Expert Review of Anti-infective Therapy

ISSN: 1478-7210 (Print) 1744-8336 (Online) Journal homepage: informahealthcare.com/journals/ierz20

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To cite this article: Susan Hills, Rebecca Martin, Anthony Marfin & Marc Fischer (2014) Control of Japanese encephalitis in Asia: the time is now, Expert Review of Anti-infective Therapy, 12:8, 901-904, DOI: 10.1586/14787210.2014.929498

To link to this article: https://doi.org/10.1586/14787210.2014.929498

Published online: 13 Jun 2014.

Control of Japanese encephalitis in Asia: the time is now

Expert Rev. Anti Infect. Ther. 12(8), 901–904 (2014)

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Japanese encephalitis (JE) virus is the most common vaccine-preventable cause of encephalitis in Asia. Recent progress in the development and availability of improved JE vaccines has revitalized the prospects for JE control. There now are a number of safe and effective vaccines, two WHO prequalified vaccines available for pediatric use, at least one vaccine considered affordable for use in lower income countries, and a GAVI Alliance commitment to provide financial support to eligible countries for campaigns for children aged 9 months through 14 years. While challenges remain, this tremendous progress means there is a better opportunity than at any time in the past to prevent the substantial morbidity and mortality from this disease.

Japanese encephalitis (JE) virus, a mosquito-borne flavivirus, is the most common vaccine-preventable cause of encephalitis in Asia. Each year, an estimated 67,900 JE cases occur. About 75% of these cases occur in children aged <15 years with an annual incidence of 5.4 cases per 100,000 children [1]. The case fatality rate is 20–30% and 30–50% of survivors have long-term physical or cognitive sequelae. Given its incidence and severity, JE is a major public health problem.

There is no antiviral therapy or other medication available to mitigate the effects of JE virus infection. The mosquitoes that transmit JE virus breed in rice paddies and other open water sources, so vector control measures are resource intensive and have limited effectiveness. Human vaccination is the most effective means of prevention and the WHO recommends that JE vaccine be incorporated into immunization programs in all areas where JE is a public health problem [2]. An international group of partners has proposed a control target of 0.5 cases per 100,000 children aged <15 years in each endemic country [3].

In several Asian countries, inactivated mouse brain-derived JE vaccine has been used for many years to effectively control disease [2]. However, this formulation is difficult to produce, relatively expensive, requires multiple doses, and has been associated with rare serious hypersensitivity and neurological adverse events. These factors have resulted in the limited use of JE vaccine in many JE-endemic countries. Fortunately, recent progress in the development and availability of improved JE vaccines has revitalized the prospects for JE control.

Three types of newer JE vaccines are increasingly available for international use. These include the live attenuated SA 14-14-2 JE vaccine, inactivated Vero cell culture-derived JE vaccines and a live attenuated chimeric virus vaccine. Manufactured by the Chengdu Institute of Biological Products, the SA 14-14-2 vaccine has been used in China for over 20 years and has been shown to be safe and effective in clinical trials and immunization programs [4–7]. The vaccine is approved as a single primary dose for children aged ≥8 months, so it can be easily incorporated into the routine immunization schedule and is often coadministered with measles vaccine around 9 months of age. SA 14-14-2 vaccine is licensed or available for use in at least nine Asian countries. In a major milestone, SA 14-14-2 vaccine was prequalified by WHO in October 2013,

Keywords: epidemiology • Japanese encephalitis vaccine • prevention and control

 10.1586/14787210.2014.929498 ISSN 1478-7210

the first JE vaccine to be prequalified for pediatric use [8]. This means the vaccine meets WHO standards for quality, safety and efficacy, and enables procurement by UN agencies and inclusion in the GAVI portfolio of vaccines.

Inactivated Vero cell culture-derived vaccines are produced in several countries. One Vero cell culture-derived vaccine manufactured by Valneva Scotland Limited (formerly Intercell Biomedical) is licensed in 38 countries and is primarily used in adult and pediatric travelers from nonendemic countries [9,10]. Following technology transfer from Intercell, Biological E produced a similar vaccine in India that is now prequalified by WHO for use in adults aged 18 through 49 years and children aged 1 and 2 years [11]. Finally, Sanofi Pasteur produces a live attenuated JE chimeric virus vaccine that has recently been licensed in four countries [12,13].

In addition to vaccine safety, effectiveness and programmatic feasibility, vaccine affordability is essential to enable sustainable JE immunization in low- and middle-income endemic countries. This is especially important as high coverage will be needed long term since JE virus is maintained in an enzootic cycle between mosquitoes and amplifying animal hosts and nonimmune people will remain at risk. Chengdu Institute of Biological Products has guaranteed a maximum public sector price for SA 14-14-2 vaccine for low-income countries; the price is comparable to the international public sector price for measles vaccine and is guaranteed through 2033 [14]. This price will allow low-income Asian countries to consider implementation of JE immunization programs. Analyses in several countries have shown that JE immunization with SA 14-14-2 vaccine is a cost–effective public health measure with substantial impact [15–17]. Taking into consideration nonmedical costs and costs due to sequelae, immunization may result in cost savings. Therefore, JE immunization has the potential to relieve JE's economic burden on national health systems.

