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Addressing Vaccine-Preventable Encephalitis in Vulnerable Populations

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Addressing Vaccine-Preventable Encephalitis in Vulnerable Populations

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Abstract

Purpose of review: Vaccinations have been pivotal in lowering the global disease burden of vaccine-preventable encephalitides, including Japanese encephalitis, tick-borne encephalitis, measles encephalitis, and rabies encephalitis, among others.

Recent findings: Populations vulnerable to vaccine-preventable infections that may lead to encephalitis include those living in endemic and rural areas, military members, migrants, refugees, international travelers, younger and older persons, pregnant women, the immunocompromised, outdoor, healthcare and laboratory workers, and the homeless. There is scope for improving the availability and distribution of vaccinations, vaccine equity, surveillance of vaccine-preventable encephalitides, and public education and information.

Summary: Addressing these gaps in vaccination strategies will allow for improved vaccination coverage and lead to better health outcomes for those most at risk for vaccine-preventable encephalitis.

Introduction

Encephalitis has a significant rising global incidence likely from increased recognition of novel immune-mediated etiologies, new and emerging infections, and improved diagnostic modalities [1–3]. Infectious encephalitis is a serious clinical syndrome marked by high case-fatality rates, long-term hospitalization, and severe complications [4]. Vaccines are a cost-effective public health intervention, which have been pivotal in lowering the global disease burden of encephalitis though major gaps exist in vaccination efforts. Of the common vaccine-preventable diseases (VPDs) enumerated by the World Health Organization (WHO), listed in **Table 1** are vaccine-preventable causes of encephalitis [2, 5–23]. The list includes top causes such as the dengue, Japanese encephalitis (JE), and rabies viruses as well as the more recent and rare cases of encephalitis associated with monkeypox virus infection, termed mpox [2, 15, 24]. Although the advances made by vaccination programs in lowering the disease burden of encephalitis have been remarkable, there is much room for improvement. In meeting targets for global vaccine coverage, it is paramount that persons most at risk from vaccine-preventable encephalitis are not left behind. Here, we highlight areas for enhanced vaccine programming and offer suggestions to better address vaccine-preventable encephalitis in vulnerable populations.

Search strategy and selection criteria

A search strategy for academic papers was conducted via PubMed and the Google search engine. The search terms employed were the following: “vaccine preventable disease”, “vaccine preventable encephalitis”, “encephalitis”, “epidemiology”, “burden of disease”, “vulnerable populations”, “vaccine”, “vaccination”, “immunization”, “programs”, “gaps”, “strategies”, “approach”, “vaccine availability”, “vaccine distribution”, “vaccine equity”, “surveillance”, “education”, “information”, and “vaccine hesitancy”. Related keywords and phrases on the specific encephalitides and vulnerable groups were further expounded. Bibliographies of accessed papers were searched for additional relevant articles. We included studies on applicable disease surveillance and epidemiology. We included reports and reviews of corresponding vaccination programs and strategies implemented worldwide. Official data from reliable health agencies were reviewed. Studies unavailable via published data and internet searches were excluded from this review.

Epidemiology

Of the more than 100 different pathogens known to cause infectious encephalitis, viruses are the most common causative agents and contribute the largest to its global impact [4]. Currently available vaccines for causes of vaccine-preventable encephalitis are listed in **Table 2** [25–46]. Vaccine properties, route of administration, and human genetic and environmental factors all contribute to the variability in immune response, while the type of vaccine and disease vulnerability by age help determine vaccine placement in the immunization schedule [47, 48].

Dengue virus

Dengue is a rapidly spreading vector-borne disease affecting primarily the tropics and subtropics [37]. It has a reported incidence of encephalopathy and encephalitis between 0·5 and 6·2% [18]. Treatment outcomes of dengue encephalitis are wide-ranging from favorable recovery with minor residual deficits to mortality rates as high as 32-33% [18, 49]. Programmatic utility of CYD-TDV, the first licensed vaccine for dengue, is limited to seropositive persons (those with prior dengue infection) given the greater risk of severe dengue in persons who were baseline seronegative [37, 50]. Model-based assessments of public health impact of dengue vaccination following pre-vaccination screening support their potential merits in reducing dengue incidence and providing population benefits [51–53].

