World Health Organization

MI4A
MARKET INFORMATION FOR ACCESS TO VACCINES

GLOBAL MARKET STUDY
HUMAN RABIES VACCINES

Key Takeaways

- The rabies vaccine manufacturer base is extremely fragmented across 24 manufacturers and 27 products. Geographically, supply is 85% concentrated in China and India.
- Limited prequalified supply (four vaccine products, representing 14% of total supply) may hinder procurement flexibility. Only three of these prequalified products are labelled for intradermal (ID) administration and available in a 1.0mL vial presentation.
- However, supply is sufficient to serve demand under all reasonable scenarios. Shortages in the period 2018–19 were linked to specific one-time events and, unless similar events were to repeat, are not expected to happen again.
- The switch to ID administration is likely to reduce annual vaccine needs considerably – from an estimated 60M vials to about 20M vials, mostly driven by China. Suppliers' plans must be carefully monitored as a significant drop in demand may trigger manufacturers to reassess their long-term market presence.
- Excluding China, this decrease in annual vaccine need is less severe and may be offset partially if PEP access increases due to new support from Gavi and the Zero by Thirty global strategic plan
- Choice of route of administration plays an important role in rabies vaccine affordability, with ID administration providing significantly less expensive vaccine costs per person than intramuscular (IM) administration, particularly in urban settings.

QUICK STATS

NUMBER OF VACCINE TYPES
1

NUMBER OF VACCINE PRODUCTS
27

2020 NUMBER OF MANUFACTURERS[1]
24

2020 ESTIMATED GLOBAL DEMAND[2]
64 million vials

2020 DEMAND/SUPPLY RATIO
Sufficient supply[3]

2019 REPORTED PER DOSE PRICE
UNICEF US$ 7.50

PAHO US$ 9.30

1 This number indicates only the companies that have full manufacturing capacity. The number does not include licensors providing a portion of the manufacturing process (e.g., filling and finishing) or distributors that simply commercialize the product in some locations.

2 Demand refers to programmatic vial requirement, defined as the average estimated number of vials a country would need to procure to meet its immunization programme needs, whether these are routine or campaign. This requirement includes wastage (depending on the presentation) and buffer.

3 Supply refers to the "Available Supply for Commercialisation," (ASC) defined as the number of doses available for sale at the global level in one typical year with normal production facilities utilization across the various vaccines (not factoring in special market, regulatory or technical events). This differs from the manufacturing capacity or the plant yearly throughput.

Disclaimer: This market study was completed before the impact of the SARS-CoV-2 pandemic was fully ascertained. Demand projections assume that any delay or disruption will be absorbed and resolved in 2021. Uncertainty on the progression of the pandemic raises the risk that disruptions will extend beyond 2021. An updated analysis of overall rabies vaccine supply-demand balance will be planned when more information is available on the impact of the SARS-CoV-2 pandemic on the rabies programme and strategies.

Context and Rationale

In December 2015, the World Health Organization (WHO), the World Organization for Animal Health (OIE), the Food and Agriculture Organization (FAO) and the Global Alliance for Rabies Control (GARC) endorsed a global framework to eliminate human deaths from dog-mediated rabies by 2030.[4] The framework, "Zero by 30," is a global strategic plan calling for implementation of programmatic changes in approximately 100 countries over the decade. Among other activities, the plan calls for expanded use of dog vaccines to reduce the risk of human rabies and increased access to human vaccines for populations at risk.