Another exciting development that greatly improves prospects for JE control came in November 2013 with the decision by the GAVI Alliance Board to provide funding support for catch-up vaccination campaigns for children aged 9 months through 14 years in eligible countries interested in introducing JE vaccine for children [18]. Unlike some other vaccine-preventable childhood diseases, JE burden is not concentrated in infancy or early childhood. Further, since JE is not transmitted from person to person, JE immunization only provides benefit to the vaccine recipient and does not result in herd immunity. The control strategy with the greatest impact is a one-time campaign in the highest risk age groups (e.g., children aged 9 months through 14 years) followed by the incorporation of JE vaccine into the routine childhood immunization program [2]. The availability of funding for initial immunization campaigns in resource-limited countries is a critical element of JE control, and GAVI financing will help overcome this barrier in eligible countries.

Current prospects for JE control are promising. There are a number of safe and effective vaccines. Two of these vaccines are WHO prequalified and at least one is considered affordable for use in low-income countries. Finally, GAVI has committed to providing financial support to eligible countries for initial vaccination campaigns. However, several issues still need to be addressed [19–22].

Understanding and awareness of disease burden in all JE-endemic countries need to be increased to provide evidence and guide countries and National Immunization Technical Advisory Groups in decisions about vaccine introduction, immunization policy, and program delivery. JE surveillance has markedly improved during the last decade. However, substantial gaps remain in many countries with regards to collection of information or quality of the data. A recent assessment suggested that JE cases reported to WHO underestimate by 10-times the true number of cases occurring annually [1]. Primary obstacles in defining disease burden include limited financial resources for surveillance programs and challenges with incorporating these programs into existing infrastructure or networks. A further concern is limited access to diagnostic and confirmatory testing. To address this issue, a WHO JE laboratory network, modeled after the polio and measles laboratory networks, has been developed [22,23]. This network aims to build laboratory capacity to support public health surveillance through training workshops, technical support, and proficiency and confirmatory testing. This network needs to be strengthened in some areas to ensure equitable access to good quality diagnostic testing.

For maximum impact, the introduction of JE vaccination will require both the incorporation of JE vaccine into a country's routine childhood immunization schedule and catch-up campaigns in children as old as 14 years. Older children are difficult to reach, particularly if they no longer attend school. Countries will need to develop strategies to implement JE vaccination in these older age groups, as has been done with measles and rubella vaccines. They must also have the capacity to monitor and evaluate the introduction [24].

To date, local transmission of JE virus has only been documented in Asia and the western Pacific. As a result, there is limited global awareness of this devastating disease. Large outbreaks sometimes generate temporary interest, but the disease and major achievements in its control have received little attention [25]. Several organizations, including the Bill & Melinda Gates Foundation, have committed resources to JE surveillance and control. However, dedicated and consistent advocacy will be needed to ensure that JE control remains on national, regional and international agendas. This is consistent with the WHO Global Vaccine Action Plan 2011–2020 goal to introduce and ensure equitable access to new and improved vaccines [26].

JE control is feasible and within reach. Japan, South Korea, Taiwan and Thailand have successful JE immunization programs that dramatically reduced disease incidence [1,21]. Other countries, such as China, India and Nepal have made substantial progress in the last few years [17,21,22]. Recent developments that include improved international availability of vaccines,

prequalification of vaccines for pediatric use, and GAVI funding for JE vaccine introduction have transformed the landscape of JE control. Better information on the distribution and burden of JE disease, and the value and impact of vaccination is increasingly available. While challenges remain, this tremendous progress means there is a better opportunity than at any time in the past to prevent the substantial morbidity and mortality from this disease. We are now at the point when achieving the JE control target is realistic. Progress towards the goal will require ongoing efforts to define and improve awareness of the burden of JE illness and the benefits of JE vaccination, adequate financial resources, support to National Immunization Technical Advisory Groups in their decision-making process, and the continued engagement of donor and international organizations. As with all public health efforts, meaningful progress will require sustained commitment. With such commitment, we have the opportunity to save and improve the lives of millions of children.

Acknowledgements

We thank K Neuzil for her review of the manuscript.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

No writing assistance was utilized in the production of this manuscript.