Japanese encephalitis virus

The JE virus is a neurotropic virus that causes widespread cellular apoptosis [18]. It has a 20-30% case-fatality rate and leaves 30-50% of those who survive with long-term neurologic sequelae [19]. Developed countries with high-quality vaccination programs, such as Japan and South Korea, have dramatically reduced JE cases to an incidence of 0·003 per 100,000 persons per year; whereas, countries with nascent or no vaccination programs, like Myanmar and Timor-Leste, saw higher annual incidence rates of 3·7 per 100,000 persons [19, 54].

Rabies virus

Rabies is a nearly always fatal zoonotic infection claiming 59,000 human lives each year, largely in Asia and Africa [37]. An acute encephalitic presentation of the disease develops subsequent to a bite, scratch or mucous lick by an infected animal [55]. Up to 99% of cases in regions endemic to human rabies is

secondary to viral transmission by dogs and interrupting this transmission by mass vaccination of dogs has been an effective strategy for rabies control [37]. For individuals at high risk of exposure, human rabies vaccines can be given preventively as pre-exposure prophylaxis and prompt post-exposure prophylaxis (PEP). In Latin America and Caribbean countries, cases of human rabies have declined substantially since the 1980s due to regional elimination programs [56]. PEP alone has averted an estimated three million deaths from rabies globally each year [57].

Influenza virus

Seasonal influenza affects 20% of unvaccinated children and 10% unvaccinated adults [37]. Influenza amounts to 1 billion cases each year with a 0·1% to 0·2% case-fatality rate and considerably impacts workforce productivity and demands on health services [37, 58]. Although the viruses are rarely neuroinvasive, influenza is responsible for 2-11% of childhood encephalitis cases [22]. Vaccination continues to be the best preventative measure against influenza and could markedly lower associated sequelae and mortality [22, 58]. In a study in Japan, comparisons of pediatric mortality rate secondary to influenza-associated acute encephalopathy/encephalitis saw a reduction during the mass immunization period of school-aged children prior to 1994 versus the succeeding period (1995-2000) [59].

Tick-borne encephalitis virus

The tick-borne encephalitis (TBE) virus is a neurotropic tick-transmitted virus that causes a zoonosis mostly occurring in Europe and Asia [26]. Case-fatality rates of TBE range from 1% to 40% depending on the virus subtype [29]. Development of long-term sequelae, such as persistent paresis and neuropsychiatric symptoms, is seen in up to 40% of adults with TBE [60]. A rise in TBE cases has been observed in some countries [61]. In a recent study in France, TBE is situated to be the third most popular cause of encephalitis [62]. Mass vaccination in Austria, with coverage reaching as high as 90% of the general population, has brought down TBE incidence rates to 16% of that of the pre-vaccine era [63].

Measles, mumps, rubella and varicella viruses

One to four per 1,000-2,000 cases of measles is complicated by encephalitis, which can lead to seizures, deafness, and intellectual disability; whereas, one in 5,000 measles infections is complicated by the universally fatal subacute sclerosing pan-encephalitis [8, 9, 65]. It is one of the most contagious viral infections and was previously the fifth leading cause of childhood under-five mortality in 2000 [64, 65].

Ten years later, its incidence fell by 66% and mortality by 74% corresponding to the increase in global first routine dose of measles-containing vaccine coverage from 72% to 85% [66]. As of 2019, a total of 83 out of 194 WHO countries have confirmed measles elimination [65]. However, sizable outbreaks mostly in undervaccinated communities threaten continued progress in elimination and contribute to the increased global measles cases seen in recent years [65].

While usually a mild infection of childhood with a case-fatality rate of 1 per 10,000 cases, mumps can also result in serious complications [37]. Mumps encephalitis, which occurs in 0·02-0·3% of cases, can lead to death and permanent disability [11, 37]. During the pre-vaccine era, annual incidences of mumps in several European countries averaged >100 cases per 100,000 persons. Post-vaccine, passively reported mumps cases in these countries dropped by 88-99%. In 1967, when the mumps vaccine first began its use in the United States (US), incidence was nearly 90 per 100,000 persons; almost three decades later, mumps incidence fell to 0·7 per 100,000 persons [11].

Rubella is a VPD that holds public health importance as the leading infectious cause of birth defects. Outside congenital infections, it is usually a benign disease. Rarely, however, rubella can be complicated by encephalitis (1 in 6,000 cases), which may be fatal [37]. Introduction of the rubella vaccine has drastically decreased the burden of rubella, with annual incidence estimates lowering to 1·7 cases per million in 2018 from 13·9 cases per million nearly ten years prior [12].

