza seasonal, inactivated	
Sinovac	Influenza, seasonal inactivated Influenza, pandemic H1N1, inactivated Influenza, avian H5N1, alum adjuvanted [NIBRG-14 A/VietNam/1194/2003(H5N1)RG strain] HAV, inactivated (Hm175 strain) HAV + HBV, inactivated, recombinant EVA71–inactivated	
Sinovac (Dalian)	Mumps, live attenuated	
Walvax Biotechnology		Hib-TT glycoconjugate Men A polysaccharide Men AC polysaccharide
Wuxi Royal (Luoyi)	HFRS, inactivated bivalent, Vero cell–derived	Men A and C, glycoconjugate, lyophilized
Xiamen Innovax	Hepatitis E, recombinant, *Escherichia coli*	
Yunnan Walvax (Wosen)		Hib-TT, conjugate (58534) Men A and C, glycoconjugate, Men ACWY PS
Zhejiang Pukang	HAV, live attenuated	
Zhejiang Tianyuan[b]	Influenza, seasonal inactivated Influenza pandemic H1N1, inactivated HFRS, inactivated bivalent, primary Mongolian gerbil kidney cell (Z10,Z37 strains) JE, inactivated, PHK cell (SA14-14-2)	Men A and C, PS Men AW135 PS
Zhejiang Vacin (Weixin)	Mumps, live attenuated (S79 strain) HFRS, bivalent inactivated, Vero cell derived	
Zhongke	Rabies inactivated PHK cell-derived (aGV strain)	
INDIA		
Bharat Biotech	Rabies, Vero cell–derived OPV, trivalent HBV, recombinant Live attenuated oral rotavirus vaccine (neonatal human strain 116E) JE inactivated Vero cell-derived (821564-XY Indian strain) H1N1 inactivated pandemic vaccine, Madin-Darby canine kidney (MDCK) cell-derived	TT DT DTP DTP-Hib DTP-HBV DTP-HepB-Hib Hib-TT glycoconjugate Typhoid Vi PS glycoconjugate
Biological E	HepB JE inactivated Vero cell-derived	TT Td DTP HBV-Hib-TT glycoconjugate
Biomed	OPV, trivalent	Typhoid Vi PS and glycoconjugate Hib glycoconjugate Men ACYW135 PS
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.	HBV, recombinant Rabies, inactivated, Vero cell–derived	TT DT DTP

Continued on following page

TABLE 75.2 Vaccines and Selected Vaccine Manufacturers in Asia[a] *(Continued)*

Manufacturer	Viral	Bacterial and Pediatric Combination
Panacea Biotech Ltd.	OPV 1 OPV 3 OPV, trivalent HBV	DTP DTP-HBV DTP-Hib-CRM_{197} glycoconjugate DTP-HBV-Hib-CRM_{197} 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) Inactivated polio	BCG TT, adsorbed DT, adsorbed DTP, adsorbed DTP-HepBV DTP-Hib DTP-HepB-Hib Td Hib-TT Meningococcal A-TT glycoconjugate
Shanta Biotech Ltd[b]	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 Influenza, inactivated seasonal, quadrivalet	
INDONESIA		
Biofarma	Influenza, inactivated seasonal OPV, trivalent OPV, type 1 OPV, types 1, 3 HBV, recombinant Measles, live attenuated (CAM-70 strain)	BCG Tetanus toxoid, adsorbed Td DT DTP DTP-HepB DTP-HepB-Hib
JAPAN		
Daiichi Sankyo-Kitasato	Influenza, inactivated split (seasonal egg-derived tetravalent); H1N1 and H5N1pandemic/prepandemic) H5N1 H5N1 pandemic, MDCK cell-culture derived Measles, live attenuated (AIK-C strain) Rubella, live attenuated (Takahashi strain) Mumps, live attenuated (Hoshino strain) MR, live attenuated	Tetanus toxoid, adsorbed DTaP, adsorbed DTPIPV (Salk strains, imported)
Denka-Seiken	Influenza, inactivated split (seasonal egg-derived tetravalent); H1N1 and H5N1 pandemic/prepandemic)	TT, adsorbed Leptospirosis polyvalent
Handai-Biken	Influenza, inactivated split (seasonal egg-derived tetravalent); H1N1 and H5N1 pandemic/prepandemic) Measles, live attenuated Tanabe strain Rubella, live attenuated Matsuura strain MR, live attenuated Varicella, live attenuated (Oka strain) JE, inactivated Vero cell–derived (Beijing strain)	TT, adsorbed DT, adsorbed DT toxoid, adsorbed DTaP, adsorbed Adsorbed diphtheria-purified pertussis-tetanus-inactivated polio (Sabin strains)
Japan BCG		BCG
Kaketsuken	Influenza, inactivated split (seasonal egg-derived tetravalent); H1N1 and H5N1 pandemic/prepandemic) H5N1 pandemic/prepandemic EB66 cell-derived HBV, recombinant, yeast-derived HAV, inactivated Rabies inactivated, cell culture–derived Smallpox, LC16m8 strain JE, inactivated Vero cell–derived (Beijing strain)	Tetanus toxoid, adsorbed DT toxoids, adsorbed DPT, adsorbed DTaP, adsorbed DPT, adsorbed IPV (Sabin strains)
Takeda	Measles, live attenuated Rubella, live attenuated Mumps, live attenuated MR, live attenuated H5N1 pandemic–Vero cell-derived	TT, adsorbed DT