References

1. Campbell GL, Hills SL, Fischer M, et al. Estimated global incidence of Japanese encephalitis: a systematic review. Bull World Health Organ 2011;89:766-774E
2. World Health Organization. Japanese encephalitis vaccines. Wkly Epidemiol Rec 2006;81:325-40
3. PATH. Japanese encephalitis morbidity, mortality, and disability: reduction and control by 2015. Available from: www.path.org/vaccineresources/files/JE_Reduction_and_Control_by_2015.pdf [Last accessed 21 April 2014]
4. Kumar R, Tripathi P, Rizvi A. Effectiveness of one dose of SA 14-14-2 vaccine against Japanese encephalitis. N Engl J Med 2009;360:1465-6
5. Gatchalian S, Yao Y, Zhou B, 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;26:2234-41
6. Victor JC, Gatchalian S, Yao Y, et al. Corrigendum to "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 2014;32:306-3085
7. Hennessy S, Liu Z, Tsai TF, et al. Effectiveness of live-attenuated Japanese encephalitis vaccine (SA14-14-2): a case-control study. Lancet 1996;347:1583-6
8. World Health Organization. Immunization standards. Japanese Encephalitis Vaccine (Live) (1 dose vial). Available from: www.who.int/immunization_standards/vaccine_quality/pq_270_je_1dose_chengdu/en/ [Last accessed 12 May 2014]
9. Fischer M, Lindsey N, Staples JE, Hills S; Centers for Disease Control and Prevention. Japanese encephalitis vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2010;59(1):1-27
10. Schuller E, Klingler A, Dubischar-Kastner K, et al. Safety profile of the vero cell-derived Japanese encephalitis virus (JEV) vaccine IXIARO. Vaccine 2011;29:8669-76
11. World Health Organization. Immunization standards. Japanese encephalitis vaccine (inactivated) (1 dose vial). Available from: www.who.int/immunization_standards/vaccine_quality/pq266_je_1dose_biologicale/en/ [Last accessed 18 April 2014]
12. Feroldi E, Pancharoen C, Kosalaraksa P, et al. Single-dose, live-attenuated Japanese encephalitis vaccine in children aged 12-18 months: randomized, controlled phase 3 immunogenicity and safety trial. Hum Vaccin Immunother 2012;8(7):929-37
13. World Health Organization. Global Advisory Committee on Vaccine Safety, 11–12 December 2013. Wkly Epidemiol Rec 2014;89:53-60
14. Yaïch M. Investing in vaccines for developing countries: how public-private partnerships can confront neglected diseases. Hum Vaccine 2009;5:368-9
15. Touch S, Suraratdecha C, Samnang C, et al. A cost-effectiveness analysis of Japanese encephalitis vaccine in Cambodia. Vaccine 2010;28:4593-9
16. Yin Z, Beeler Asay GR, Zhang L, et al. An economic evaluation of the use of Japanese encephalitis vaccine in the expanded program of immunization of Guizhou province, China. Vaccine 2012;30:5569-77
17. Upreti SR, Janusz KB, Schluter WW, et al. Estimation of the impact of a Japanese encephalitis immunization program with live, attenuated SA 14-14-2 vaccine in Nepal. Am J Trop Med Hyg 2013;88:464-8
18. GAVI Alliance. Japanese encephalitis vaccine support guidelines. Available from: www.gavialliance.org/support/apply/ [Last accessed 18 April 2014]
19. Elias C, Okwo-Bele JM, Fischer M. A strategic plan for Japanese encephalitis control by. 2015;Lancet Infect Dis 2009;9(1):7
20. Senior K. Is Japanese encephalitis control achievable by 2013? Lancet Infect Dis 2008;8(9):534
21. Fischer M, Hills S, Staples E, et al. Japanese encephalitis prevention and control: advances, challenges, and new initiatives. In: Scheld WM, Hammer SM, Hughes JM, editors. Emerging Infections 8. ASM Press; Washington, DC: 2008. p. 93-124
22. Centers for Disease Control and Prevention. Status of Japanese encephalitis surveillance and immunization – Asia and the Western Pacific, 2012. MMWR Morb Mortal Wkly Rep 2013;62(33):658-62
23. Centers for Disease Control and Prevention. Expanding poliomyelitis and measles surveillance networks to establish surveillance for acute meningitis and encephalitis syndromes – Bangladesh, China, and India, 2006–2008. MMWR Morb Mortal Wkly Rep 2012;61(49):1008-11
24. Wang SA, Hyde TB, Mounier-Jack S, et al. New vaccine introductions: Assessing the

impact and the opportunities for immunization and health systems strengthening. Vaccine 2013;31S:B122-8

25. Bill & Melinda Gates Foundation. A big milestone for saving children. Available from: www.impatientoptimists.org/Posts/2013/10/A-Big-Milestone-for-Saving-Children [Last accessed 18 April 2014]

26. World Health Organization. Global vaccine action plan 2011-2020. Available from: www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en [Last accessed 18 April 2014]