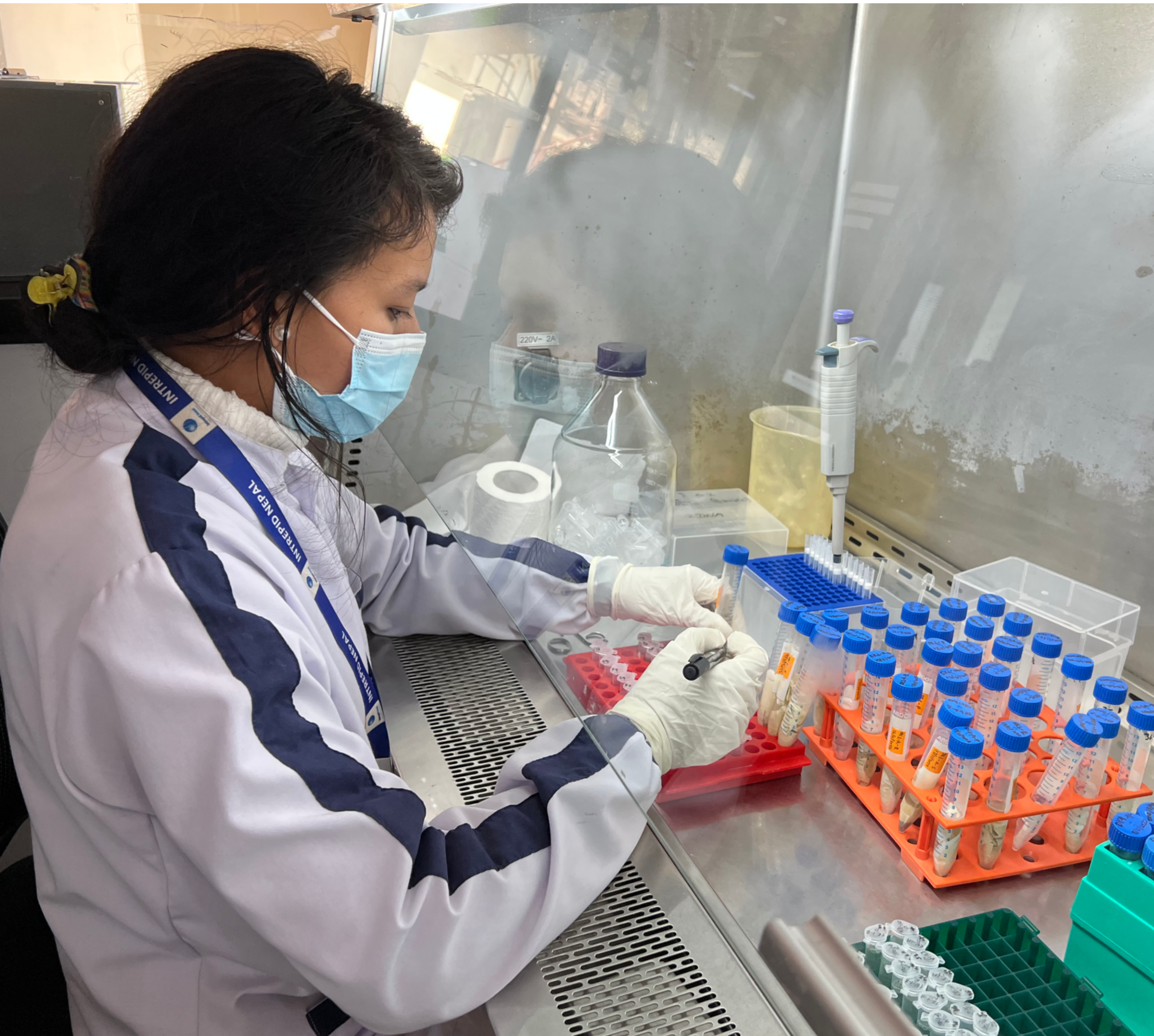
The Value of Vaccines to Mitigate Antimicrobial Resistance

GARP - Nepal Policy Brief



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ABBREVIATIONS AND ACRONYMS

AOR	adjusted model odds ratio
AMR	antimicrobial resistance
AMC	antimicrobial consumption
AMS	antimicrobial stewardship
AMU	antimicrobial use
ARI	acute respiratory infection
BCG	Bacillus Calmette-Guérin
CoNS	coagulase-negative Staphylococcus
DALYs	disability-adjusted life years
DDA	Department of Drug Administration
DOHS	Department of Health Services
DPT	diphtheria pertussis tetanus
GARP	Global Antibiotic Resistance Partnership
GBD	Global Burden of Disease
GRAM	Global Research on Antimicrobial Resistance
GLASS	Global Antimicrobial Resistance and Use Surveillance
HepB	hepatitis B
Hib	*Haemophilus influenzae* type b
HPV	human papillomavirus
IHME	Institute for Health Metrics and Evaluation
IPV	inactivated poliovirus vaccine
LRTI	lower respiratory tract infection
MDR	multidrug resistant
MR	measles-rubella

ABBREVIATIONS AND ACRONYMS

MRSA	methicillin-resistant *Staphylococcus aureus*
NIP	National Immunization Program
OPV	oral polio vaccine
OR	odds ratio
OTC	over the counter
PCV	pneumococcal conjugate vaccine
RSV	respiratory syncytial virus
RV	rotavirus
TB	tuberculosis
TCV	typhoid conjugate vaccine
Td	tetanus diphtheria toxoid
VPD	vaccine-preventable disease

EXECUTIVE SUMMARY

Antimicrobial resistance (AMR) presents a significant public health threat, contributing to higher mortality rates, prolonged illnesses, and increased health care expenses. In 2021, AMR was responsible for approximately 19,579 deaths in Nepal alone. Vaccinations are crucial in mitigating AMR because they reduce infections by providing direct protection against the targeted disease, and lower transmission rates by promoting herd immunity. In preventing infections, vaccines reduce the need for antimicrobial use – a critical driver for AMR.