TABLE 75.2 Vaccines and Selected Vaccine Manufacturers in Asia[a] *(Continued)*

Manufacturer	Viral	Bacterial and Pediatric Combination
KOREA		
Berna Biotech, Korea	HBV, recombinant HAV, virosomal	DTwPHibHepB
Boryung Biopharma	JE, inactivated, Vero cell-derived (Beijing Handai strain) JE, inactivated, SMB-derived	DTaP Typhoid, polysaccharide Vi (oral)
CJ Healthcare	Smallpox, cell culture-derived	
Daewoong	IPV	DTP, adsorbed
Green Cross	Influenza, inactivated split (seasonal trivalent and H1N1 pandemic) Influenza, inactivated split, MF59-adjuvanted H1N1 pandemic HFRS, inactivated SMB-derived (ROK84–105 strain) Varicella, live attenuated (MAV/06 strain) JE–SMB-derived JE, inactivated, Vero cell-derived (Beijing-Handai strain)	
Il-Yang Pharm	Influenza, inactivated, seasonal, quadrivalent	
LG Life Sciences	HBV, recombinant	DTaP Hib-TT glycoconjugate
SK Chemical	Influenza, trivalent, inactivated subunit Influenza, quadrivalent, MDCK cell-derived, inactivated subunit HBV, recombinant	DTaP Td
MYANMAR		
Department of Medical Research	HBV, recombinant Rabies, Vero cell–derived	
PAKISTAN		
CIRIN	Rabies, Vero cell–derived	
TAIWAN		
Adimmune	Influenza vaccine, inactivated split (seasonal and H1N1 pandemic) JE, inactivated, SMB (Nakayama strain)	TT, adsorbed
CDC		BCG TT, adsorbed DT, adsorbed dT, adsorbed
THAILAND		
Government Pharmaceutical Organization[b]	LAIV H1N1 pandemic JE inactivated SMB-derived, Beijing strain Rabies, Vero cell-derived OPV, trivalent Measles, MMR DTwP-HepB JE-YF17d chimeric live recombinant (Sanofi technology transfer)	
Queen Saovabha Memorial Institute		BCG
VIETNAM		
IVAC	Severe acute respiratory syndrome (SARS) virus, inactivated	BCG TT, adsorbed Td, adsorbed DTP, adsorbed
POLYVAC	OPV Measles MR (Daiichi-Sankyo technology transfer)	
Vabiotech	JE, inactivated, SMB-derived (Beijing-1 and Nakayama strains) HBV, recombinant yeast-derived HAV, inactivated Varicella (Green Cross technology transfer) Rubella (India Serum Institute technology transfer)	Oral cholera, whole cell, heat and formalin inactivated including toxin coregulated pilus (O1 classical and El Tor biotypes and O 139 strains) Men B-C (Finlay Institute technology transfer)

[a]Information obtained through surveys of local governments and manufacturers, through April 2015.
[b]Major investment/partnership with multinational company.

initiative is a collaboration among the nongovernmental organizations, the Dengue Vaccine Initiative, and the World Health Organization (WHO) Developing Countries Vaccine Regulatory Network (DCVRN). The WHO through the DCVRN has been actively working toward harmonizing procedures in affiliated countries, including China, India, and Indonesia, to bring those regulators under the WHO prequalification umbrella and to facilitate approval and supply of their products for Gavi and United Nations Children's Fund (UNICEF).[31]

The requirement of some national regulatory authorities for clinical data in local populations is based on a concern that racial, ethnic, or environmental differences could affect responses of the local population, both immunologically and in their risk for adverse events. 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 in Asia, for example, have found higher prevaccination and postvaccination antibody titers among Philippine and Taiwanese infants compared with European or historical control subjects, and in Korea, a considerably higher proportion of subjects were seropositive to meningococcal serogroup W135 polysaccharide at baseline than in the United States.[32–34] While the basis for these differences may be an earlier exposure in life to cognate or cross-reacting antigens (e.g., because of regional differences in host microbiomes), genetically restricted responses, as have been observed with HepB, measles, vaccinia, rubella, Hib, and other antigens, or, in the case of oral rotavirus vaccine, in genetically determined viral attachment or receptor binding molecules, have been described.[35–38] From the perspective of adverse events following immunization, the example of narcolepsy occurring in some recipients of an adjuvanted pandemic H1N1 vaccine illustrates the role of genetic background as a cofactor in risk.

In many examples, regulatory systems and processes in the region have had the effect of markedly slowing or effectively blocking the introduction of novel vaccines developed externally. In China, the introduction of an internationally registered and otherwise widely used product nevertheless necessitates recapitulating the entire clinical development program in China, including Phase I studies, despite an abundance of previously scrutinized evidence. This requirement introduces a delay of a decade or more for registration of internationally developed, as opposed to domestically developed, vaccines. Specifications in national pharmacopeias that deviate from established compendia, for example, exclusion of well-accepted excipients or methods, also have seriously impeded or prevented registration of foreign products or, when imposed with a revision of the pharmacopeia, have led to withdrawal of a previously registered product. Clinical trial processes also have hindered local introduction of established or novel products (e.g., a 2013 Indian Supreme Court ordered suspension of ongoing clinical trials and reexamination of previously approved trials was followed by a wholesale revision of clinical trial guidelines, leading to a temporary cessation of all industry-sponsored clinical trial activity). The potential inclusion of video recording of the informed consent process, newer insurance requirements and further proposed but unclear amendments to the Drug and Cosmetics Act that could impose criminal penalties against trial investigators for poorly defined violations may further limit trial activity.[39] China and Indonesia place severe restrictions on the exportation of clinical samples from study subjects, thereby requiring that validated laboratories and procedures are established locally, adding a barrier that has led to delays of or avoidance of clinical studies in those countries. Whether resulting from inexperience, a dearth of trained personnel, trade protection, or other reasons, administrative mechanisms in various countries in the region have had the effect of delaying the registration of proven vaccines that otherwise could have prevented significant morbidity and mortality with more timely introductions.

