Considering the potential programmatic impact of new vaccines, with reference to Japanese Encephalitis vaccines

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Rationale and analytic framework

In April 2014, the WHO SAGE reaffirmed the importance of considering programmatic impacts when assessing the merits of new vaccines or new uses of existing vaccines. This was in the context of calls to strengthen immunization supply chains in concert with other investments[1]. Earlier, in 2012, SAGE reviewed studies they had commissioned on a systematic approach to new vaccine introduction (see [2] [3]), resulting in an EPI guidance document ***"Principles and considerations for adding a vaccine to a national immunization programme: from decision to implementation and monitoring"***, published by WHO in April 2014. The appendix to that guidance includes evidence on broader health system impacts, both positive and negative. It is also important to note the relevance of WHO's Programmatic Suitability Pre-Qualification (PSPQ) process in assessing potential programmatic impact.

Introduction to this briefing paper

This paper gives a brief overview of how these frameworks can help analyse the programmatic implications of deploying the Japanese encephalitis (JE) vaccines under discussion, covering:

1. Review of PSPQ status;
2. Potential impact on immunization supply chain;
3. Potential impact on immunization programmes and other aspects of the health system;
4. Product characteristics that apply to these potential impacts; and
5. Rapid brief literature review of published programmatic impact of JE vaccine introduction.

We have assumed the vaccines under consideration are: IXIARO (Valneva, formerly Intercell); JEEV (BioE); CD-JEVAX (also known as JE-vaccine-Live, live attenuated SA 14-14-2, CDIBP); Imojev (Sanofi Pasteur); and JenceVac (Green Cross). The points raised in this brief may be especially relevant to later sessions in the Working Group meeting: *Age of administration and schedules (day 2)*; *Public health and economic impact (day 2)*; and the *Tentative conclusions on impact (day 3)*: which could note the need to consider positive and negative immunization programme and health system impacts.

This brief cannot provide a full assessment of programmatic impacts, although such an exercise would be useful. For a full assessment, programmes should use their population targets, transportation estimates, and open vial wastage rates together with other resources to help estimate programme impact. Other tools are available through WHO and UNICEF Supply Division, particularly for supply chain storage and distribution. These include a Cold Chain Weight and Volume Calculator, a Supply Chain Sizing Tool (2012), Logistics Forecasting Tool (2012), and a Vaccine Volume Calculator.

1. Programmatic Suitability Pre-Qualification (PSPQ)

Two vaccines under consideration, JEEV and CD-JEVAX have been pre-qualified, which means that they have met programme suitability criteria including thermostability, preservatives, storage, dose volume, administration, schedule of doses, and ease of disposal after use (PSPQ criteria are being revised in 2014).

The use of JEEV in a younger age group (12 to 35 months) entails half-doses, which required special PSPQ review of: how to measure these doses (as a suitably marked AD syringe was then not available); how to manage the resultant creation of a two-dose unpreserved presentation; and the dose scheduling requirement for two visits 28 days apart. Pre-qualification was awarded with acknowledgement of the extra training and other programme adaptations that would be required.