Nepal has adopted policies to tackle AMR, including a National Action Plan, which focuses on building infection prevention, surveillance, and regulatory frameworks while taking a One Health approach. The plan also outlines several strategies that emphasize the importance of vaccinations to mitigate AMR.

The typhoid conjugate vaccines (TCVs) have effectively controlled typhoid fever outbreaks caused by drug-resistant *Salmonella typhi*. Similarly, integrating pneumococcal conjugate vaccines (PCVs) into the National Immunization Programme (NIP) in 2015 significantly reduced cases of pneumonia and meningitis. NIP aims to enhance vaccine coverage and ensure timely administration across Nepal.

The program includes vaccines against high-burden diseases, such as tuberculosis, hepatitis B, influenza, polio, measles, and rubella, with plans to incorporate new vaccines, such as for human papillomavirus (HPV). Effective vaccination campaigns can significantly avert antibiotic-treated cases of many of these diseases. For instance, modeling estimates find that more than half of the antibiotic-treated cases of acute respiratory infections caused by *Streptococcus pneumoniae* and diarrhea caused by rotavirus in Nepal are preventable by PCV and the rotavirus vaccine, respectively. Such high aversion is also projected in both antibiotic-treated cases and deaths for typhoid fever after the introduction of routine immunization with TCVs.

Addressing the AMR burden requires a multifaceted approach involving collaborative efforts across sectors. This includes implementing vaccination programs, conducting extensive research, and gathering data to understand drug resistance and develop effective strategies against it. Promoting vaccine uptake faces challenges, such as comprehension gaps among policymakers and logistical barriers in remote areas. Efforts to bolster evidence for vaccine promotion that assess cost-effectiveness, and understand the role of herd immunity in reducing rates of disease transmission are crucial.

Nepal's commitment to the Global Action Plan on AMR provides an opportunity to evaluate national progress.

*Photo courtesy of Center for Molecular Dynamics Nepal (CMDN) (2024)

Enhancing the capacity for AMR surveillance in the National Public Health Laboratories is paramount. Stakeholders advocate prioritizing economic cost quantification and intervention impact assessment through localized case studies to effectively address AMR challenges.

The following are a few key recommendations by the Global Antibiotic Resistance Partnership Nepal that can be taken into consideration to inform decisions, develop strategies for effective immunization programs, and tackle AMR.

- Strengthen surveillance systems to monitor AMR trends, and enhance local data on AMR and vaccines.
- Ensure equitable vaccine access.
- Highlight the role of vaccines in containing highly resistant infections and increase awareness among policymakers.
- Advocate for including the livestock sector in addressing zoonotic disease burdens via vaccination and community stewardship.
- Foster global collaboration, target high-risk populations, and advocate for regulatory support.

BACKGROUND AND CONTEXT

The health landscape in Nepal presents a mix of challenges and progress. As of 2023, Nepal has a population of approximately 29.7 million (World Bank 2024a), with the majority living in rural areas (78 percent) (World Bank 2023b). The life expectancy at birth as of 2022 is 70 years, and the mortality rate for children under five is 27 per 1,000 live births (World Bank 2022a; 2022b). The out-of-pocket expenditure for health care was 51.3 percent of the health care expenditure in 2021(World Bank 2021). Although 91 percent of the total population has access to basic drinking water services (World Bank 2022c), only 16 percent has access to safely managed drinking water services as of 2022 (World Bank 2022d).

Similarly, safely managed sanitation services were used by nearly half of the population (World Bank 2022f), and 80 percent had access to basic sanitation services (World Bank 2022e). Over half of the population (63.54 percent) in 2022 had access to basic handwashing facilities, including soap and water (World Bank 2022g); 50 percent of the health care facilities have been reported to have handwashing stations with hand hygiene materials as of 2021 (UNICEF South Asia 2022). The facilities also have been reported to have Water, Sanitation and Hygiene along with infection prevention and control guidelines, although these are not fully implemented. (World Health Organization 2023a).

Antimicrobial resistance (AMR) presents a significant global public health challenge, compromising the effectiveness of standard treatments, increasing mortality rates, prolonging illnesses, and escalating health care costs, especially in resource-limited settings. Contributing factors to its emergence and spread include the injudicious use of antimicrobials, inadequate infection prevention and control measures, and poor sanitation and hygiene practices (Rai 2018). Globally, 4.95 million people who died in 2019 suffered from drug-resistant infections, and AMR directly caused 1.27 million deaths. One in five of these deaths occurred among children under five (IHME and University of Oxford 2022). In 2021, Nepal reported 19,579 deaths associated with AMR, with 4,707 of these deaths directly attributable to AMR. The leading causes of death in the country included lower respiratory tract infections (LRTIs), tuberculosis, and diarrheal diseases. Resistant bloodstream infections were linked to over 7,000 deaths, with 1,830 deaths directly attributable to bacterial AMR. Likewise, LRTIs led to 6,690 AMR-associated deaths, of which 1,629 were directly attributable to AMR. (IHME and University of Oxford 2024).

A situational analysis report by the Global Antibiotic Resistance Partnership (GARP) Nepal published in 2015, revealed a concerning trend: common bacterial infections are increasingly resistant to treatment, emphasizing the urgent need to address AMR (GARP-Nepal National Working Group 2015). This requires a multifaceted approach, necessitating collaboration across diverse sectors, stakeholders, and programs, including stewardship programs, infection prevention and control practices, robust surveillance systems, effective vaccination programs, educational initiatives, and governing and regulatory mechanisms. In rural Nepal, continuous access to medicines is challenging, especially given the high burden of infectious diseases. In this context, vaccines offer a promising solution, by preventing infections and reducing the need for antimicrobial use.

INFECTIOUS AND VACCINE-PREVENTABLE DISEASE BURDEN IN NEPAL

Despite a notable reduction in the burden of infectious diseases, as evidenced by data from 2021 (Nepal Health Research Council (NHRC) 2021; R. Li et al. 2020), combating infections remains a significant challenge. According to the 2021 Global Burden of Disease (GBD) report, LRTIs, tuberculosis (TB), and diarrheal diseases are the leading causes of death in Nepal (Institute for Health Metrics and Evaluation 2024).