Human rabies vaccines are recommended for pre-exposure prophylaxis (PrEP) for individuals at high risk of rabies exposure and for post-exposure prophylaxis (PEP) after a potential exposure

4 Global Elimination of Dog-mediated Human Rabies: https://apps.who.int/iris/bitstream/handle/10665/204621/WHO_HTM_NTD_NZD_2016.02_eng.pdf;jsessionid=F3A39C6DCF22CD70088CF483BE3286E9?sequence=1

to rabies virus. PEP use following an animal bite drives the majority of global rabies vaccine use (97%). In 2018, to support programme improvements and increased access to human rabies vaccine for PEP, WHO recommended the intradermal (ID) route of administration, which requires less vaccine, and PEP regimens that require fewer visits and shorter duration. WHO specifically recommended the 6-dose Institut Pasteur du Cambodge (IPC) ID regimen as the most vaccine- and cost-reducing regimen.[5] In November 2018, the Gavi Alliance Board approved support[6] for human rabies vaccine for PEP beginning in 2021.[7] Pushes to improve rabies programmes, including switches to administration method and regimens that use much less vaccine, will have a significant impact on the market dynamics.

In addition to providing the most up-to-date understanding of the current and future trajectory of global supply and demand of rabies vaccines for PrEP and PEP,[8] this study identifies actions to help address the anticipated market dynamics and serves as an important resource for the implementation of the Zero by 30 strategy.

Demand

For standard comparison to available supply, demand in this market study is presented as programmatic vials required (PVR) rather than programmatic doses required. Rabies vaccine vials can either contain 0.5mL or 1mL of vaccine. An IM-administered dose requires a whole vial of vaccine (either 0.5mL or 1mL). An ID-administered dose requires 0.1mL of vaccine.

This global demand forecast for rabies vaccine is based on historical data and the latest available information on country introduction plans, and takes into account the extent and pace of programme improvements. Such improvements include switching to ID regimens, increasing access to PEP (which can be considered vaccination coverage), and increasing dog vaccination (which will decrease the target population for PEP). Gavi support and the success of the Zero by 30 plan will affect how quickly and with what magnitude these programme changes occur over the next ten years.

Most countries (181 countries, by estimates[9]) still use intramuscular (IM) administration for rabies vaccine (for PEP). Six countries use IM and ID regimens in combination,[10] and an additional six only use ID regimens. Few countries currently use the WHO-recommended IPC ID regimen.[11] The upcoming Gavi support focused on ID delivery is expected to attract additional attention and accelerate the shift to ID administration.

FIGURE 1: CURRENT RABIES VACCINE REGIMEN USE

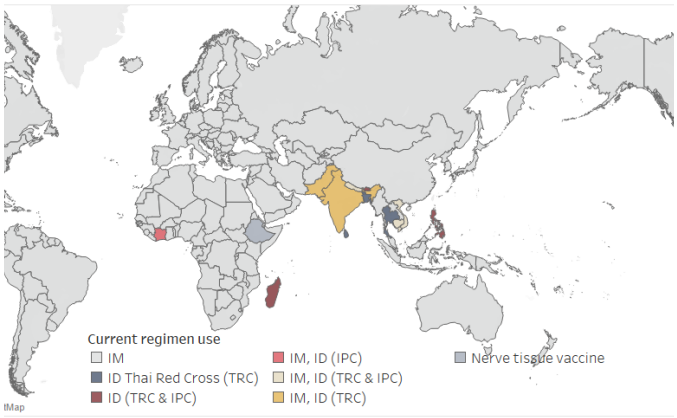
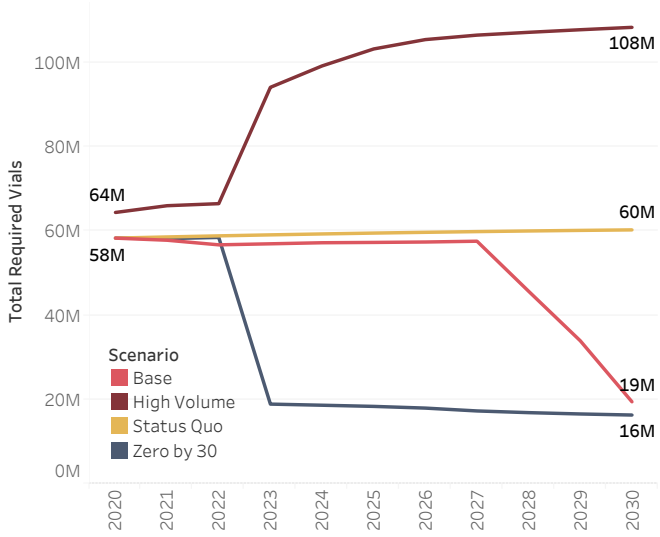