2. Potential impact on immunization supply chain

Supply Chain area	*Potential Impact*	*Relevant Product Characteristics*	*Note on JE vaccines under discussion*
Storage Capacity	Adding any new vaccine affects storage, potentially needing expansion of: - Cold storage rooms, fridges, icepack freezers, cold boxes - Cold store equipment, including ice packs, refrigeration engines - Fuel for cold storage equipment - Temperature monitoring devices - Dry storage - Waste management/refuse facilities	Vial volume/dose Presentation (SDV/MDV) Carton sizes Storage temperature Lyophilisation Shelf life Vaccine schedule Wastage rates Materials needing disposal PSPQ status	• The biggest impact on storage relates to total number of doses, thus depends on schedule (inc. boosters). • All new JE vaccines will add to storage requirements: the table shows significant variation in sizes, with lower volume/dose preferable. There seems only one MDV option (one uncertain), and estimated wastage based on session size, will determine preference. • Lyophilized will need additional diluent storage. • No vaccines with unusual temperature, wastage or materials needing special disposal.
Supply chain human resources	New training may be needed on temperature monitoring or other storage or distribution needs. New logistics, supply management or maintenance staff may be needed.	Cold chain monitoring PSPQ status *Other changes necessitated by the considerations above*	• All the above considerations have implications for supply chain staff numbers and training. • PSPQ vaccines may be somewhat less likely to need additional provision. • If VVMs are not in common use, and a VVM vaccine chosen, this will entail additional training.
Distribution Capacity	Distribution Capacity impact may require expansion in the following: - Number or size of vehicles - Vehicles (fuel, vehicular storage etc.) - Vaccine Carriers and/or ice packs	Vial volume/dose Carton sizes Storage temperature Vaccine schedule Wastage rates	• All the above considerations apply, noting that some vaccines have more favourable carton sizes.
National receiving and distribution schedules	Consideration is needed in the schedules for national receipt (procurement) and internal distribution. This affects the forecasting of the maximum amount of holding inventory for the new vaccine the National Level. It also affects maximum holding at intermediate and Service Delivery Levels.	Carton sizes Storage temperature Shelf life Vaccine schedule Wastage rates PSPQ status *Global availability*	• All the above considerations apply, noting that some vaccines have more favourable carton sizes. • PSPQ makes a difference to availability, noting that global availability is not a product characteristic we assessed, but clearly important here.

3. Potential impact on general immunization programme and the health system

Programme or System area	*Potential Impact*	*Relevant Product or Disease* Characteristics*	*Note on JE vaccines under discussion*
Service delivery	Fit with current schedule, or need additional sessions? Which staff can/should give the vaccine? Location of vaccination? Extra locations for special populations? Campaigns needed? Can vaccination sessions integrate with other services?	Administration route/equipment Population and vaccine schedule	• The biggest impact relates to total number of doses, thus depends on schedule (including boosters). • Need integration with services beyond infancy: ages 1+ years, not all fit standard EPI schedule. Dose intervals of 1 year may be easier than 1 month. • Injections all standard. No special injection device (eg Uniject) that could allow new vaccinators.
Human Resources	Adding a new vaccine may require expansion in: - Numbers of vaccinating staff and their managers - Training on new injection equipment, or new vaccine management, discard of MDV - Counselling and community education?	Presentation (SDV, MDV) Administration route/equipment Population/vaccine schedule Disease characteristics*	• Ordinary levels of additional training. • Additional staff likely if school, adults or campaigns • Surveillance and disease control integration with public health, clinical and environmental health staff.
Medical technologies	If additional equipment needed beyond that for vaccine, eg for diagnostics or treatments?	Disease characteristics*	• Surveillance and diagnostic technologies
Information Systems	Potential expansion or revision of: - Child health cards, other patient records - Vaccine stock and logistics forms - Disease surveillance and outbreak reporting? - Change to administrative coverage reporting?	*Service delivery impacts from above.* Disease characteristics.	• Consider how to integrate JE-specific surveillance for disease control with immunisation programme • Significant impact, but needed for disease control purposes in any case.
Vaccine Financing	Financed by government, GAVI, other donor? Long-term cost to government? Payment to providers, any incentives? Payment by patients, any subsidies?	Vaccine costs. Payment mechanisms. Incentives or cash transfers.	• Cost-benefit not assessed in this brief. • Need to review provider or patient payment or subsidy mechanisms, especially to mitigate unintended perverse incentives.
Leadership and Governance	Change to policy needed to promote new vaccine or authorise new vaccinators, new service delivery? Leadership needed to champion new vaccine or counteract community concerns?	*Service delivery needs from above.* Disease characteristics	• Minor policy change needed in service delivery. • Leadership likely to be needed to make JE control a priority, including advocacy with public.
Community Engagement	What public education is needed, who will do it? Immunization program role in education.	Disease characteristics.	• Need health-worker led communications. Potential to integrate with other disease control and environmental health messages. • No special stigma, beyond usual vaccine hesitancy.