One per 33,000-50,000 cases of varicella is complicated by encephalitis [37]. Varicella-zoster virus encephalitis generally portends poor prognosis with mortality rates of 15% and almost 100% reported for immunocompetent and immunocompromised patients, respectively [7, 37]. Since first introducing universal varicella vaccination, the US has seen a marked decline of more than 90% in varicella incidence, hospitalization rates, and death as compared to the pre-vaccine era [67]. Countries in Latin America, Europe, Oceania, Asia and the Middle East have likewise observed high impact of varicella vaccination on disease burden [67].

Poliovirus

Poliomyelitis (polio) results in acute flaccid paralysis in 0·1-1% of infections and rarely is it complicated by encephalitis [14, 68]. Once a worldwide scourge, polio cases have dramatically declined since the introduction of polio vaccines. Sustained vaccination efforts brought a more than 99·9% reduction in

paralytic cases secondary to wild poliovirus by the end of 2021 [37]. New targets of the Global Polio Eradication Initiative aspire to certify eradication of wild poliovirus globally by 2026 and stop circulating vaccine-derived poliovirus transmission worldwide by 2028 [69].

Other viruses associated with encephalitis

Coronavirus disease 2019 (COVID-19) and mpox infections may be associated with encephalitis [2, 15]. Although reports of direct neuroinvasion are scant, the burden of encephalitis among those infected is non-negligible – a pooled incidence of 0·215% for COVID-19 and pooled prevalence of 2·0% for mpox [15, 70]. Encephalitis associated with COVID-19 has an average mortality rate of 13·4% [70]. Mpox has an estimated mortality rate of 10% and outcomes of associated encephalitis cases ranges from complete neurologic recovery to death [24, 71]. Estimates of deaths averted from the first year of COVID-19 vaccination worldwide amounted to almost 20 million [72]. Data on overall health impact of vaccines on mpox disease burden are limited and still developing [34].

Recent outbreaks of enterovirus A71 (EV-A71) over last two decades in the Asia-Pacific region have posed an important global health issue [73, 74]. In addition to causing herpangina and hand-foot-and-mouth disease (HFMD) in children, neurologic complications of the infection may include brainstem and/or cerebellar encephalitis. Severe cases can progress to autonomic dysregulation and/or cardiopulmonary breakdown and result in long-term sequelae or even death [74]. Although no vaccine against EV-A71 has been granted approval by the US Food and Drug Administration, three inactivated vaccines have been licensed in China [75]. Following their introduction in Chinese urban centers, a significant drop in EV-A71-associated HFMD cases was observed [76].

Vulnerable populations

Vaccine-preventable diseases disproportionately impact certain groups. Sustained prioritization of these groups is integral as we move forward to expand vaccination coverage. **Figure 1** outlines the populations most vulnerable to vaccine-preventable encephalitis.

Those living in areas where the infection is endemic are evidently at risk [2]. Travel and occupational exposures play a major role in transmission risk. Close-quarter living, deployment to endemic regions, and engagement in outdoor activities are factors that place military members at greater risk specifically for

TBE, but also for encephalitis due to other infectious agents [77, 78]. Similarly, occupations in forestry, farming, animal husbandry, healthcare, and laboratory and veterinary work increase exposure to potential health threats [79, 80].

Migrants, refugees, and tourists face comparable risks related to travel; however, the former two are even made more vulnerable by abject living environments, deprivation and poor hygiene whilst migrating, and halted vaccination programs during times of war, conflict, or social unrest [81, 82]. Due to civil war, polio vaccination coverage in Syria decreased from 99% in 2010 to 68% in 2012 [68]. More recently, Ukrainian refugees face similar challenges with VPDs as more than five million Ukrainians have fled to neighboring countries five months after the onset of the war between Russia and Ukraine in February 2022 [83, 84].

Communicable diseases are strongly related to poverty; this, together with substance abuse, mental illness, malnutrition, comorbidities, and limited access to public health services, leave those who are homeless at higher risk for VPDs [82, 85, 86].

Increased morbidity and mortality seen among children, elderly persons, pregnant women, and those immunocompromised likewise make them vulnerable. On long-term follow-up, 54% to 78% of children with encephalitis had persistent symptoms [87, 88]. In addition to their age as an aggravating factor for increased disease severity, elderly persons may be uniquely susceptible due to the possibility of never having been vaccinated with the vaccines now given in routine childhood immunization programs [25].