FIGURE 2: VIALS BY SCENARIO (2020–2030)



	PEP	PrEP	Grand Total
Status Quo	614M	40M	654M
Base	518M	40M	558M
Zero by 30	276M	40M	316M
High Volume	989M	40M	1,029M

Global rabies vaccine PVR for 2020 is approximately 64M vials, including demand from public and private sectors. Current demand is 97% IM administration. Though ID regimens occupy only 3% of current global vials required, 10% of people vaccinated for PEP were vaccinated intradermally, due to the increased number of doses that can be delivered from each vial. Using IM regimens, China currently represents an estimated 84% of all rabies vaccine vials required.[12]

5 Rabies vaccines: WHO position paper – April 2018. www.who.int/rabies/resources/who_wer9316/en/
6 This support is subject to the availability of funding for the 2021–2025 period following Gavi's replenishment.
7 Gavi Board meeting, November 28–29, 2018 – Review of Decisions www.gavi.org/sites/default/files/board/minutes/2018/Board-2018-Mtg-2-Review%20of%20Decisions.pdf
8 Access to animal rabies vaccines and rabies immunoglobulins for humans are also important tools in achieving the Zero by 30 goals. However, due to the unique features of those markets, they are not discussed here. Nerve tissue vaccines for humans are also excluded because they are no longer recommended for use by WHO.
9 Regimen use is known for 29 countries, including all countries using ID regimens. Remaining countries were assumed to use the most common regimen: 5-dose IM regimen.
10 Côte d'Ivoire, Cambodia, India, Nepal, Pakistan, Viet Nam
11 Bangladesh, Bhutan, Madagascar, Philippines, Sri Lanka, Thailand
12 Estimated vials required for China can vary widely, depending on the source of data inputs. For this study, the publicly available lot release data for China was determined to be the most accurate and up-to-date data source and was used to estimate vials required. Given the country's large share of global demand, understanding current use and future plans in China is critical to achieve good visibility into PVR.

Four scenarios have been developed to assess the possible trajectory of rabies vaccine use. The base case assumes 56% of countries switch to ID regimens,[13] moderate coverage growth,[14] and no increase in dog vaccination rates. The Zero by 30 scenario models a more ambitious future where all countries switch to ID regimens, achieve high coverage growth, and increase dog vaccination rates.[15] The high-volume scenario models the impact of no switch to ID combined with the achievement of high coverage; such a scenario is meant to test available supply against the highest possible volume of vials required. Finally, the status quo scenario provides a counterfactual reference point to other scenarios, showing vials required under a continuation of current programmes.

Among the different forces influencing demand, the switch to ID is likely to reduce annual vaccine needs most substantially – from 60M vials to about 20M vials. China is the most significant driver of this switch. Over the whole period (2020–2030), the total volume of vials required could reduce from 654M doses to 558M doses if China were to switch in 2029 (as in the base case), or to 316M if China were to switch in 2023 (as assumed in the Zero by 30 scenario). Therefore, understanding China's rabies vaccine programme and future plans is imperative to understanding rabies vaccine demand.

Excluding the outsized impact of China's potential actions, the total vial requirement from 2020 to 2030 remains relatively stable. The Zero by 30 scenario reduces the total volume required to 91M vials from the 113M vials required in the status quo scenario, over the decade, while the base case requires 92M vials in total. The decrease in vaccine needed from switching to ID regimens and increasing dog vaccination may be offset partially by improved access to PEP. More impact can be achieved using similar vaccine volumes to what is used currently.