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 (i.e., government-owned corporations) has occurred (e.g., Commonwealth Serum Laboratories in Australia was privatized, and the six major government vaccine institutes in China now operate as a state-owned enterprise, China National Biotech Group; see Table 75.2). 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 and biologicals for domestic needs (e.g., 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). These and other facilities also fill and distribute bulk vaccines supplied by international manufacturers. Several private and state-owned enterprise manufacturers in the region are members of the DCVMN, a consortium that seeks to identify and develop solutions to common challenges faced by manufacturers in developing countries.[2,4,8,40]

A number of manufacturers (including 12 in five Asia-Pacific countries) operate under practices and procedures that have prequalified them to produce certain vaccines for UNICEF, PAHO, and Gavi purchases (e.g., pentavalent DTP combinations, oral polio vaccine, inactivated polio vaccine, HepB, rabies, influenza, oral cholera, and measles-containing vaccines) or that allow them to export vaccine to other countries in the region. A reliable supply of inexpensive diphtheria and tetanus toxoids combined with whole-cell pertussis (DTwP)-Hib-HepB combination vaccines, made possible largely by Indian and Korean manufacturers, has facilitated the introduction of Hib antigen into schedules of economically disadvantaged countries that otherwise would not have adopted the monovalent vaccine. Similarly, provision of measles and measles containing vaccine by Indian manufacturers was key to the elimination of that disease in Latin America and the current state of polio elimination could not have been achieved without supplies from Asian regional manufacturers. The provision of oral cholera vaccine for outbreak control in Haiti, Pakistan and other countries is an important example of the increasing ability of and global dependence on these manufacturers.

WHO prequalification requires that the manufacturers and plants not only must satisfy WHO good manufacturing practices 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 prequalification aided by WHO Blueprint and other vaccine safety-related guidelines have facilitated the improvement of vaccine-related pharmacovigilance in the region.

In China, the state-owned China National Biotec Group is the dominant supplier of vaccines in the country, providing 82% of doses used in the public program and 28% taken up

privately. The Group comprises 12 manufacturing sites, which produce some 40 products, including the first WHO prequalified vaccine produced in China (SA14-14-2 JE vaccine). Other private companies compete principally to provide vaccines for out-of-pocket sales at local centers for disease control and prevention and hospitals.

Within the ASEAN community, comprised principally of low- and middle-income countries, regional vaccine security has been a focus of discussion, reflected in the establishment of the ASEAN-Network for Drug, Diagnostics and Vaccines Innovation that focuses on a broad agenda of health technology development and collaborations on vaccine manufacturing and plans for regional vaccine purchasing—similar to PAHO's revolving fund. Similarly, the eight-nation South Asian Association for Regional Cooperation includes biotechnology in its agenda for cooperative research. A goal to achieve self-reliance in vaccine supply also has been articulated in Korea, in its 2020 horizon-setting.

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 75.2 lists the region's principal vaccine manufacturers and their licensed products. The list is not intended to be comprehensive, as the sometimes rapid emergence or disappearance of pharmaceutical and vaccine companies in China and elsewhere is difficult to track. 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 U.S. 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. Even for low-middle-income countries in the region, the total per capita expenditure for all healthcare may be less than the cost of a full course of a novel vaccine! On the other hand, national schedules in the region can be as comprehensive as to include the HPV vaccine (Australia) and influenza and varicella vaccines (e.g., 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 healthcare purchases (see subsequent text). As shown in Table 75.1, some national schedules provide optional recommendations for some antigens; 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 (e.g., 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 in the region, public health authorities now draw on external advisors to help formulate national vaccine recommendations in National Immunization Technical Advisory Groups (NITAG), resulting, in part, from activities of the Supporting Independent Immunization and Vaccine Advisory Committees Initiative (at the Agence de Médecine Préventive).[41–44] 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, National Technical Advisory Group for Immunization in India, and the Australian Technical Advisory Group on Immunization are examples of such medical advisory groups. In China, vaccine recommendations are made through the National Centers for Disease Control based on recommendations of the Chinese Expert Committee on EPI under the Ministry of Health and Family Welfare; however, provincial or local Centers for Disease Control may issue independent recommendations for specific vaccines or modify the national recommendation for routine vaccines (see Tables 75.1 and 75.3).

The issues considered by Asian NITAGs in formulating vaccine recommendations parallel those of other NITAGs, focusing on medical need, vaccine safety and efficacy, national resources, as well as implementation issues, including supply, cold-chain, fit within the national schedule, vaccine presentation, etc. Health economic analyses are considered in the deliberation of some committees or are provided by an independent body (e.g., the Health Intervention and Technology Assessment Program in Thailand); although, in general, the use of health technology assessments in the region lag behind the United States and United Kingdom. In some cases, industry sponsors, in providing such analyses to NITAGs in their justifications to include new vaccines into national programs, have played a role in introducing cost-to-benefit analyses to the recommendation process. In Indonesia and Malaysia, the halal status of vaccines is an important factor in public acceptance of a product and also is a consideration in the vaccine recommendation process, although there is movement to remove this consideration from debate.

In certain Asian countries, as well as in Latin America, the approval process to include a new vaccine into the national program is used to leverage multinational companies to foster local manufacturing expertise. In Brazil, technology transfer of the vaccine production process is required in turn for the vaccine's inclusion into the national schedule while, in Indonesia, all EPI vaccines are locally produced by BioFarma, and no new vaccine has been introduced into the national schedule unless it was produced locally. Technology transfer of some element of the manufacturing process also is a factor in introduction of new vaccines to Thailand and Malaysia. Such requirements may be tested as costly vaccines manufactured by more complex technologies are introduced to the region.