Pregnant women are another special group with increased susceptibility to severe infection by virtue of the immunologic changes they undergo during pregnancy [89]. Poor outcomes have been reported in about 10% and 17% of encephalitis-associated hospitalizations related to human immunodeficiency virus and tissue or organ transplant, respectively [90]. Encephalitis may also be more difficult to diagnose and manage in the immunocompromised due to atypical clinical presentations, oftentimes benign cerebrospinal fluid profiles, and the presence of uncommon or novel pathogens [91]. Vaccines provide not only a direct preventive measure for persons at risk but also an indirect protection through herd immunity to immunocompromised individuals not eligible for live-attenuated immunization or are poorly responsive to vaccination [64, 67, 92]. This added value in establishing and maintaining herd immunity places higher demands on vaccine uptake and coverage [92].

A careful balance between the benefits of and burdens of participation in research is also important when thinking about vulnerable populations so as to not undermine their representativeness and to improve evidence-based decision-making [93]. With new vaccines against other causes of encephalitis in the pipeline, such as that for the chikungunya, Lassa fever, Nipah, and herpes simplex viruses, factoring in these vulnerable groups in clinical trials for vaccine development right from the start might be beneficial if safety is supported by earlier trial data [5, 94–96].

Areas for enhanced vaccine programming

To address vaccine-preventable encephalitis in vulnerable populations, we sought to highlight areas for enhanced vaccine programming.

1. Availability and distribution of vaccines

Since 2016, 62% of JE-endemic countries have a JE vaccination program implemented, a moderate increase from 46% in 2012 [97, 98]. In Europe, TBE vaccine recommendations vary widely, with only Switzerland and Austria having universal immunization programs nationally [99]. Although all 194 countries have included a measles vaccine in their routine childhood immunization programs, only 36 countries have reached the WHO target of ≥ 95% coverage with both doses [65, 92]. Global coverage for rubella vaccination is estimated to be at 66% and has been introduced nationwide in 173 WHO member states [100]. Sixteen of the 21 countries that had not yet commenced vaccines containing rubella are in Africa and five are in the Eastern Mediterranean region [37]. There is no routine varicella vaccination in any country in Africa [67]. In a convenience sample of 22 countries from Asia and Africa, only 57% reported having a national program or strategy for rabies control and prevention, despite all having rabies vaccines available [57]. CYD-TDV introduction has only been underway in two subnational public health programs in Brazil and the Philippines since first licensed in 2015 [50]. Less than half of countries in the tropics and subtropics with low and middle-incomes had a national strategy against seasonal influenza [101]. Only 58 WHO member states had reached the target of 70% global COVID-19 vaccination as of June 2022 [102]. In high-income countries, ¾ people have received at least one dose of COVID-19 vaccine, compared to ¼ in low-income countries, as of November 2022 [103]. In resource-limited areas, incomplete childhood vaccination remains a significant public health concern as it can put children at greater risk for

acquiring VPDs [104, 105]. More vaccination programs need to be introduced and improvements in vaccine coverage sought among those currently implemented. Barriers to vaccine introduction include a dearth in disease surveillance data, insufficient funding, prioritization conflicts in vaccination, and the necessity for technical support [106]. Immunization policies need to be adaptable to the changes in demographics of at-risk groups and the effect of climate change on disease burden. In China, for instance, changes in occupational distribution as more people visit endemic forest areas, including students and tourists, have called for adjustments in the TBE immunization policy to cover these populations [107]. Rising numbers of environmental refugees and geographic range expansion of insect vectors partly due to climactic conditions are topical issues that need to be addressed [108, 109]. Threats to a steady vaccine supply brought about by long procurement lead times and reliance on a single regional manufacturer, as is the case for JE vaccines, remain a challenge [98, 110]. While the global supply of COVID-19 vaccines is not presently a binding constraint, exports of some vaccination-related products remain restricted [102].

2. Vaccine equity

Multiple factors can limit fair and just access to vaccines. Affordability is an important driver; low-income countries have to increase their healthcare spending by 57% on average to cover the cost of vaccinating 70% of the population against COVID-19, compared to a 0·8% increase in spending in high-income countries [103]. Affordability must be weighed with the cost of production of vaccines, especially for diseases not as prevalent as common illnesses. According to a Swedish survey, having free TBE vaccines could raise the rate of vaccination by 78% with low-income homes most greatly affected [99]. Rabies PEP can cost anywhere from US$3,000 to as high as US$40,000 in the US [47]. The intradermal administration of the rabies vaccine offers a cost-effective and dose-sparing alternative to the intramuscular route; however, most countries in Asia and Africa still administer these vaccines intramuscularly [37, 57]. Communities outside major urban areas may have restricted access to healthcare facilities and, therefore, to vaccination [99]. Immunization campaign operations disrupted and key geographies restricted due to war and conflict also add to vaccine inequity. In 2018, a house-to-house vaccination ban in Afghanistan led to missed poliovirus vaccinations of more than a million children [69]. More recently in Ukraine, there is an acute risk of missed or delayed vaccine doses due to disruption to healthcare services [111].