Enteric infections are the seventh leading cause of years of life lost (Sherchand et al. 2018). Diarrhea remains a significant public health concern and a prevalent cause of morbidity and mortality among children, particularly those under five (Shrestha et al. 2021; Li et al. 2020).

Rotavirus (RV) causes severe diarrhea in children under five. Studies have shown that rotavirus infections are prevalent among children with acute gastroenteritis, with a significant percentage requiring hospitalization. In a study conducted among children in Nepal, about 28 percent of stool samples tested positive for rotavirus A, reflecting a substantial burden among young children (Shrestha et al. 2019). A four-year surveillance study (January 2013–December 2016) analyzed 3,310 stool samples from 2,849 hospitalized and 461 non-hospitalized cases. Rotavirus was detected in 24 percent of hospitalized and 12 percent of the non-hospitalized children (Sherchand et al. 2018). Notably, 86 percent of the children hospitalized with rotavirus gastroenteritis were under two.

Similar results were observed in another study focusing on community-acquired cases of asymptomatic and symptomatic RV infections in children from birth to 36 months. This study found that rotavirus detection was highest among children 3–21 months old (Shrestha et al. 2021). Both studies identified genotypes G2P [4], G1P [8], G12P [6], and G9P [8] as the most prevalent in Nepal.

Globally, respiratory syncytial virus (RSV) is the primary cause of acute LRTI in young children, leading to high mortality and morbidity rates among children under five (Li et al. 2022). It is estimated that one in every 50 deaths in children aged 0–60 months and one in every 28 deaths in children aged 28 days to 6 months is attributable to RSV (Bhattarai et al. 2023). Nepal also bears a considerable burden of pneumonia caused by RSV. An active home-based surveillance for acute respiratory infection (ARI) reported that 9 percent of 3,509 infants had an RSV-associated ARI (Chu et al. 2016). Preterm infants had a higher incidence (551/1000 person-years) compared to full-term infants (195/1000 person-years), warranting their prioritization for RSV preventative interventions (Chu et al. 2016).

A retrospective analysis of 610 nasopharyngeal aspirate specimens from children aged 2–35 months with severe pneumonia admitted in a children's hospital in Kathmandu, Nepal, from January 2006 to June 2008 revealed that RSV was initially detected in 49 percent of the cases (Mathisen et al. 2021). Additionally, Jha et al. (2023) examined 294 SARS-CoV-2-negative samples from children under 2 years and found that more than one-third (36 percent) tested positive for RSV. This suggests that a significant proportion of RSV infections in such negative samples may have gone undiagnosed, potentially leading to inadequate management and control of respiratory illnesses in children (Jha et al. 2023). The co-occurrence of RSV with other prevalent diseases, such as measles, meningitis, and TB, reinforces the necessity for comprehensive public health strategies. According to GBD 2021, measles is the leading cause of death among vaccine-preventable diseases in Nepal, followed by meningitis, encephalitis, acute hepatitis, tetanus, and typhoid (Institute for Health Metrics and Evaluation 2024).

A nationwide measles outbreak between November 24, 2022 and March 10, 2023 reported 690 cases and one associated death. The outbreak occurred in a population with low vaccination coverage and suboptimal herd immunity. A significant contributor to this coverage gap was the disruption in routine immunization services during the COVID-19 pandemic. The ineffectiveness of the nationwide measles-rubella (MR) supplementary immunization campaigns carried out in 2020 also played a role in this outbreak (World Health Organization 2023b).

Tuberculosis is a significant public health issue and one of the top 10 causes of death worldwide and in Nepal. WHO reported 70,000 cases and 17,800 deaths due to TB in 2022. Of 1,087 people in Nepal diagnosed with drug-resistant TB, 681 sought treatment (World Health Organization 2024). TB causes more deaths than the diseases mentioned earlier, but may not be fully categorized as 'vaccine-preventable.' However, the Bacillus Calmette-Guérin (BCG) vaccine remains an essential tool in combating it. Although it does not consistently prevent TB, it has been shown to reduce the severity, especially in children and resource-limited settings (Okafor, Rewane, and Momodu 2023).

Although low in Nepal, malaria impacts the southern plains. Nepal is working toward the complete elimination of malaria by 2025 with activities rolled out across the 77 high, moderate, low, and no-risk districts (ECDC - Nepal 2023). A study has highlighted a significant decline (80 percent) in annual reported cases, from 5,393 in 2005 to 1,064 in 2018 (Bhattarai et al. 2023). However, concerning trends have been observed: cases of indigenous malaria increased by 114 percent in a cluster of three nonendemic mountainous districts, and cases of imported malaria increased by 156 percent in prominent clusters, including Kathmandu (Paul et al. 2022). Another study corroborates these findings, emphasizing a growing number of imported cases, with all reported cases in 2021–2022 caused by *Plasmodium falciparum* (Department of Health Services 2022).

Table 1 presents the morbidity, mortality, incidence, and prevalence for some of the vaccine-preventable diseases in Nepal.