Similarly, under the assumption of Gavi support starting in 2022 and recommending ID administration, Gavi countries' demand rises from 12% of global vials required in 2020 to 32% of vials required in 2030 in the base case, but the annual rabies vaccine need stays about the same (approx. 6M–7M vials per year).

NOTE: The SARS-CoV-2 pandemic is having an unknown impact on rabies vaccine programmatic vials requirement. Further investigation is needed to establish visibility on global vaccine demand in the short- and mid-term.

Supply

This assessment of the current and future global supply for rabies vaccines is based on consultations with manufacturers and experts, as well as a review of publicly available information.

The manufacturer base is extremely fragmented. Out of 24 manufacturers, 10 are located in China and six in India with the others spread across multiple countries. Nine additional affiliates sell – but do not themselves manufacture – rabies vaccine.

From a geographical standpoint, 85% of supply is concentrated in

FIGURE 3: CURRENT BASE ASC

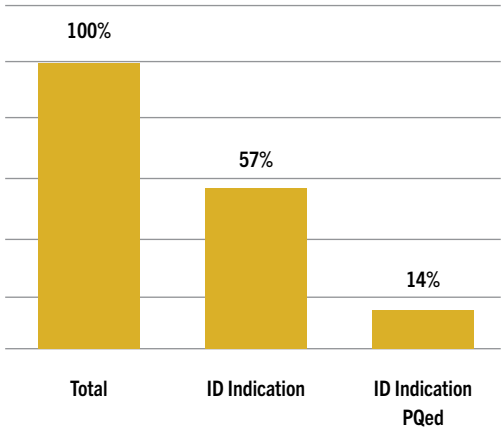
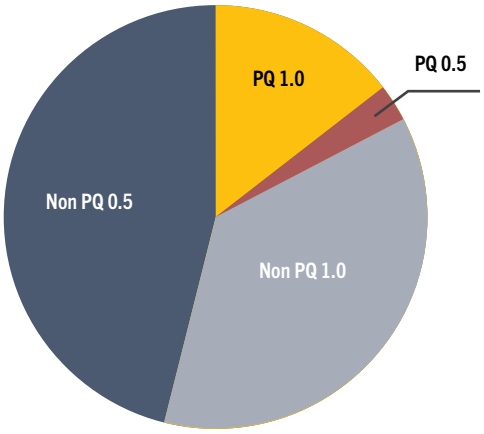


FIGURE 4: CURRENT BASE ASC BY VIAL SIZE



two countries – China and India – with the largest manufacturers representing a quarter of the global supply.

Twenty-seven rabies vaccines are currently available on the global market. Sixteen are labelled for ID administration in addition to IM (57% of global supply) and eight of those are presented in 1.0mL vials, which is preferred by WHO for ID administration (see figure 3). Only four of the 27 vaccines are prequalified (from BBIL, Sanofi, SII, and Zydus Cadila), representing 14% of the total supply and allowing for limited flexibility in procurement. Three of the four prequalified vaccines are indicated for ID administration and 1.0 mL vial presentation.

A pipeline of 11 vaccines (seven originating in China) may increase future vaccine choices, mostly in the medium- to long-term.

In the future, the ASC profile is expected to remain very stable, with a forecasted increase of approximately 25% over the next 10 years. This growth is almost completely dependent on pipeline vaccine and a modest increase of existing suppliers.

13 Based on expert intelligence: Gavi countries, the USA and middle-income countries (MICs) that are not in the AMRO region are expected to switch to ID, but high-income countries (HICs) and Latin American countries are unlikely to switch.

14 Uses the base variant of access improvement from the 2019 WHO Rabies Modelling Consortium impact analysis: Hampson, K et al. (2019). The potential effect of improved provision of rabies post-exposure prophylaxis in Gavi-eligible countries: a modelling study. The Lancet Infectious Diseases, 19(1), 102-111.