3. Surveillance

There is a need to enhance the quality of surveillance systems. Although an increase to 92% in 2016 from 75% in 2012 was seen in the number of JE-endemic countries conducting JE surveillance, challenges remain in some countries where a limited scope of surveillance may result in case ascertainment that is incomplete [97]. Sufficient data is necessary to better suspected case classification as well as to monitor geographic dissemination of infection [97, 98]. A lack of disease surveillance data can be a barrier to vaccine introduction and safety assessment as well as to the proper evaluation of the impact of vaccination programs [98, 106]. Incomplete TBE surveillance in Europe, for example, can lead to under-reporting of endemicity and perhaps inadequate vaccine recommendations [99]. In a Polish pilot project of enhanced TBE surveillance, doubling laboratory testing in select provinces led to the detection of 38 new endemic areas queued for possible TBE vaccination [99, 112]. Accurate and timely data also help guide the scheduling of seasonal vaccinations and the choice of formulation [101]. It is important to note, however, that beyond having high-quality surveillance systems, comparison and interpretation of data may also be complicated by differences in case definition, laboratory capacity, and notification regulations between regions and countries [2].

4. Public education and information

Lack of knowledge and minimization of disease can lead to poor healthcare-seeking behavior. In a survey of pig farmers in Nepal, where JE is endemic, less than half (42%) of them have heard of JE [80]. Likewise, a fairly low general understanding of tick-borne infections was reported in a survey of farmers in Italy, with only 43% of them knowing about the availability of TBE vaccines [79]. Pre-vaccination data showing substantial hospitalizations and complications from varicella infection contests the prevailing perception in some European countries that varicella is a low public health priority [113]. Underestimation by the traveler and even healthcare providers of disease risk and severity is also a barrier to vaccination [114]. In another survey, only 11% of travelers at high risk for JE received at least one dose of the JE vaccine [115]. Lastly, rising vaccine hesitancy is proving to be a challenge. Indeed, the WHO entered it as one of the top ten global health threats [116].

An overview of approaches

In response to these areas highlighted, we have proposed an overview of approaches as outlined in **Figure 2** that can be considered to improve vaccine coverage and health outcomes for populations at risk for vaccine-preventable encephalitis.

For vaccine prioritization, accurate burden data should be provided to policy-makers and public health officials. Following this, sufficient funding should be allocated to support the introduction and optimization of vaccination programs. In Nepal, solid evidence about the threat of JE aided in building political will, credence, and public backing for JE vaccination [106]. They were also able to tap resources, such as the WHO, the World Bank, and Gavi – the Vaccine Alliance – for financing and technical assistance [106]. Including indirect non-medical costs, like parental absenteeism, improves cost-effectiveness models as it allows for a more representative picture of the wider financial savings provided by vaccines [113]. The judicious shift to intradermal regimens of rabies vaccine in Brazil has been forecasted to reduce vaccine waste by 64%, potentially saving over US$6 million annually [117]. To improve adherence, vaccine schedules should be simplified and the rollout of new vaccine recommendations be coordinated alongside existing lifesaving ones [99, 106]. The development of national vaccine reminder systems may prove to be helpful in this regard, as was the case for the COVID-19 vaccine [99]. Vaccine delivery should be made more convenient whenever possible and administration be done by well-trained staff trusted by the community [118]. Off-site bulk storage and finding alternative manufacturers are ways to ensure a steady global supply and availability of vaccines [98]. Immunization policies should be adaptable to changing demographics and be made more climate-sensitive via increased inter-sectorial collaboration and data integration for better preparedness and response [107, 108].

All groups should have access to vaccines without discrimination. The recommendation by the European Center for Disease Prevention and Control to offer all Ukrainian refugees with no proof of prior vaccination scheduled vaccines corresponding to the host country, preferably within 14 days of entry, is in line with the European Vaccine Action Plan 2015-2020 [82, 83]. Effective mobile and drive-through vaccination initiatives should be expanded to improve vaccine access in rural communities [99]. Increasing affordability and monetary incentives will likewise improve local uptake [85, 101].