*Disease characteristics include: Rationale for control; Involvement of other disease control entities; Public awareness of disease threat, public attitudes to disease and/or stigma; Public awareness and attitudes to vaccine options.

4. Product characteristics for five JE vaccines

Vaccine	*PSPQ*	*Present-ation: SDV or MDV*	*Vial Volume/ Dose (cm^3)*	*Primary Carton Size (cm^3)*	*Secondary Carton Size (m^3)*	*Tertiary Carton Size (m^3)*	*Shelf Life (mth)*	*Storage temp-erature*	*Cold chain monit-oring*	*Lyophil-isation*	*Admin-istration route and equipment*	*Population and vaccine schedule*
JEEV	Yes	1	14.7	705 (48 boxes)	0.1 (24 cartons	n/a	24	2-8 C	VVM (Type 7)	No	IM injection	2 doses 28 days apart for ages 3 years and older. Half dose for age 12 - 35 months.
IXIARO	No	1	277	277 Pack of 1 single-dose syringe with or without a separate needle	None	None	24 Months	2-8 C	None	No	IM injection (Syringe & needle included)	2 doses 28 days apart for ages 3 years and older. Half dose for age 12 - 35 months.
CD-JEVAX *(SDV)*	Yes	1	21.2	140 (carton of 10) (unclear if diluent included)	.02 (10 cartons)	0.18	18 Months	2-8 C	VVM (Type 14)	Yes	SC injection (Recons-titute with sterile diluent)	1 dose at 1 year of age (from age 8months in package insert). 1 dose at 2 years of age Boosters in some programs.
CD-JEVAX *(MDV)*	Yes	5	4.2	140 (carton of 10) (unclear if diluent included)	.02 (10 cartons)	0.18	18 Months	2-8 C	VVM (Type 14)	Yes	SC injection Recons-titute with sterile diluent	1 dose at 1 year of age (from age 8months in package insert). 1 dose at 2 years of age Boosters in some programs.
IMOJEV	No	1 (MDV also ?)	?	Probaly larger than others (incl. vial, diluent vial, syringe, 2 needles)	?	?	30 months	2-8 C	None	Yes	SC injection (Recons-titute)	1 dose at 1+ year of age
JenceVac	No	1	?	?	?	?	18 Months	2-8 C	None	No	SC injection	3 doses at days 0, 7, 28 or 2 doses at intevals of 1 to 4 weeks Half dose (.5 mL) for under 3 years of age

Note: some product characteristics of importance are not tabulated, because there is no differentiating information available for this analysis. These include: a) *monovalent vs combined* (all here are monovalent); b) *specialised autodisable device (eg Uniject^{TM}) available?* (none here had an AD device); c) *materials needing special disposal?* (not applicable here); and d) *specific information on wastage rates, including SDV vs MDV* (not available for these vaccines). This information was difficult to retrieve and consolidate, and this table will require review and updating.

5. Brief literature review of published JE programme experiences

Systematic reviews on the general impact of new or changed vaccines[2, 3] suggest that the key points of potential impact (after a financial case has been made) involve stress on the ***supply chain***, the need for ***human resource investments*** in training and sometimes new staff, and stress on ***service delivery***; especially if the changes do not fit with existing schedules. There are special stresses if a ***campaign*** is required as declines in coverage of other services during campaigns have been documented[4]. New vaccine introductions can be associated with stronger systems, e.g. in staff training or upgrade of equipment, but opportunities to integrate improvements for other vaccines or services are often missed[2].