The recommendation process in Japan illustrates how, even after registration, organizational and administrative processes can result in a lengthy interval before a new vaccine is introduced to the national schedule.[44] Although, since 2009, Japan has recovered from a "vaccine gap"—the self-acknowledged interval during which antigens such as Hib and pneumococcal conjugate, rotavirus, HPV, inactivated polio and various combination vaccines were not introduced into Japan despite their widespread use in other developed countries—adoption of new vaccines into the National Immunization Program after their registration still lags several years. A number of sequential approvals lengthens the process: the Immunization Policy and Vaccination Committee provides an initial recommendation whether the newly registered vaccine should

TABLE 75.3 Adult Immunization Recommendations by Antigen and Jurisdiction, Asia-Pacific Region[a]

Jurisdiction	Tdap Variations[b]	Seasonal Influenza	Pneumococcal	MMR
Australia	DT 45, 54 y	65 y+, pregnant women, *>15 y+*	PPS 65 y+, *50 y+,* 15–49 y high-risk	
Brunei Darusalaam		Chronic illness, pregnancy, HCW, Hajj travelers		
Cambodia	TT pregnant women ×3 + 2 boosters			
China[c]		60 y+, high-risk groups, pregnant women	PPS 60 y+ (Shanghai)	
Hong Kong		50 y+, 6 mo–64 y with risk conditions, pregnant women, healthcare workers, poultry workers, pig farmers, and abattoir workers, BMI 30+	65 y+	
India	TT pregnant women	**>50 y**	>65 y	
Indonesia	**19–64 y: 3 primary doses, TdaP, Tdx2; 19 y+: Td every 10 years;** TT 15–39 y child-bearing-age women	**50 y+; 19–49 y (at-risk)**	**65 y+; 19–64 y (at-risk)**	**Varicella: 19–49 y, 2 primary doses; zoster: 50 y+ (at-risk)**
Japan		65 y+, 50–64 y with chronic disease	PPS 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**
Lao People's Democratic Republic		50 y+, chronic illness, pregnant women, HCW		
Malaysia	**19 y+, every 10 y**	Chronic illness, HCW, Hajj and other travelers, other high-risk groups; **19 y+**	**PPS 65 y+**	
New Zealand	Td, 45, 65 y TdaP–pregnant women 28–38 wk	65 y+, pregnant women, chronic disease, HCW, Hajj and other travelers, other high-risk groups		Rubella-susceptible women of childbearing age
Mongolia		15 y+, chronic illness, HCW, Hajj and other travelers		
Myanmar	TT pregnant women ×2			
Nepal	TT pregnant women			
Pakistan	Pregnant women ×3 + 2 boosters			
Philippines	Pregnant women ×2; **dT, primary vaccination for susceptible persons, every 10 y**	**50 y+, high-risk groups, healthcare workers and workers in essential services, all wanting to reduce risk, including travelers;** chronic disease, pregnancy, HCW, Hajj and other travelers, other high-risk groups	PPS, 60 y+, high-risk groups	**All, particularly high-risk groups**
Sri Lanka	TT pregnancy, schedule not specified			Rubella, 15–44 y not previously vaccinated
Thailand		>65 y, HCW, at risk		
Timor-Leste	TT pregnant women ×3 + 2 boosters			
Vietnam	TT pregnant women ×3 + 1 booster			

[a]**Bold type** indicates recommendations of academic or practitioner societies: italic type indicates recommendations for certain geographic areas or groups.
[b]Tetanus toxoid vaccine for pregnant women is recommended in nearly all Expanded Program of Immunizations schedules within the region. In the region, only Cambodia, Indonesia, Pakistan, and Papua New Guinea have not eliminated neonatal tetanus.
[c]Hepatitis E vaccine is recommended for food handlers in Xiamen.
HCW, healthcare workers.

Zoster	Hepatitis B	Hepatitis A	JE	Meningococcal	HPV	Typhoid	Rabies
70 y	Catch-up, all nonimmune						
>60 y							
60 y+	**19 y+: 3 doses (at-risk)**	**19 y+: 2 doses (at-risk)**		**19 y+: (at-risk)**	**19–49 y: 2 doses**		
Unvaccinated and seronegative	**Seronegative**	**30- to 39-y-olds**		**Military recruits; dormitory residents**	**Unvaccinated up to 29 y old**		
60 y+	**19 y+: 3 doses (at-risk)**	**19 y+: 2 doses (at-risk)**		ACWY, Hajj travelers	**females 19–26 y; males 19–21 y**	Food handlers	
	Contacts of hepatitis B surface antigen carriers						
All, particularly high-risk groups	**All, particularly high-risk groups**					**Food handlers, healthcare workers and trainees, laboratorians, contacts of case**	**Healthcare workers, veterinarians and trainees, laboratorians, field workers**
						Food handlers	

be classified as either "routine" or "voluntary," based on available data; the technical recommendation is considered by the Tuberculosis & Infectious Diseases Control Division which makes the administrative decision for the vaccine's inclusion in the national schedule; however, that decision requires additional legislative approval whether the disease (category A or B) qualifies for full or partial vaccine funding (up to circa 70%), respectively. The recommendation process is even lengthier than appearances suggest, as the Immunization Policy and Vaccination Committee does not convene a deliberative vaccine working group until after the product is registered, unlike the parallel activities of the U.S. ACIP and Food and Drug Administration. Only then does the committee assemble a dossier (Fact Sheet) that establishes the epidemiology of the disease and its local burden; if insufficient data are available, de novo studies might be required to establish need. The overall interval between vaccine approval and issuance of a recommendation typically is 3 years.

Other Asian countries have similar or even lengthier intervals between vaccine registration and full EPI implementation. In Thailand, for example, after a preliminary NITAG recommendation, a new vaccine is implemented in a pilot program to establish effectiveness and to collect additional safety experience. Such a program may be gradually extended to other localities over a period of as long as a decade before the antigen is provided nationally. For diseases with regional differences in disease burden, high-risk provinces may be covered first (e.g., JE vaccine initially was introduced in Thailand to eight high-incidence provinces and progressively, from 1990 to 2000, to all 76 provinces, while local production was established and expanded). For new, often costly vaccines, phased introduction provides a mechanism to accommodate their full EPI coverage costs over time. In the interim, local governments of wealthier provinces or municipalities have issued their own recommendations for vaccines to be reimbursed (e.g., Shanghai provides pneumococcal polysaccharide vaccine free of cost to older adults and Bangkok established a school-based HPV vaccination program, while neither vaccine is included in respective national schedules).

Innovative financing mechanisms have played an important role in the introduction of vaccines to low-income countries, and their extension to graduating Gavi will enable more rapid adoption of new vaccines in those countries. At the same time, tiered pricing, negotiated between sponsors, local government and other entities will aid middle income countries to accelerate vaccine adoption, as exemplified by introductions of PCV and rotavirus vaccines.