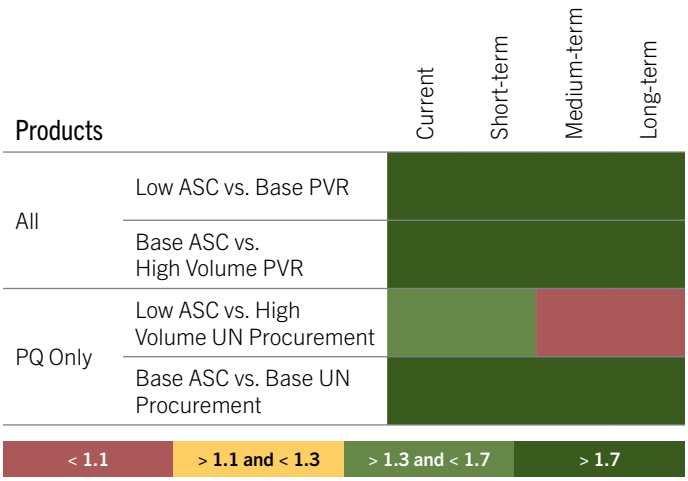
15 Uses the high coverage variant and dog vaccination rates from the 2019 WHO Rabies Modelling Consortium impact analysis.

NOTE: The SARS-CoV-2 pandemic, including COVID-19 vaccine production, may have an impact on development and production of rabies vaccines. This situation is currently under investigation and requires careful attention.

Demand and supply balance

In 2018 and 2019, shortages of rabies vaccine affected several countries – in 2019, 31 countries experienced difficulties in procuring this vaccine. Shortages were caused by one-time events linked to the discontinuation of a product and issues with production and lot releases for some other vaccines. Those imbalances were temporary, have since been resolved and unless similar events were to repeat - are not expected to affect countries in the future. Currently, supply is sufficient to serve demand under all scenarios, even in circumstances where the largest manufacturers are not able to serve the market. Even the supply from the four prequalified products alone is sufficient to meet the global base demand and may become insufficient only if demand increases significantly due to no additional uptake of ID regimens. Overall, the implementation of the Zero by 30 plan can be supported by the current supply availability.

FIGURE 5: RABIES VACCINE DEMAND-SUPPLY BALANCE



Red = insufficient supply or high risk of shortages; yellow = some risk of shortages; green/dark green = no risk

Country-specific shortages may still occur as a result of limited demand flexibility (resulting from limited use of streamlined regulatory procedures or mutual recognition among NRAs) if supply of specific products becomes limited.

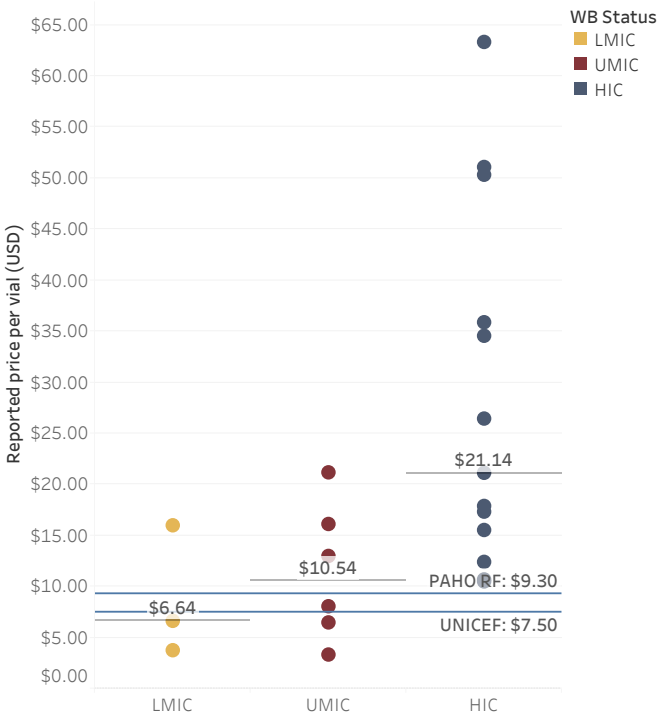
The condition of significant oversupply in most scenarios raises some questions about long-term market sustainability, though the IM to ID switch may trigger a market shift. A significant drop in demand as a result of widespread switch to ID – as in the base case or Zero by 30 scenario – will likely trigger manufacturers to reassess their long-term market presence particularly in the absence of ongoing engagement and discussion on the evolution of the market.