We did a ***rapid exploratory literature review*** for published experiences of programmatic impact of JE vaccine deployment. Our review is likely to be incomplete: we limited the search to Medline (searched using Ovid SP) and English language, but without date restriction. We used 34 different terms to capture concepts of *Japanese encephalitis*, *vaccines and immunization,* and *health system or immunization programme elements*. When these concepts were combined, the search identified 330 titles (from over 3,000,000 individual citations). 174 potentially relevant papers had abstracts reviewed, with 62 selected for full text review. These comprised a range of efficacy trials, pilot introductions, and reviews of country and regional experiences. There was a dearth of programme information recorded in these studies; only 23 contained any programmatic information.

Service delivery information recorded in these studies included the recognition that introduction is optimal when matched with existing schedules – these vary significantly across countries, for the second year of childhood, and a CDC regional review[5] shows that five of 11 countries integrating JE with routine immunisation schedules used a variant different to that recommended in current WHO standards[6]. The benefit of integrating with measles vaccination (given rough concordance in age targets) was noted, along with potential synergies in laboratory services [5, 7]. The CDC review, and many other papers noted the potential importance and likely challenges, of reaching adults[8] or at risk populations. A number of countries noted the need for campaigns[5] with some providing information on the conduct of campaigns[9, 10]. One study in Nepal demonstrated the benefits of spatial analysis in planning for vaccination and other JE control measures[11]. Some studies raised the potential need for booster doses[12] but without discussion of programme implications. No studies were found with information on supply chain or logistics specific to JE vaccine. Regarding ***human resources,*** when discussed, this was in tandem with service delivery considerations noted above. We found no studies on the human resource impact of JE vaccination introduction; nor in relation to its delivery in campaigns, to adults or to special populations.

Mentions of ancillary ***medical technologies*** to support JE introduction noted equipment and supplies needed for laboratory diagnosis and surveillance [11, 13-18]. These authors also discussed ***health information system*** upgrades, needed for disease control as well as vaccine monitoring, and their additional demands on the public health system, with some suggesting sentinel[16] or early warning[11] approaches. CDC's regional review noted that in 2012, 18 of 24 countries had integrated surveillance, some recently and with external support[5]. One paper noted the complexity of monitoring JE immunisation program effectiveness, given the variable incidence of JE over time[19], and studies from China discussed the use of electronic vaccination records to track JE programmes[20].

Studies relevant to ***community engagement*** included the importance of community education and mobilisation as part of campaigns[9], noted relatively high awareness of the disease and vaccine in some settings[18, 21, 22], and included a report from China on the need for enhanced public education following a period of heightened public fears over vaccine safety[23]. ***Leadership and governance*** from national levels was important to community uptake, as was central commitment to provide the vaccine free of charge[9, 10, 20, 22, 24].