Disease surveillance systems should be strengthened. Expansion of laboratory diagnostic testing and improved financing for and access to them should be a continued and concerted effort from countries and

international partners and agencies [99, 119]. A move towards standardization would yield more accurate comparative data analysis [2]. Enhanced surveillance also improves transparency on vaccine safety and allows the provision of relevant and evidence-based data needed for continued awareness and public support. Gradual replacement of older vaccines with safer new-generation options should be continuously undertaken [37]. Integration of VPD surveillance with existing surveillance infrastructure will help maximize prevention and response [120].

Vaccine awareness campaigns and outreach programs should be collaborative, culturally appropriate, and locally responsive. Improving media coverage and using an assortment of promotive materials, such as posters and vaccination invitation letters written in multiple languages, are effective education tools [106, 111]. Involving local stakeholders in the campaign and engaging them to carry the message to populations prove to be powerful strategies to improve vaccine coverage in at-risk groups, such as the homeless [85, 118]. To increase awareness of travel-related encephalitis and encourage travelers to make informed decisions, more travel clinics should be set up, manned by healthcare providers who are kept up-to-date on VPDs and vaccine recommendations [114]. Joint efforts to fight misinformation and disinformation are important to address vaccine hesitancy. This requires not only providing transparent and reliable information but also approaching safety-related concerns with care and engaging trusted community representatives [111].

Conclusion

Vaccine-preventable encephalitis is of great public health importance. Certain groups are disproportionately impacted by its high burden of disease. There are a number of areas for enhanced vaccine programming and addressing them will help improve vaccination coverage and, thus, lead to better health outcomes for vulnerable populations.

Key points

- Vaccines have been pivotal in lowering the global disease burden of encephalitis.
- Vaccine-preventable diseases disproportionately impact special groups at risk.

- Areas for enhanced vaccine programming include issues relating to the availability and distribution of vaccinations, vaccine equity, surveillance, and public education and information.
- Addressing gaps in vaccination strategies will allow for improved vaccination coverage and lead to better health outcomes for vulnerable populations.

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Author contributions

BLCP, A Easton, and KTT participated in the conceptualization of work and original draft writing. BLCP, GKW, and KTT have verified the underlying data reported in the manuscript. BLCP and GKW contributed to designing the figures. All authors took part in the review and editing of the manuscript. All authors have read and agreed to the published version of the manuscript.

Potential conflicts of interest

JG has received consultancy fees from the Encephalitis Society in the past. KTT has received research funding from the US National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC), consultancy fees from the CDC and WHO, and honoraria and meeting support from the American Academy of Neurology. TS has received support from the National Institute for Health and Care Research (NIHR) Health Protection Research Unit in Emerging and Zoonotic Infections (Grant Nos. IS-HPU-1112-10117 and NIHR200907), NIHR Programme Grant for Applied Research (No. RP-PG-0108-10,048), NIHR Global Health Research Group on Brain Infections (No. 17/63/110), and The Pandemic Institute, Liverpool, which has received funding from Innova, CSL Seqirus, Aviva and DAM Health; he has received royalties from the Oxford University Press, Elsevier, Liverpool University Press, and Cambridge University Press; he was a consultant for the Medicines and Healthcare Products Regulatory Agency (MHRA) Vaccine Benefit Risk Expert Working Group and a member of the Commission on Human Medicines (CHM) committee of the MHRA; he was an advisor to the GSK Ebola Vaccine Programme and the Siemens Diagnostic Programme; he was a part of the Data Safety Monitoring Committee of a study to

assess the safety and immunogenicity of a candidate Ebola Vaccine in children - GSK3390107A (ChAd3 EBO-Z) vaccine; he was chair to the Siemens Healthineers Clinical Advisory Board and co-chaired the WHO Neuro-COVID task force as well as sat on the UK Government's Advisory Committee on Dangerous Pathogens and the MHRA Expert Working Group on COVID-19 vaccines; he advised to the UK COVID-19 Therapeutics Advisory Panel (UK-CTAP); he previously held shares in Medefer Solutions; and he has a blood-based diagnostic test for bacterial meningitis with a pending patent filed. The remaining authors have no conflicts of interest to declare.