Table 1. Vaccine-Preventable Disease Burden

Diseases	Deaths		DALYs		Incidence		Prevalence	
	Number	Rate*	Number	Rate*	Number	Rate*	Number	Rate*
Tuberculosis	7,488.1	24.6	252,679	830.7	46,339.9	235.0	4,291,298.1	14,108.5
Measles	6,64.6	2.2	56,976	187.3	155,771	512.1	4,267.7	14.0
Meningitis	469.1	1.5	23,734.6	78.0	6,065.0	19.9	26,975.7	88.7
Encephalitis	1,041.7	3.4	49,331.2	162.2	9,608.8	36.6	32,118.9	105.6
Hepatitis B (Acute)	1,44.2	0.5	6,918.2	22.7	147,678.6	485.5	17,039.8	56.0
Tetanus	380.7	1.3	29,817	98.0	914.3	3.0	-	4.7
Typhoid	918.8	3.0	68,186.1	224.2	82,449.4	217.1	52,15.3	17.1

* per 100,000 DALYs = disability-adjusted life years
Source: Nepal Health Research Council (NHRC) 2021

AMR IN NEPAL

In 2021, Nepal reported 4,707 deaths directly attributed to and 19,579 deaths associated with AMR (IHME and University of Oxford 2024). AMR-related deaths in Nepal surpass those caused by neoplasms, respiratory infections, TB, digestive diseases, maternal and neonatal disorders, diabetes and kidney diseases (IHME and University of Oxford 2019). Five key pathogens contribute significantly to AMR deaths in Nepal: *Klebsiella pneumoniae* (2,933 deaths), *Staphylococcus aureus* (2,663 deaths), *Escherichia coli* (2,613 deaths), *Pseudomonas aeruginosa* (2,155 deaths), and *Streptococcus pneumoniae* (2,496 deaths). These pathogens are commonly responsible for lower respiratory infections, bloodstream infections, and peritoneal and intra-abdominal infections (IHME and University of Oxford 2024).

Adding to the concern, antimicrobial susceptibility studies reveal a challenging situation in Nepal. A study carried out during 2016–2019 in urban and periurban health settings showed that more than 85 percent of both *S. typhi* and *S. paratyphi* isolates were resistant to the antibiotics ciprofloxacin and pefloxacin, which are listed under the Watch category of WHO's AWaRe classification for antibiotic consumption (Table 2) (Shrestha et al. 2021).

Table 2: Resistance Levels of *S. typhi* and *S. paratyphi*

	Resistance (percent)	
	S. typhi	***S. paratyphi***
Ciprofloxacin	89.6	91.0
Pefloxacin	88.6	85.0
Maxifloxacin	33.6	84.2

Source: Shrestha et al. 2021.

Similarly, another study revealed that more than 89 percent of *S. typhi* were resistant to ciprofloxacin, ofloxacin, and levofloxacin (Shrestha et al. 2021). Both cause typhoid fever, a life-threatening infection that spreads through contaminated food or water. Antibiotics are an effective therapy, but the complexity of treatment has been rising due to the spread of antibiotic resistance (World Health Organization 2023d). Nepal has one of the world's highest typhoid burdens with an incidence rate of over 100 per 100,000 population in 2022; typhoid fever causes roughly 82,000 cases annually resulting in 900 fatalities (Gavi Zero-Dose Learning Hub 2023; Coalition Against Typhoid 2022). In addition to the typhoid burden, neonatal sepsis remains a leading cause of mortality in neonatal intensive care units in Nepal (Pokhrel et al. 2018). A study in 2021 at Tribhuwan University Teaching Hospital of 372 cases of newborns with clinical suspicion of sepsis reported 132 (35.5 percent) positive cases (Sah R. 2021). The most common isolates were coagulase-negative *Staphylococcus* (CoNS) (37.9 percent), followed by *K. pneumoniae* (12.9 percent), with 36.6 percent of these isolates being multidrug resistant (MDR). Among 16 *S. aureus* isolates, 18.7 percent were methicillin resistant

*Photo courtesy of Center for Molecular Dynamics Nepal (CMDN) (2024)

(MRSA), as were 18 percent of the 50 CoNS isolates. The mortality rate among blood-culture-positive neonatal sepsis cases was 7.6 percent (Sah R. 2021).

Similarly, a retrospective study at Patan Hospital (April 2014–April 2017) identified 69 (20.5 percent) culture-positive sepsis cases out of 336 neonates (Pokhrel et al. 2018). The majority of the bacterial isolates were gram negative (77 percent), with *Klebsiella* species, CoNS, and *Enterobacter* being the most common and displaying resistance to first- and second-line antibiotics. *Klebsiella* showed high resistance to cefotaxime (90.5 percent), gentamycin (75 percent), ciprofloxacin (76.2 percent), and chloramphenicol (65 percent) but good susceptibility to stronger antibiotics, such as carbapenems (100 percent), colistin (88.8 percent), and tigecycline (81.8 percent). CoNS exhibited high resistance to oxacillin (80 percent), cefotaxime (66.7 percent), and meropenem (80 percent), but good susceptibility to vancomycin (100 percent) and linezolid (100 percent) (Pokhrel et al. 2018).

The 2022 antibiogram report from the National Public Health Laboratory revealed alarming levels of drug resistance (National Public Health Laboratory 2022). Among 10,950 *E. coli* isolates, 42 percent were MDR, with 91 percent showing resistance to third-generation cephalosporins and 12 percent to carbapenems (Table 2). Similarly, 42 percent of the 4,631 *Klebsiella spp.* isolates were MDR, with almost all (93 percent) resistant to third-generation cephalosporins and 40 percent to carbapenems (Steinhoff et al. 2017). In 2021, 1–5 percent of the reported typhoidal *Salmonellae* showed resistance to third-generation cephalosporins, and azithromycin resistance was reported in a few centers. Additionally, 59 percent of *Shigella spp.* isolates were resistant to ciprofloxacin, and 53 percent were resistant to third-generation cephalosporins. Resistance among *Neisseria gonorrhoeae* to third-generation cephalosporins was 20–40 percent (Table 3) (National Public Health Laboratory 2022).

Table 3: *E. coli* Resistance in Various Settings

Study Area	Antibiotics	Resistance (percent)
Siddhi Memorial Hospital, Bhaktapur (*n* = 114)	Ampicillin	72
	Cefixime, Cefodoxime	60
	Cephalexin	60
	Cotrimoxazole	50
	Ofloxacin	46
	Cefotaxime	42
BPKIHS (*n* = 168)	Ampicillin	87
	Ceftriaxone, Ofloxacin	62
	MDR	32
	XDR	5
PAHS (*n* = 60)	Ampicillin	85
	Ofloxacin	82
	Cefotaxime	75
	Gentamicin	28

Source: Ganesh et al. 2019; L.B. Shrestha et al. 2019; Shah G. 2016.
BPKIHS = B.P. Koirala Institute of Health Sciences; PAHS = Patan Academy of Health Sciences.