References

1. Immunization Practices Advisory Committee (IPAC), *Immunization Supply Chain and Logistics: a neglected but essential system for national immunization programmes. A Call-to-Action for national programmes and the global community by the WHO Immunization Practices Advisory Committee.*, 2014: Geneva.
2. Wang, S.A., et al., *New vaccine introductions: assessing the impact and the opportunities for immunization and health systems strengthening.* Vaccine, 2013. 31 Suppl 2: p. B122-8.
3. Hyde, T.B., et al., *The impact of new vaccine introduction on immunization and health systems: a review of the published literature.* Vaccine, 2012. 30(45): p. 6347-58.
4. Mounier-Jack, S., et al., *Meningococcal vaccine introduction in Mali through mass campaigns and its impact on the health system.* Glob Health Sci Pract, 2014.
5. Centers for Disease Control, *Japanese encephalitis surveillance and immunization--Asia and the Western Pacific, 2012.* MMWR - Morbidity & Mortality Weekly Report, 2013. 62(33): p. 658-62.
6. World Health Organization, http://www.who.int/immunization/policy/immunization_schedules/en/. Table 2.
7. Gatchalian, S., et al., *Comparison of the immunogenicity and safety of measles vaccine administered alone or with live, attenuated Japanese encephalitis SA 14-14-2 vaccine in Philippine infants.* Vaccine, 2008. 26(18): p. 2234-41.
8. Lee, D.W., et al., *Epidemiology of Japanese encephalitis in South Korea, 2007-2010.* International Journal of Infectious Diseases, 2012. 16(6): p. e448-52.
9. Upreti, S.R., et al., *Estimation of the impact of a Japanese encephalitis immunization program with live, attenuated SA 14-14-2 vaccine in Nepal.* American Journal of Tropical Medicine & Hygiene, 2013. 88(3): p. 464-8.
10. Yen, N.T., et al., *Surveillance for Japanese encephalitis in Vietnam, 1998-2007.* American Journal of Tropical Medicine & Hygiene, 2010. 83(4): p. 816-9.
11. Robertson, C., et al., *Comparative spatial dynamics of Japanese encephalitis and acute encephalitis syndrome in Nepal.* PLoS ONE [Electronic Resource], 2013. 8(7): p. e66168.
12. Choi, U.Y., et al., *Is a booster dose necessary in children after immunization with live attenuated Japanese encephalitis vaccine?* Journal of Tropical Pediatrics, 2013. 59(5): p. 423-5.
13. Centers for Disease Control, *Expanding poliomyelitis and measles surveillance networks to establish surveillance for acute meningitis and encephalitis syndromes--Bangladesh, China, and India, 2006-2008.* MMWR - Morbidity & Mortality Weekly Report, 2012. 61(49): p. 1008-11.
14. Gupta, N., et al., *Bellary, India achieves negligible case fatality due to Japanese encephalitis despite no vaccination: an outbreak investigation in 2004.* Indian Journal of Pediatrics, 2008. 75(1): p. 31-7.
15. Touch, S., et al., *Epidemiology and burden of disease from Japanese encephalitis in Cambodia: results from two years of sentinel surveillance.* Tropical Medicine & International Health, 2009. 14(11): p. 1365-73.
16. Hills, S., et al., *Evidence and rationale for the World Health Organization recommended standards for Japanese encephalitis surveillance.* BMC Infectious Diseases, 2009. 9: p. 214.
17. Khalakdina, A., et al., *Field evaluation of commercial immunoglobulin M antibody capture ELISA diagnostic tests for the detection of Japanese encephalitis virus infection among encephalitis patients in Nepal.* International Journal of Infectious Diseases, 2010. 14 Suppl 3: p. e79-84.
18. Yin, Z., et al., *Japanese encephalitis disease burden and clinical features of Japanese encephalitis in four cities in the People's Republic of China.* American Journal of Tropical Medicine & Hygiene, 2010. 83(4): p. 766-73.
19. Impoinvil, D.E., et al., *The effect of vaccination coverage and climate on Japanese encephalitis in Sarawak, Malaysia.* PLoS Neglected Tropical Diseases [electronic resource], 2013. 7(8): p. e2334.
20. Zheng, Y., et al., *Japanese encephalitis and Japanese encephalitis virus in mainland China.* Reviews in Medical Virology, 2012. 22(5): p. 301-22.
21. Kumar, K.R., et al., *A coverage evaluation survey of JE vaccination in two districts of Karnataka.[Erratum appears in J Commun Dis. 2010 Sep;42(3):2 p preceding 171].* Journal of Communicable Diseases, 2010. 42(3): p. 179-84.
22. Zhang, S., et al., *Knowledge, attitudes and practices of caregivers regarding Japanese encephalitis in Shaanxi Province, China.* Public Health, 2011. 125(2): p. 79-83.
23. Ahmad, K., *Fury after children's adverse reaction to Japanese encephalitis vaccine.* Lancet, 2002. 360(9330): p. 395.
24. Yin, Z., et al., *An economic evaluation of the use of Japanese encephalitis vaccine in the expanded program of immunization of Guizhou province, China.* Vaccine, 2012. 30(37): p. 5569-77.