During the interval between a vaccine's registration and its inclusion in the national schedule, after which it is available without cost, out-of-pocket sales still may result in considerable uptake. While rotavirus vaccine is still considered a voluntary vaccine in Japan, coverage among infants is estimated to be approximately 50%. In Korea, although almost all pediatric vaccines are self-paid by parents, vaccine coverage for antigens such as Hib and pneumococcal conjugate vaccine rapidly reached coverage rates of approximately 90% that, with herd effects, led to disappearance of the respective diseases as quickly as in other countries. Although in Japan, the "voluntary" vaccine recommendation emanates from a government committee, in other countries, academic societies play the principal role in recommending vaccines that are not included in the EPI schedule. The Malaysian Pediatric Association, The Pediatric Society of Thailand, and The Philippines Foundation for Vaccination not only advise their respective ministries and NITAGs in formulating national recommendations, but also promulgate recommended schedules of administration for other approved but not EPI-covered antigens, emulating in large part or entirely from U.S., Australian, or European schedules. Table 75.1 distinguishes schedules of such bodies from respective national EPI schedules.

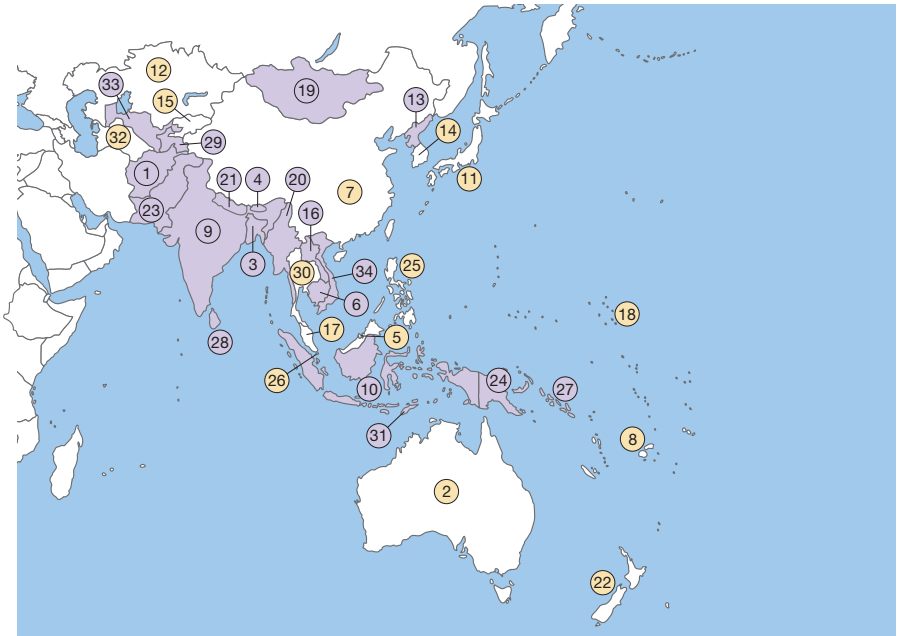
VACCINE DELIVERY AND COVERAGE

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 (e.g., 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 offices in Japan, and Australia). As vaccines generally are available free in public clinics, even in affluent countries, families may obtain them in government clinics or hospitals (e.g., 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, general practitioner, or other private clinics. In addition, as newer vaccines may be delayed in their introduction to the national reimbursement scheme, it is common for parents to pay voluntarily for these vaccines (see earlier). 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 centers for disease control and prevention; therefore, nearly all Chinese children receive free EPI vaccines, as well as payable optional vaccines (e.g., Hib, pneumococcal conjugate vaccines, varicella, rotavirus, and others) at public clinics. Fig. 75.1 summarizes the coverage for EPI vaccines for selected countries.[45]

Supplementary immunization activities have played a critical role in the elimination of polio from the WHO Southeast Asian Region that was achieved in 2014, and in ongoing efforts to eliminate measles and congenital rubella syndrome. Routine and supplementary immunization activities tetanus vaccinations have eliminated maternal and neonatal tetanus in all but four countries in the region: Cambodia, Indonesia, Papua New Guinea, and Pakistan.

FUTURE TRENDS AND CHALLENGES

Economic growth and development in Asia and secular trends in population structure and the evolution of healthcare 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 of age will nearly double, from 250.6 to 480.6 million. A demographic crossover point with more adults 60+ years of age than children younger than 15 years of age was reached in Europe in the 1990s, and will occur within another generation in Asia (Fig. 75.2).[46] 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



Country	2013 WHO-UNICEF estimated coverage, %*					
	DTP3	HepB3	Pol3	Hib3	MCV	MCV2
1 Afghanistan	71	71	71	71	75	40
2 Australia	91	91	91	91	94	92
3 Bangladesh	97	97	97	97	93	91
4 Bhutan	97	97	97	97	94	89
5 Brunei Darussalam	90	99	90	90	99	96
6 Cambodia	92	92	77	92	90	63
7 China	91	99	99	–	99	99
8 Fiji	99	99	99	99	94	94
9 India	72	67	70	20	74	42
10 Indonesia	85	85	86	4	84	79
11 Japan	98	–	99	–	95	93
12 Kazakhstan	98	99	98	98	99	99
13 Korea, DPR	93	93	99	32	99	99
14 Korea, Republic of	99	99	99	–	99	95
15 Kyrgystan	97	97	97	97	99	97
16 Lao, PDR	87	87	86	87	82	95
17 Malaysia	97	96	97	97	95	99
18 Marshall Islands	36	41	36	21	70	42
19 Mongolia	98	98	98	98	97	97
20 Myanmar	75	72	76	72	86	80
21 Nepal	92	92	92	92	88	–
22 New Zealand	92	93	92	92	92	86
23 Pakistan	72	72	72	72	61	58
24 Papua New Guinea	68	68	69	68	70	–
25 Philippines	94	94	88	94	90	53
26 Singapore	97	97	97	–	95	95
27 Solomon Islands	83	83	85	83	76	–
28 Sri Lanka	99	99	99	99	99	99
29 Tajikistan	96	96	97	96	92	92
30 Thailand	99	99	99	–	99	94
31 Timor Leste	82	82	82	82	70	–
32 Turkmenistan	98	98	98	–	99	99
33 Uzbekistan	99	99	99	99	97	99
34 Vietnam	59	59	93	59	98	86

*Estimates may not include coverage achieved through private channels

Figure 75.1. Estimated coverage of basic childhood vaccines by country, 2015. DPT3, at least 3 doses of DPT vaccine; Hep3, at least 3 doses of hepatitis B vaccine; Pol3, at least 3 doses of polio vaccine; Hib3, at least three doses of *Haemophilus influenzae* type b-containing vaccine; MCV, at least one dose of a measles-containing vaccine; MCV2, second dose of a measles-containing 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.