ANTIMICROBIAL USE AND CONSUMPTION

Inappropriate antibiotic use and consumption is a leading factor contributing to AMR. An analysis of the demographic health survey data from 2006 to 2016 reveals a concerning trend in antibiotic usage ARIs; it rose from 14 percent to 29.7 percent in urban areas and 27 percent to 50 percent in rural areas. Similar trends were observed for fever and diarrhea (Zheng et al. 2021).

A significant portion of the population obtains antimicrobials from pharmacies without valid prescriptions, a practice known as 'over-the-counter' (OTC) use (Khadka et al. 2023). In addition, many who acquire antimicrobials this way often fail to complete the prescribed course due to concerns about side effects. In Nepal, apart from public health facilities and private hospitals/clinics, a vast number of formal/informal pharmacies, similar to grocery stores, dispense antimicrobials without valid prescriptions (Pokharel and Adhikari 2020).

In developing countries, such as Nepal, it is common for minimally qualified or unqualified health professionals to dispense OTC medications for commonly occurring respiratory tract infections, urinary tract infections, and typhoid fever. Practices such as self-medication increase antimicrobial selection pressure, contributing significantly to AMR. This is especially problematic with OTC drugs, which are often selected inappropriately, including incorrect dosing and treatment durations (Pokharel and Adhikari 2020).

A prescription analysis study at six public health facilities involving approximately 6,860 patient records highlights increased improper antimicrobial prescribing practices. The rate of prescribing at least one antibiotic (44.7 percent) exceeded WHO recommendations (20.0–26.8 percent), particularly in primary health care centers (50.4 percent) and health posts (52.2 percent). Third-generation cephalosporins are the most frequently prescribed antibiotic class in this setting (Ghimire et al. 2023; Nepal et al. 2020).

The indiscriminate use of antimicrobials in agricultural practices, including in plant and animal feeds, poses a significant risk to human health. These antimicrobials are often imported as feed additives or supplements due to lower customs duty rates and registration charges, contributing to the escalating AMR crisis (Acharya K.P. and Wilson 2019).

A study analyzing the trends of antimicrobial use in Nepal (2018–2020) identified 96 trade-name antimicrobials registered for animal use, spanning 35 different genera and 10 different classes of antibiotics (Upadhyaya et al. 2023). Due to a legal ban on antimicrobials as growth promoters, all authorized antibiotics were reported for treatment purposes. However, AMC in food-producing animals, including critically important class I antibiotics, declined during this period.

To address the growing concern of AMR due to increasing AMU and AMC rates, it is crucial to implement good husbandry practices and enhance biosecurity in livestock farms. These measures can significantly reduce the reliance on antimicrobials, helping authorities mitigate the AMR crisis.

VACCINES FOR AMR AND INFECTION PREVENTION

Vaccines are crucial in combating AMR because they prevent primary and secondary infections and reduce the need for antibiotics, thereby slowing the spread of resistant strains (Gavi 2024; GSK NRCM 2024). This reduction not only maintains antibiotic effectiveness but also prevents their misuse, a significant driver of AMR. WHO has developed an action framework that details the role of vaccines against AMR, stressing the importance of increasing vaccine uptake, particularly in high-disease-burden areas, to prevent infections, decrease treatment needs, and mitigate misuse (World Health Organization 2020). This approach reduces the opportunities for resistant strains to develop, ensuring treatment effectiveness. In addition, high vaccination levels provide herd immunity, protecting unvaccinated individuals from resistant infections. The impact of vaccines on childhood morbidity and mortality has been globally recognized. This brief examines the potential of TCV, PCV, rotavirus, and influenza vaccines in Nepal as evidenced by various studies.

1. TCV

Typhoid is endemic to Nepal. Vaccines for typhoid fever can serve as a cost-effective measure to significantly reduce the disease incidence and associated AMR. Despite the availability of licensed vaccines, their usage has primarily been restricted to travelers. WHO recommends TCV for the control of endemic and epidemic typhoid fever. In a double-blind, individually randomized controlled trial of a single dose of TCV in Lalitpur Metropolitan City, 20,019 children aged 9 months to 16 years were given TCV or MenA vaccine. During follow-up, 75 cases of blood-culture-confirmed typhoid fever were reported (13 in the TCV group and 62 in the MenA group) over two years. TCV showed 79.0 percent protective efficacy against blood-culture-confirmed typhoid fever. The incidence of typhoid fever in the TCV and MenA groups were 72 and 342 cases per 100,000 person-years, respectively (Shakya et al. 2021).

Another study, using mathematical modeling, estimated the potential impact of introducing the TCV program for the original 73 Gavi-eligible countries on their country-specific burden of antibiotic-resistant typhoid fever, including Nepal. The models' results demonstrated that introducing a routine TCV infant program with a 15-year catch-up campaign could prevent about 68 percent of fluoroquinolone-non-susceptible typhoid fever and 70 percent of MDR typhoid fever in Nepal in a 10-year time horizon, and avert about 63 and 66 percent of these deaths, respectively (Birger et al. 2022).

2. PCV

The 10-valent pneumococcal conjugate vaccine (PCV10) was added to Nepal's routine infant immunization schedule in 2015. An observational cohort study by Shreshtha et al. (2019) aimed to assess the impact of PCV10 on pneumococcal carriage and disease in children. The study—conducted at the a tertiary hospital serving the communities of Kathamandu and Okhladhunga districts—involved children aged 2 months to 14 years with clinician-suspected pneumonia, and healthy children aged 0–8 weeks, 6–23 months, and 24–59 months. The study analyzed nasopharyngeal swabs, chest radiographs, and blood cultures to confirm pneumonia or invasive bacterial infections before and 4–5 years after the introduction of the PCV10 vaccine. Integrating PCV10 into the immunization schedule at 6 weeks, 10 weeks, and 9 months of age led to a decrease in vaccine serotype carriage among both healthy children in urban and rural areas, and children under 2 years admitted with pneumonia. However, the rising carriage rates of serotypes 19A and 3 in healthy children emphasize the need for ongoing surveillance to guide optimal vaccine policy and selection (Shrestha et al. 2022).