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Figures legends

Figure 1. Populations most vulnerable to vaccine-preventable encephalitis

Figure 2. Approaches addressing vaccine-preventable encephalitis in vulnerable populations

Figure 1


LIVING IN ENDEMIC AREAS
MILITARY
REFUGEES
MIGRANTS/TRAVELERS
IMMUNOCOMPROMISED
YOUNGER AND OLDER PERSONS
OUTDOOR WORKERS / LIVING IN RURAL AREAS
HOMELESS
LABORATORY WORKERS

Figure 2


• Simplified and coordinated rollouts
• Convenient delivery
Distribution
• Sufficient funding allocation
• Off-site bulk storage
Availability
Equity
• Improve rural access via mobile and drive-through initiatives
• Monetary incentives
• Build political will, credence, and public backing
• Tap resources
Leadership
Surveillance
• Accurate burden data
• Expansion of laboratory diagnostic testing
Public Education
• Awareness campaigns and outreach programs
• Set up travel clinics

Table 1

Table 1. Vaccine-preventable causes of encephalitis and their epidemiology

Causes	Estimated number of encephalitis cases
Dengue virus	250,000 – 6·2 million cases per year [6–8]
Japanese encephalitis virus	68,000 cases per year [9]
Rabies virus	28,000 – 42,000 cases per year [10]
Influenza virus	16,000 – 90,000 childhood encephalitis cases per year [11,12]
Tick-borne encephalitis virus	5,000 – 13,000 cases per year [13]
Varicella-zoster virus	1,600 – 2,400 cases per year [14,15]
Measles virus	140 – 1,100 cases per year [16,17]
Mumps virus	80 – 1,700 cases per year [18,19]
Rubella virus	2 cases per year [20,21]
Severe acute respiratory syndrome coronavirus 2	1 million cases associated with encephalitis cumulatively [2]
Poliovirus	Rare, mostly in infants [22]
Monkeypox virus	Rare, 283 pooled cases [23]

Table 2

Table 2. Vaccines available for causes of vaccine-preventable encephalitis

Cause	Vaccine [25,26,40-42]	Efficacy and effectiveness	Schedule Recommendation [a] [30,36,38,39]
Dengue virus	- Live attenuated (recombinant) tetravalent vaccine: only one licensed, CYD-TDV	80% efficacy preventing symptomatic virologically confirmed infection, hospitalization, and severe infection among children age 9-16 years with prior dengue infection [43]	Age 9-16 years, seropositive living in endemic areas only, 3-dose series (at 0, 6, and 12 months)
Japanese encephalitis virus	Four main types of vaccine: - Inactivated Vero cell-derived vaccines (JE-VC) - Live attenuated vaccines (CD-JEV) - Live recombinant (chimeric) vaccines (JE-CV) - Inactivated mouse brain-derived vaccines (MB)	99% of children and 98% of adults were seroprotected at 1 month after two doses of JE-VC [44] 96% 5-year efficacy after a single dose of CD-JEV [45] 94% and 99% seroprotection at 14 days and 1 month, respectively, after one dose of JE-CV [45]	JE-VC: travel-related to endemic areas and those at increased risk, 2-dose series completed ≥ 1 week prior to travel
Rabies virus	For pre- (PrEP) or post-exposure prophylaxis (PEP): - Inactivated cell culture vaccines (e.g. human diploid cell culture, rabies vaccine adsorbed, purified chick embryo cell, purified Vero cell rabies vaccine) - Inactivated embryonated egg-based vaccine (e.g. purified duck embryo vaccine) - Inactivated nerve tissue vaccine [b]	92% of those who received PrEP vaccination developed an immune response [46] PEP is 100% effective in preventing rabies when given promptly following severe exposures; PEP includes thorough wound washing, a series of timely administered rabies vaccine, and rabies immunoglobulins (RIG) if indicated [37]	Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV): high risk for exposures as 2-dose PrEP series (on days 0 and 7); for PEP, 4-dose series (on days 0, 3, 7, and 14) for non-immunized (5th dose on day 28 for those who are immunocompromised) and 2-dose series (on days 0 and 3) for previously immunized
Influenza virus	Seasonal vaccines (egg-, cell- or recombinant-based): - Inactivated vaccine: trivalent, quadrivalent - Live attenuated vaccine: trivalent, quadrivalent	19-60% effectiveness of seasonal vaccines at preventing outpatient and emergency visits, hospitalizations, and severe infection from 2009-2021 flu seasons [27]	Routine annual vaccination 1 or 2 doses, age- and health status-appropriate
Tick-borne encephalitis (TBE) virus	Five approved inactivated vaccines: - Two inactivated cell culture-derived vaccines in Europe: FSME-IMMUN/TicoVac, Encepur - Two inactivated vaccines in Russia: TBE-Moscow, EnceVir - One inactivated vaccine in China: SenTaiBao	96-99% effectiveness after at least three doses of FSME-IMMUN/TicoVac [28] 62–89% protective effectiveness with the TBE-Moscow vaccine [29]	TicoVac: travel-related to endemic areas and for laboratory workers, 3-dose series, age ≥ 1 year
Varicella-zoster virus	- Live attenuated vaccine: monovalent, combined multiantigen vaccine (MMRV)	82% effective at preventing varicella and almost 100% effective against severe varicella after a single dose [30]	VAR or MMRV: routine 2-dose series at age 12–15 months, age 4–6 years [c]
Measles virus	- Live attenuated vaccine: monovalent, combined multiantigen vaccine (MR, MMR or MMRV)	Effectiveness of one dose of MMR vaccine is 93% against measles, 78% against mumps, and 97% against rubella [30]	MMR or MMRV: routine 2-dose series at age 12-15 months, age 4-6 years [c]
Mumps virus	- Live attenuated vaccine: monovalent, combined multiantigen vaccine (MM, MMR or MMRV)	Effectiveness of two doses of MMR vaccine is 97% against measles and 88% against mumps [30]	MMR or MMRV: routine 2-dose series at age 12-15 months, age 4-6 years [c]
Rubella virus	- Live attenuated vaccine: monovalent, combined		MMR or MMRV: routine 2-dose series at age 12-15 months, age