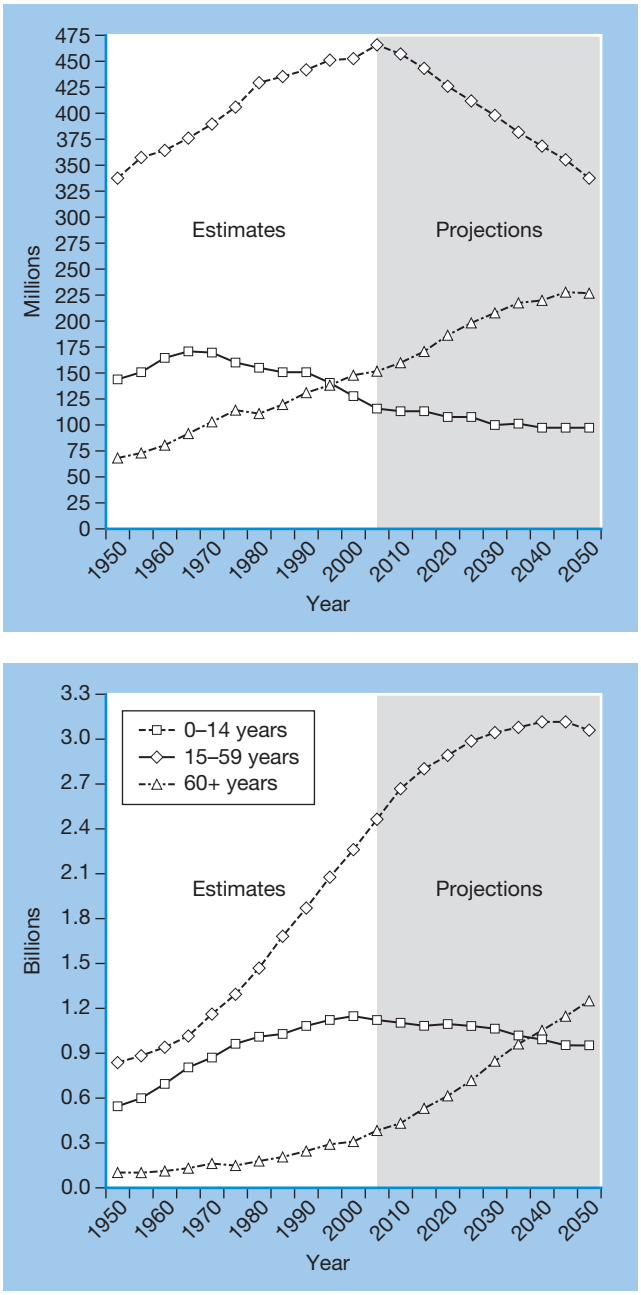


Figure 75.2. Population strata by age in Europe (top) and Asia (bottom), 1950 to 2050 (projected). The crossover point when the population of adults older than 60 years of age exceeded the population of children younger than 14 years of age was crossed in Europe around 1995; that crossover is projected to occur in Asia around 2037, within a generation from now.

for travelers to temperate locations. However, the severe acute respiratory syndrome 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, and the role of children in influenza transmission is being recognized while it is rediscovered in Japan. 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 of age, reflecting the intrinsic biological susceptibility of older adults to neurotropic flaviviruses and suggesting a future need for adult vaccination.[47] 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.[48] A catch-up program to address this epidemiological shift has been recognized by adult vaccination recommendations in some countries (see Table 75.3). In China, adult measles vaccination is under discussion, as more than 100,000 cases have occurred annually in recent years, in equal proportion in adults older than 20 years and in infants who had not received their first vaccine dose. Growing awareness of adult vaccination is reflected in an increasing number of countries with adult vaccination recommendations (see Table 75.3).

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.[49] While the growing size and number of large cities may increase transmission of certain infections, delivery of vaccine and of healthcare in general is better organized in cities than in rural areas. Specific interventions are needed to ensure that the existing disparity in access to healthcare 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 healthcare, 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 75.1, pediatric societies in a number of countries promulgate recommendations emulating those of the U.S. ACIP, and these schedules, aimed at practitioners serving private-paying families, may 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. Governments and ASEAN have expressed increased interest in providing for national and regional vaccine security. The collaboration of industry sponsors with nongovernmental organizations and government in public private partnerships for new product development has been highlighted by the successful introduction of vaccines and drugs for several neglected diseases, for which the DCVMN view a responsibility. For example, the Japan International Cooperation Agency and Kitasato Daiichi Sankyo provided technical assistance to establish domestic measles-rubella vaccine production in Vietnam's public corporation, Center for Research and Production of Vaccines and Biologicals, POLYVAC. At the same time, the entry of nongovernmental organizations as actual sponsors of novel vaccine development for certain target diseases introduces competition with DCVMN manufacturers and multinational companies that might also consider similar development programs. Asian academic institutions and companies possess elements

of the scientific and technical expertise needed to develop vaccines for current and emergent needs and, seemingly, the will to establish themselves on the global stage and contribute to their development. Regional institutions responded rapidly to threats of Middle East Respiratory Syndrome virus and Ebola virus with candidate vaccine development even when transmission was geographically remote. Further participation of regional institutions in global responses in the future is likely.