Another study (Lewnard et al. 2020), which looked at ARIs among children, analyzed data from several large-scale household surveys from 2015 in 18 LMICs, including Nepal, and estimated the number of antibiotic-treated cases prevented by pediatric vaccination programs. The study considered PCV active against 10 and 13 serotypes of *S. pneumoniae.* Researchers found that a large proportion of antibiotic-treated cases of ARI attributable to *S. pneumoniae* in Nepal are preventable by vaccination, thereby reducing both disease burden and antibiotic consumption. They found around 28.7 antibiotic-treated cases of acute otitis media (a bacterial infection associated with ARI) attributable to *S. pneumoniae* per 100 children aged 2–5, but with the vaccination program, about 16 of those cases are avertable (Lewnard et al. 2020).

3. Rotavirus

Lewnard et al. (2020) also studied diarrhea as a leading cause of antibiotic use among children in 18 LMICs, including Nepal. Using data from several large-scale household surveys, the study estimated the number of antibiotic-treated cases of diarrhea prevented by the live attenuated rotavirus vaccine. Researchers found around 10.6 antibiotic-treated cases of diarrhea caused by rotavirus per 100 children under 2 in Nepal, but with the vaccination program, about six cases per 100 are avertable (Lewnard et al. 2020). Hence, vaccines can reduce antibiotic consumption, thereby reducing the scope of the spread of resistant genes.

4. Influenza immunization during pregnancy

A randomized, placebo-controlled trial evaluated the safety and effectiveness of maternal influenza immunization among mothers and their infants in Nepal, where influenza viruses are present year round. The trial was conducted in two consecutive sequential annual cohorts of pregnant women from the Sarlahi district in southern Nepal. The results showed that immunization reduced maternal febrile influenza-like illnesses by 19 percent in the combined cohorts. The efficacy was 9 percent in the first cohort and 36 percent in the second cohort (Steinhoff et al. 2017).

For laboratory-confirmed influenza infections among infants aged 0–6 months, immunization showed an overall efficacy of 30 percent in the combined cohort. The efficacy was 16 percent in the first cohort and 60 percent in the second cohort. The study found that maternal vaccination with a trivalent inactivated influenza vaccine significantly lowered the incidence of laboratory-confirmed influenza in infants, reduced influenza-like illness in women, and decreased the proportion of low-birthweight babies by 15 percent over a two-year period (Steinhoff et al. 2017).

5. Haemophilus influenzae Type b (Hib) vaccine

A comparative study of before and after the diphtheria-tetanus-pertussis/Hib/hepatitis B (DTP-Hib-HepB) vaccine was introduced in 2021 showed that the prevalence of Hib carriage declined among children aged 6 months to 5 years after vaccine introduction. Hib was not detected in the vaccinated age group. The reduction in Hib carriage from 5 percent in 2007 to 0 percent in 2018 in oropharyngeal swabs indicated the country's progress toward eliminating Hib circulation in children (Shrestha et al. 2021).

6. Maternal *K. pneumoniae* vaccine

K. pneumoniae is the leading cause of neonatal sepsis in many LMICs. A recent study modeled the global effects of a hypothetical maternal vaccine program. Assuming that women were routinely immunized at a level similar to the maternal tetanus vaccine and that the vaccine has an efficacy of 70 percent (a good estimate based on promising candidates in trials), researchers found that 2,273 cases of neonatal sepsis and 456 deaths could be averted annually in Nepal. To contextualize, these numbers account for more than 4.7 percent of annual neonatal deaths in the country (Kumar et al. 2023). Hence, a maternal *K. pneumoniae* vaccine could help avert a significant proportion of neonatal cases of sepsis and deaths.

Despite strong evidence of being highly effective in preventing infections and minimizing antibiotic use, vaccines have been underappreciated as a strategy for containment of AMR and associated infectious diseases. Many modeling studies have clearly demonstrated the impact of vaccines on reducing AMR burden, morbidity and mortality rates, and economic losses. However, quantifying the impact of vaccines on these reductions is challenging owing to factors such as study designs affected by confounding factors and potential selection and information bias (Tadesse et al. 2023).

NATIONAL IMMUNIZATION PROGRAM

The National Immunization Program (NIP) is Nepal's foremost priority program. Initially launched as the Expanded Program on Immunization, it encompasses a range of vaccines, including BCG, DPT-HiB-HepB, oral polio vaccine (OPV), and a fractional dose of inactivated polio virus. Preparations are underway to include HPV. Table 4 shows a complete list of program vaccines.

Table 4: Routine Immunization Schedule in Nepal

	Vaccination	Disease	Time of dose administration
1	Bacillus Calmette-Guérin (BCG)	Tuberculosis	1 dose at birth
2	Rotavirus	Rotavirus	2 doses at 6 weeks and 10 weeks
3	Oral polio vaccine (OPV)	Polio	3 doses at 6, 10, and 14 weeks
4	Fractional-dose inactivated polio vaccine (fIPV)	Polio	2 doses at 14 weeks and 9 months
5	Pneumococcal conjugate vaccine (PCV)	Pneumococcal diseases (meninges, ear and chest infections)	3 doses at 6 weeks, 10 weeks, and 9 months
6	DPT-HepB-Hib (Pentavalent)	Diphtheria Pertussis Tetanus Hepatitis B Haemophilus influenzae	3 doses at 6, 10, and 14 weeks
7	Measles—rubella (MR)	Measles, rubella	2 doses given at 9 months and 15 months
8	Japanese encephalitis (JE)	Japanese Encephalitis	1 dose at 12 months
9	Typhoid Conjugate Vaccine (TCV)	Typhoid	1 dose at 15 months
10	Human Papilloma Virus (HPV) Vaccine	Human Papilloma Virus (HPV)	1 dose for schoolgirls in grades 6-10 and out-of-school girls aged 10-14 years

Source: World Health Organization – South East Asia, Nepal EPI Factsheet 2024; Department of Health Services 2024.