Pricing

This pricing analysis utilizes country-reported purchase data; rabies prices reported through this system only represent approximately 15% of global demand and thus are not representative of the global picture. From the reported data, price tiering between MICs and HICs is evident, as is a wide range of prices, particularly in middle- and high-income countries (see figure 6).

Choice of route of administration plays an important role in rabies vaccine affordability, with ID administration providing significantly less expensive vaccine costs per person than IM administration, particularly in urban settings. Improvements to vaccine characteristics, such as exploring the use of higher temperature labelling or addition of preservatives to reduce wastage, might help reduce vaccine wastage in rural settings, increasing affordability.

FIGURE 6: RABIES VACCINE– MEDIAN SELF-PROCURED COUNTRY PRICES AND AVERAGE UNICEF AND PAHO PRICES, 2019



Areas for Action

To enhance sustainable access to supply of rabies vaccines and support achievement of the Zero by 30 goals, WHO (in coordination with immunization partners) will:

- Seek information from countries on the time and extent of the IM to ID switch (country plans and constraints) to ensure quality forecasts of programmatic vial requirements. In particular, work to improve the understanding of current use and upcoming plans in two largest rabies vaccine markets, China and India
- Continue ongoing effort to ensure prequalification of additional vaccines to reduce risks in UN procurement segment and increase flexibility of global supply
- Engage proactively with manufacturers to monitor ongoing state of supply, assess risk of production issues, and pre-empt negative impact of market exits to ensure continuity of supply under all circumstances
- Develop a better understanding of drivers of vaccine affordability (e.g., impact of higher temperature labelling, use of preservatives, ID to IM switch) to facilitate unconstrained access

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Methodology & Resources

MI4A Technical Advisory Group of Experts:

MI4A benefits from the expertise of a standing advisory group for input, review and validation of market analyses. The group includes members from regional Technical Advisory Groups on immunization, UNICEF supply division (SD), PAHO Revolving Fund (RF), Gavi, the Bill & Melinda Gates Foundation, JSI, and WHO SAGE, along with manufacturers associations (Developing Country Vaccine Manufacturers Network and International Federation of Pharmaceutical Manufacturers & Associations) and independent experts.

Supply resources:

MI4A annual data collection from manufacturers, high-level validation of outputs of analysis with studies from Gavi and the Bill & Melinda Gates Foundation, bilateral discussions with manufacturers on capacity drivers and pricing prospects, review of clinical trials information, review of available cost of goods studies, review of manufacturing processes documentation (e.g., EMA), analysis of vaccine products registration.

Demand resources:

Historical procurement: WHO MI4A purchase data (2013–2019).

Current use (regimens and administration): WHO Regional Offices, Sreenivasan, N., et al. “Overview of rabies post-exposure prophylaxis access, procurement and distribution in selected countries in Asia and Africa, 2017–2018.” Vaccine 37 (2019): A6-A13.

Planned/projected country introductions: WHO JRF, WHO Regional Offices.

Estimates used to model future trends were developed in collaboration with the MI4A Advisory Group, rabies subject matter experts and the WHO Rabies Modelling Consortium (Hampson, Katie, et al. “The potential effect of improved provision of rabies post-exposure prophylaxis in Gavi-eligible countries: a modelling study.” The Lancet Infectious Diseases 19.1 (2019): 102-111.)

Pricing resources:

WHO MI4A Purchase data, PAHO RF, UNICEF SD (2019 data).

Rabies vaccines: WHO position paper April 2018
https://apps.who.int/iris/bitstream/handle/10665/272371/WER9316.pdf?ua=1