	multiantigen vaccine (MR, MMR or MMRV)		4-6 years [c]
Severe acute respiratory syndrome coronavirus 2	Types of coronavirus disease 2019 vaccine: - mRNA vaccine (e.g. Pfizer/BioNTech, Moderna) - Viral vector vaccine (e.g. Janssen/Johnson & Johnson, Oxford/AstraZeneca) - Protein subunit vaccine (e.g. Novavax) - Inactivated vaccine (e.g. Sinovac, Sinopharm)	94-95% efficacy at preventing infection among adults after two doses of mRNA vaccine [31,32] 72% efficacy against symptomatic infection after two standard doses of Oxford/AstraZeneca vaccine [33] 72% efficacy after one dose of Janssen/Johnson & Johnson vaccine and an increased efficacy of 94% after two doses [33] 90% efficacy against mild, moderate, and severe infection with Novavax vaccine in two Phase 3 trials [33] 51% efficacy against symptomatic infection, 100% against severe infection, and 100% against hospitalization after two doses of Sinovac vaccine in a Phase 3 trial [33]	6 months – age 17 years: 2 or 3-dose primary series, age- and health status-appropriate Age ≥ 18 years: 2 or 3-dose primary series, health status-appropriate
Poliovirus	Two types of vaccine: - Orally administered live attenuated polio vaccine (OPV): monovalent, bivalent, trivalent,[d] mixed OPV-IPV - Inactivated polio vaccine (IPV): trivalent, combined multiantigen vaccine (DTaP-HepB-IPV, DTaP-IPV/Hib, DTaP-IPV, DTaP-IPV-HibHepB)	90% effective or more against paralytic polio after two doses of IPV and 99-100% effective after three doses [30]	IPV: routine 4-dose series (at ages 2, 4, 6–18 months, 4–6 years) or ≥ 4 doses can be given before 4 years old when using IPV-containing combination vaccine; a dose should be given on or after 4 years old and at least 6 months following the previous dose
Monkeypox virus	Two available vaccines: - Live non-replicating vaccine (JYNNEOS) - Live replicating vaccinia virus vaccine (ACAM2000)	Clinical efficacy or effectiveness data for mpox are currently not available [34] Limited data on performance of JYNNEOS vaccine in the current outbreak showed that unvaccinated people have 10 times the risk of infection compared to those who were fully vaccinated and 7 times the risk compared to those with only the first dose received [35]	JYNNEOS: 2-dose series (on days 0 and 28)

[a] Recommendations from the U.S. Centers for Disease Control and Prevention
[b] The discontinuation of production and use of inactivated nerve tissue vaccines has been strongly recommended by the WHO since 1984; their substitution by up-to-date, concentrated, purified cell culture and embryonated egg-based rabies vaccines has instead been endorsed.
[c] The recommendation is to give MMR and varicella vaccines separately for the first dose in children 12-47 months old; however, may use MMRV if parents or caregivers prefer.
[d] In 2016, trivalent OPV has been withdrawn from routine immunization. Since then, bivalent OPV is used in routine immunization and supplementary immunization activities (SIAs), while monovalent OPVs are used in SIAs. Trivalent OPV or monovalent OPV2 is used exclusively in outbreak response to type 2 poliovirus.