Fully immunized children have substantially increased, from 65 percent in 2019-2020 to 91.2 percent in 2021-2022. Although NIP has achieved a commendable 90 percent crude coverage target for all childhood vaccines, age-appropriate coverage is remarkably low (Rauniyar et al. 2021). Analysis of the Nepal Demographic and Health Survey (2016–2017) data, focusing on 460 children aged 12–36 months, revealed that age-appropriate coverage was only 41.5–73.9 percent (Rauniyar et al. 2021). Figure 1 shows vaccine coverage trends from 2019–2020 to 2021–2022.

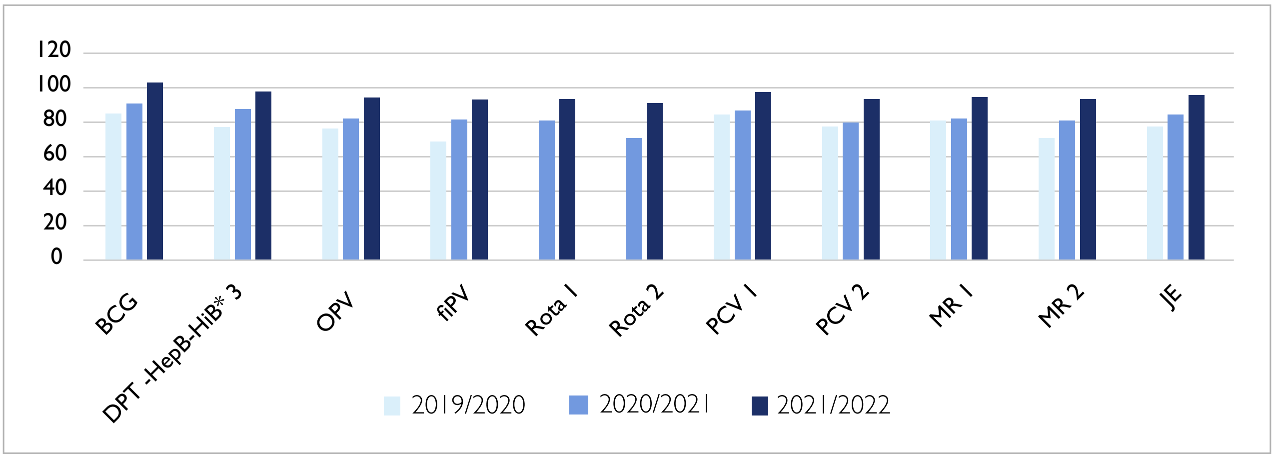

Figure 1. Vaccine Coverage Trends 2019/2020–2021/2022

Source: Annual Report, Department of Health Services, 2021/2022 (Department of Health Services 2022)
BCG = Bacillus Calmette-Guérin; DPT-HepB-HiB*3 = Diphtheria, tetanus, pertussis, Hepatitis B and *Haemophilus Influenza* vaccine 3rd dose; OPV = Oral polio vaccine; fiPV = fractional dose of inactivated polio vaccine; Rota 1 = rotavirus vaccine (first dose); Rota 2 = rotavirus vaccine (second dose); PCV 1 = Pneumococcal conjugate vaccine (first dose); PCV2 = Pneumococcal conjugate vaccine (second dose); MR1 = measles-rubella vaccine (first dose); MR2 = measles-rubella vaccine (second dose); JE = Japanese encephalitis vaccine.

Overall, vaccination coverage rates have increased over the reported period. Notably, dropout rates for DPT-HepB-Hib1 vs. MR1, BCG vs. measles, and DPT-HepB-Hib1 vs. MR2 have declined, but those of DPT-HepB-Hib1 vs. DPT-HepB-Hib3 have increased. The latest data show that Nepal is among the top countries in the South East Asian Region to have a high coverage for the COVID-19 vaccine, at 83 percent (World Health Organization 2023c).

The immunization program is one of the most successful initiatives in the country. However, several barriers need to be addressed to further increase coverage. A study conducted across six countries—Bangladesh, India, Maldives, Pakistan, Afghanistan, and Nepal—showed that the inequality in vaccination coverage is more strongly linked to maternal education than household-wealth-based inequalities (Acharya K. et al. 2022).

Another study focused on one district in Nepal identified a lack of mutual trust among service seekers and service providers. The study highlighted a few infrastructural barriers, such as inconvenient opening hours and neglected facilities, as the key barriers to attaining full coverage (Paul et al. 2022).

NATIONAL AMR-RELATED POLICIES

The National Health Policy from 2019 affirms the goal of reducing AMR (Department of Health Services 2019). Nepal has also adopted a National Action Plan (NAP) for AMR for 2021–2026 (Ministry of Health and Population 2023a). This plan outlines several strategies that connect vaccination and immunization to contain AMR. Some key strategies that link vaccination and immunization with AMR containment in the NAP include the following:

Table 5: Strategic priority 3: Reduce the incidence of infection through effective infection prevention and control (IPC) guidelines.