Trends toward increasing local development and manufacturing in the region and the accompanying need to strengthen respective regulatory agencies have been recognized by the WHO and local national regulatory authorities. Revising and harmonizing guidelines and procedures to international standards and enforcing procedures in a consistent and predictable manner will improve the timely regional introduction of vaccines developed internationally. As important, compliance with international standards will be required of regional manufacturers hoping to license locally developed vaccines more broadly. Indian and Chinese manufacturers currently export a limited number of vaccines, mainly regionally and to African and Latin American countries, but their horizons undoubtedly will expand.

In the six-component framework of product development capability—manufacturing; national and international distribution systems; private and public R&D capabilities; intellectual property system; and drug and vaccine regulation—regional manufacturers are at different stages of maturation.[50] In its ascendance to an advanced country producing complex biologicals as well as other high technology products, Korea followed a path that might be emulated by others in the region, highlighted by its arrival at a stage with a national system of innovation in science and technology, linking government, universities and industry, a strong regulatory system and observation of intellectual property rights, including adherence to Trade-Related Aspects of Intellectual Property Rights (TRIPS agreement).

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 requiring strengthening. Investigations of adjuvanted H1N1 and H5N1 pandemic and prepandemic vaccines administered in Korea and Taiwan, respectively, illustrated the interest in and epidemiological capacity of local investigators but also the limitations of existing systems and databases. Japan is establishing a database of clinical encounters that if linked to immunization records could be used as a future adverse events surveillance system.

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 serve an important role in strengthening local 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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References for this chapter are available at ExpertConsult.com.