Strategic Area 5.3.1 Infection Prevention and Control (IPC) in Healthcare
Objective: Develop and implement IPC plans and interventions in health care settings. **Working policy 5.3.1.1:** Ensure the implementation of IPC guidelines in every health care setting. **Activity 9:** Ensure appropriate immunization of health care workers against VPDs. **Lead:** Ministry of Health and Population **Timeline:** Short, midterm, and long-term activity (1.5 years)

Strategic Area 5.3.2 IPC in Animal Health
Objective: Develop and implement IPC plans and interventions in animal treatment, animal husbandry and aquaculture. **Working policy 5.3.2.1:** Develop mechanisms to ensure the development and implementation of IPC measures (biosafety and biosecurity) in animal treatment, animal husbandry and aquaculture sector. **Activity 5:** Promote vaccination in the livestock sector to control infection and adopt biosecurity measures during outbreaks. **Lead:** Department of Livestock Services **Timeline:** Short and midterm activity (1.5 years)

Strategic Area 5.3.3 Infection Prevention in Community Through Healthy Eating, Lifestyle and Hygiene
Objective: Strengthen the IPC practices in community to minimize AMR. **Working policy 5.3.3.1:** Promote healthy eating, lifestyle and personal hygiene through behavioral change activities. **Activity 3:** Conduct mass awareness campaigns in the community about the importance of vaccines to prevent VPDs. **Lead:** Family Welfare Division **Timeline:** Short, midterm, and long-term activity (1.5 years)

The National Infection Control Guidelines (2022) mandated that all levels of government form an integrated monitoring committee to evaluate and monitor the implementation of AMR-related plans, policies, rules, and regulations. The guidelines also recommend that all health care facilities should develop and implement antimicrobial stewardship (AMS) programs and adhere to the Antimicrobial Treatment Guidelines to treat illnesses (Department of Health Services 2023). The government of Nepal has imposed a ban on the sale, import, and use of antibiotics that are not recommended by the Department of Drug Administration (DDA). Similarly, the antibiotic colistin has been banned in treating livestock, fish, and poultry due to evidence showing that rampant use in livestock increases the risk of AMR.

Recently, to increase knowledge and understanding of antibiotics among the general public and nonmedical personnel, the DDA has issued a directive to mark labels of OTC antibiotics with a red line (Department of Drug Administration 2023). The government of Nepal has also endorsed the National Antimicrobial Treatment Guidelines 2023 (Ministry of Health and Population 2023b).

RECOMMENDATIONS

Various studies have shown that vaccines have significantly reduced the burden of infectious diseases in humans and reduced AMR and its driving factors. Several current and potential vaccines could have a significant impact on the disease burdens in Nepal. The country's NAP on AMR emphasizes the importance of vaccination in disease prevention. Despite this, Nepal continues to struggle with achieving sufficient coverage for all vaccines.

The underuse of vaccines in tackling AMR may be impacted by a lack of clinical evaluations, policy, and economic research issues, weak regulatory systems, and challenges in procurement and distribution capabilities. Collecting and presenting comprehensive data on vaccine use and its effects on AMR to stakeholders and policymakers can be a significant step toward advocacy.

The following are key recommendations from a workshop on Vaccines and AMR organized by GARP Nepal on January 11, 2024.

1. **Policy Advocacy:** Emphasize the importance of vaccines in combating AMR through continuous advocacy efforts targeting policymakers. Highlight the role of vaccines in containing infections demonstrating high resistance to current therapeutics.

2. **Health Economics:** Use health economics data to demonstrate the economic benefits of vaccines over treatment in addressing AMR, facilitating effective communication and advocacy efforts.

3. **Highlighting of Best Practices:** Emphasize the importance of learning from and adopting best practices, leveraging successful immunization programs to introduce new vaccines effective in infection prevention and AMR containment.

4. **Inclusion of the Livestock Sector:** Recognize the high burden of zoonotic diseases and the importance of including the livestock sector in efforts to tackle AMR through measures such as vaccination, community stewardship, and biosecurity.

5. **Adherence to Treatment Protocol and Guidelines:** Promote adherence to antibiotic treatment guidelines to ensure rational use, focusing on aligning prescribing practices with WHO recommendations, particularly in primary health care centers and health posts.

6. **Promotion of Rational Use of Antibiotics:** Adopt a pragmatic approach to reducing AMU by promoting vaccines as a sustainable alternative, aligning with the National Policy Guidelines, and emphasizing vigilant monitoring.

7. **AMR Threat Assessment:** Establish robust surveillance systems to monitor evolving microbial

threats, including comprehensive data analysis, pathogen prioritization, and health care infrastructure strengthening.

8. **Disease-Specific Priorities:** Evaluate the burden of specific AMR infections to prioritize vaccination efforts, focusing on common pathogens and diseases with limited treatment options.

9. **Evidence Generation:** Prioritize research to demonstrate the impact of vaccines on disease prevalence, burden reduction, and economic advantages to leverage their development and usage in combating AMR.

10. **Targeted Population Groups:** Identify priority populations for vaccination based on epidemiological data analysis, prioritizing high-risk groups to curb AMR spread effectively.

11. **Vaccine Development and Deployment:** Address key challenges in vaccine development and deployment, such as research funding and regulatory hurdles, through increased investment, public–private partnerships, and streamlined regulatory pathways.

12. **Regulatory and Funding Support:** Advocate for regulatory frameworks and increased funding to facilitate vaccine development, approval, and distribution.

13. **Global Collaboration and Coordination:** Advocate for international collaboration to accelerate vaccine development and deployment efforts, ensuring equitable access globally.

14. **Surveillance and Monitoring:** Strengthen surveillance systems to monitor AMR prevalence and vaccination program effectiveness, emphasizing real-time data sharing and transparency.

15. **Health Equity and Access:** Ensure equitable vaccine distribution strategies to address affordability, accessibility, and vaccine hesitancy issues, particularly for marginalized populations.

16. **Education and Awareness:** Conduct public education campaigns to raise awareness of AMR and the role of vaccines, incorporating AMR into school curricula and leveraging health care networks for engagement.

By addressing these recommendations, Nepal can safeguard public health against the growing threat of antimicrobial resistance.

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Initiated in 2008, the Global Antibiotic Resistance Partnership (GARP) has played a critical role in advancing country-led national strategies and policies to address antimicrobial resistance (AMR) in several countries in Africa and Asia.

GARP's current focus is generating cross-disciplinary evidence highlighting the impact of vaccines on AMR in country-specific contexts.

This policy brief lays out the situation in Nepal and recommends policy measures to use vaccines as tools to control AMR in the country.

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