REFERENCES

1. Country Hub. Gavi, The Vaccine Alliance. Available at: <http://www.gavi.org/country/>.
2. Jadhav S, Gautam M, Gairola S. Role of vaccine manufacturers in developing countries towards global healthcare by providing quality vaccines at affordable prices. *Clin Microbiol Infect*. 2014;20(suppl 5):37-44.
3. Chakma J, Sun GH, Steinberg JD, et al. Asia's ascent–global trends in biomedical R&D expenditures. *N Engl J Med*. 2014;370:1-6.
4. Rezaie R, McGahan AM, Frew SE, et al. Emergence of biopharmaceutical innovators in China, India, Brazil and South Africa as global competitors and collaborators. *Health Res Policy Syst*. 2012;10:18.
5. Chakma J, Chakma H. Developing countries can contribute to global health innovation. *Nat Med*. 2013;19:129.
6. Frew SE, Kettler HE, Singer PA. The Indian and Chinese health biotechnology industries: potential champions of global health? *Health Aff (Millwood)*. 2008;27:1029-1041.
7. Frew SE, Sammut SM, Shore AF, et al. Chinese health biotech and the biollion-patient market. *Nat Biotechnol*. 2008;26:37-53.
8. Chakma J, Masum H, Perampaladas K, et al. Indian vaccine innovation: the case of Shantha Biotechnics. *Global Health*. 2011;7:9-18.
9. Andrea MC, Freed GL, Katz SL. Safety concerns regarding combination vaccines: the experience in Japan. *Vaccine*. 2004;22:3911-3916.
10. Larson HJ, Wilson R, Hanley S, et al. Tracking the global spread of vaccine sentiments: the global response to Japan's suspension of its HPV vaccine recommendation. *Hum Vaccin Immunother*. 2014;10(9):2543-2550.
11. Sohn YM. Japanese encephalitis immunization in South Korea: past, present and future. *Emerg Infect Dis*. 2000;6:17-24.
12. Holbrook RM. Kyasanur forest disease. *Antiviral Res*. 2012;96(3):353-362.
13. Pattnaik P. Kyasanur forest disease: an epidemiological view in India. *Rev Med Virol*. 2006;16:151-165.
14. Dandawate CN, Desai GB, Achar TR, et al. Field evaluation of formalin inactivated Kyasanur Forest disease virus tissue culture vaccine in three districts of Karnataka state. *Indian J Med Res*. 1994;99:152-158.
15. Kasabi GS, Murhekar MV, Sandhya VK, et al. Coverage and effectiveness of Kyasanur forest disease (FKD) vaccine in Karnataka, South India, 2005-10. *PLoS Negl Trop Dis*. 2013;7(1):1-4.
16. Wang J, Zhang H, Fu S, et al. Isolation of Kyasanur forest disease virus from febrile patient, Yunnan, China. *Emerg Infect Dis*. 2009;15:326-328.
17. Zaki Am. Isolation of a flaviirus related to the tick-borne encephalitis complex from human cases in Saudi Arabia. *Trans R Soc Trop Med Hyg*. 1997;91:179-181.
18. Jonsson CB, Figueiredo LT, Vapalahti O. A global perspective on hantavirus ecology, epidemiology, and disease. *Clin Microbiol Rev*. 2010;23:412-414.
19. Cao CY, Dong GM. Quality control of vaccines against hemorrhagic fever with renal syndrome. In: *Quality Control and Evaluation of Vaccines*. Beijing, China: People's Health Press; 2013:434-450.
20. Ruan YH, Xu XP, On ZQ, et al. A randomized, controlled field trial of Gerbil kidney cell derived-, mono-valent vaccine against Hantaan virus of hemorrhagic fever with renal syndrome in Jiende City. *Public Health China*. 1999;15(7):574-576.
21. Chen HX. A study of mass immunization against hemorrhagic fever with renal syndrome in China. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2002;23(2):145-147.
22. Song G. *Guidelines for Control of Hemorrhagic Fever with Renal Syndrome*. 2nd ed. Beijing, China: People's Health Press; 1998.
23. Zhu ZY, Yao PP, Lu QY, et al. Observation of purified Gerbil kidney cell derived- vaccine against hemorrhagic fever with renal syndrome on human volunteers. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2008;29(10):1056-1078.
24. Dong GM, Han L, An Q, et al. Immunization effect of purified, bivalent primary hamster kidney cell derived vaccine against hemorrhagic fever with renal syndrome. *Zhongguo Sheng Wu Zhi Pin Xue Za Zhi*. 2003;16(1):53-55.
25. Liu CP, Maa SP, Hua RH, et al. Study of immunization effectiveness in people vaccinated with a bivalent HFRS vaccine. *J Pathogen Biol*. 2012;7(2):113-114.
26. Wu YS, Zu RQ, Song L, et al. Clinical study on safety and serology of a bivalent, purified vaccine against hemorrhagic fever with renal syndrome. *Zhongguo Mei Jie Sheng Wu Xue Ji Kong Zhi Za Zhi*. 2004;15(5):380-382.
27. Xu MT, Zhu FC, Ying L, et al. Investigation of immunogenicity of purified, bivalent hemorrhagic fever with renal syndrome vaccine e (Vero Cell) in children and the elderly people. *Guoji Shengwu Zhipinxue Zazhi*. 2008;31(6):256-258.
28. Wang JJ, Wei ZZ, Wei J, et al. Long-term epidemiologic effects of vaccination against hemorrhagic fever with renal syndrome (HFRS) in areas of Shaanxi Province endemic for HFRS. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2012;33(3):309-312.
29. Zhang GQ, Xue FZ, Wang JZ, et al. Long-term epidemiological effect of vaccine against hemorrhagic fever with renal syndrome in a large population. *J Shandong Univ (Health Sci)*. 2007;45(10):981-984.
30. Harmonization of Standards and Technical Requirements in ASEAN. Available at: <http://apac-asia.com/images/achievements/pdf/5th/ATIM_06_Dato'AISAH.pdf>.
31. Mahoney R, Chacarro L, Southern J, et al. Dengue vaccines regulatory pathways: a report on two meetings with regulators of developing countries. *PLoS Med*. 2011;8(2):e1000418.
32. Puumalainen T, Dagan R, Wuorimaa T, et al. Greater antibody responses to an eleven valent mixed carrier diphtheria- or tetanus-conjugated pneumococcal vaccine in Filipino than in Finnish or Israeli infants. *Pediatr Infect Dis J*. 2003;22:141-149.
33. Shao PL, Lu CY, Chang LY, et al. Safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in Taiwanese infants. *J Formos Med Assoc*. 2004;103:613-617.
34. Lee HJ, Chung MH, Kim WJ, et al. Immunogenicity and safety of a novel quadrivalent meningococcal conjugate vaccine (MenACWY-CRM) in healthy Korean adolescents and adults. *Int J Infect Dis*. 2014;28:204-210.
35. Trück J, Ramasamy MN, Galson JD, et al. Identification of antigen-specific B cell receptor sequences using public repertoire analysis. *J Immunol*. 2015;194(1):252-261.
36. Haralambieva IH, Simon WL, Kennedy RB, et al. Profiling of measles-specific humoral immunity in individuals following two doses of MMR vaccine using proteome microarrays. *Viruses*. 2015;7(3):1113-1133.
37. Nordgren J, Sharma S, Bucardo F, et al. Both Lewis and secretor status mediate susceptibility to rotavirus infections in a rotavirus genotype-dependent manner. *Clin Infect Dis*. 2014;59(11):1567-1573.
38. Duan Z, Chen X, Liang Z, et al. Genetic polymorphisms of CXCR5 and CXCL13 are associated with non-responsiveness to the hepatitis B vaccine. *Vaccine*. 2014;32(41):5316-5322.
39. Barnes M, Caron MM, Varghese A, et al. India's proposed amendments to the drug and cosmetics Act: compensation for injuries to clinical trial participants and the criminalization of clinical research. Life sciences law and industry report. 09 LSLR 117, 01/23/201 Bloomberg BNA 2015. Available at: <https://www.ropesgray.com/newsroom/news/2015/January/Health-Care-Attorneys-Write-Bloomberg-BNA-Article.aspx>.
40. Pagluisi S, Jain R, Suri RK. Vaccines, our shared responsibility. *Vaccine*. 2015;33(19):2197-2202.
41. Muangchana C, Thamapornpilas P, Karnkawinpong O. Immunization policy development in Thailand: the role of the Advisory Committee on Immunization Practice. *Vaccine*. 2010;28(suppl 1):A104-A109.
42. Cho HY. An overview of the national immunization policy making process: the role of the Korea expert committee on immunization practices. *Korean J Pediatr*. 2012;55(1):1-5.
43. Duclos P, Dumolard L, Abeysinghe N, et al. Progress in the establishment and strengthening of national immunization technical advisory groups: analysis from the 2013 WHO/UNICEF joint reporting form, data for 2012. *Vaccine*. 2013;31(46):5314-5320.
44. Saitoh A, Okabe N. Recent progress and concerns regarding the Japanese immunization program: addressing the "vaccine gap". *Vaccine*. 2014;32:4253-4258.

45. WHO-UNICEF estimates of DTP3 coverage. Available at: <http://www.who.int/immunization/monitoring_surveillance/routine/coverage/en/index4.html>.
46. World Health Organization Department of Economic and Social Affairs Population Division. Available at: <http://www.un.org/esa/population/>.
47. Arai S, Matsunaga Y, Takasaki T, et al. Vaccine Preventable Diseases Surveillance Program of Japan. Japanese encephalitis: surveillance and elimination effort in Japan from 1982 to 2004. *Jpn J Infect Dis*. 2008;61:333-338.
48. Chung GE, Yim JY, Kim D, et al. Seroprevalence of hepatitis A and associated socioeconomic factors in young healthy Korean adults. *Gut Liver*. 2011;5:88-92.
49. Weaver SC. Urbanization and geographic expansion of zoonotic arboviral diseases: mechanisms and potential strategies for prevention. *Trends Microbiol*. 2013;21(8):360-363.
50. Abuduxike G, Aljunid SM. Development of health biotechnology in developing countries: can private-sector players be the prime movers? *Biotechnol Adv*. 2012;30:1589-1601.