Application for Inclusion of Anti-Rabies Virus Monoclonal Antibodies to the World Health Organization's Model Lists of Essential Medicines and Essential Medicines for Children

1. Summary statement of the proposal for inclusion

Rabies is an acute, progressive, encephalitic viral zoonosis and NTD, present in >150 countries. Virions are transmitted during an animal bite and dogs are the main source of human infection. Tens of millions of suspected exposures occur annually, with tens of thousands of human deaths, primarily in lesser developed countries (LDC) throughout Asia and Africa (Hampson et al., 2015). The highest incidence and deaths are reported on the Indian subcontinent. Approximately 40% of persons bitten by suspect rabid animals are children under 15 years of age.

After a transdermal or mucosal rabies virus (RV) contamination (i.e. defined as a WHO category 3 exposure), predominantly from an animal bite, human rabies postexposure prophylaxis (PEP) entails wound care by washing with copious amounts of soap and water, prompt administration of a series of modern tissue culture-derived rabies vaccine doses and thorough infiltration of rabies immune globulin (RIG) into the wounds (WHO, 2018a). These biologics work to inactivate RV after exposure via viral neutralization during the critical period before active immunity occurs from vaccination. Although RIG, both human (hRIG) or heterologous, derived from horses (eRIG), have been used effectively for decades to help ensure positive survivor outcomes from this highly virulent viral zoonosis, concerns have been raised regarding the high costs and/or availability of these biologics in LDC, where the greatest burden of human rabies occurs. In addition, RIG, as a plasma product, carries a risk, albeit very low, of bloodborne pathogens or adventitious agents (e.g., perceptions about pathogens causing transmissible spongiform encephalopathies). For these reasons, many patients do not receive RIG, even after multiple and severe bite wounds to the face and head (Tarantola et al., 2015).

In contrast to the historical use of passive immunization by serum products for over a century, anti-RV monoclonal antibodies (MAbs) were first generated during the late 1970s (Wiktor and Koprowski, 1978). Some of these Anti rabies virus (ARV) MAbs narrowly recognized very distinctive epitopes on a given RV variant, whereas other cross-reactive MAbs directed to the outer viral glycoprotein more broadly neutralized global RV of public health relevance and were shown to protect laboratory animals, even after severe experimental viral exposure (Schumacher et al., 1989). After years of development, the first to be used in humans was a cocktail of 2 ARV MAbs, CR57 and CR 4098 (together called CL184), which were shown to be broadly neutralizing across many RV isolates, during pre-clinical research (Bakker et al., 2005; Bakker et al., 2008). Dose ranging studies were conducted in animals, with values quantified in µg/kg. A dose of ~12 µg/kg in combination with vaccine was found to be non-inferior to RIG and vaccine. Both phase 1 and 2 trials, conducted in India, the Philippines and the U.S., showed these MAbs to be safe, well tolerated and demonstrated adequate RVNA levels in all subjects, with doses of CL184 at 20 IU/kg or 40 IU/kg, before the product was withdrawn from further clinical development, after changes in pharmaceutical ownership and direction. Thereafter, given the progress shown by CL184, other ARV MAbs, directed against the outer RV glycoprotein, have proven to be an effective and safe option for use in PEP, as an alternate to RIG (WHO, 2018b).

The first ARV MAb product to be registered for use in humans occurred during 2016, which was 17C7 (also known as RAB1, SII RMAB or Rabisheld), a single human MAb directed against the RV glycoprotein, antigenic site III. This MAb neutralized a large panel of street RV isolates in vitro and protected animals from lethal challenge either alone or in combination with vaccine (Wang et al., 2011). Pre-clinical toxicity

and allergenicity and hypersensitivity testing, as well as Phase I clinical testing, indicated product safety. Phase II/III clinical trial demonstrated non-inferiority to standard RIG in RV-exposed individuals in India (Gogtay et al., 2012; Gogtay et al., 2018). A further phase IV, randomized, controlled study of the safety and immunogenicity in patients with potential RV exposure is underway at ~13 study sites in ~ 4,000 persons, to be followed over the course of 1 year.

The second ARV MAb product licensed, M777-16-3/62-71-3 (also known as Rabimab or Twinrab), was developed in collaboration with WHO, comprised of two MAbs, both of which are murine in origin (Mueller et al., 2009). These ARV MAbs are broadly cross-reactive against RV isolates and protected laboratory animals against severe RV challenge. Phase II/III clinical trial demonstrated non-inferiority in safety and efficacy to standard RIG in RV-exposed individuals in India (Kansagra et al., 2020).

Two other ARV MAbs are under clinical evaluation in RV-exposed humans. One is CR57 (also known as rhRIG), a human ARV MAb produced in China, in collaboration with investigators in the U.S. (Dietzschold et al., 1990; Sparrow et al., 2019). The investigators submitted their application files to the NMPA (i.e., the Chinese FDA) at the end of April, 2020. They concluded that the MAb was non-inferior to RIG. This conclusion was based upon results of the GMC antibody comparison of RVNA activity on the 7th day after injection in persons exposed to WHO category 3 suspected RV virus, which showed that MAb, combined with rabies vaccine, was not inferior to RIG combined with rabies vaccine. Three months after initiation, the survival rate of both groups of exposed subjects was 100%. There was no significant difference in the incidence of adverse events, which was mainly manifested by pain, swelling and erythema at the injection site. The incidence of systemic reactions was uncommon, mainly consisting of low-grade fever.

The other ARV MAb product under current clinical assessment is an equimolar mixture of two humanized IgG1 kappa antibodies, CTB011 and CTB012 (also known as SYN023). These MAbs bind non-competitively to non-overlapping epitopes in highly conserved regions of the RV glycoprotein and each exhibit cross-reactive neutralizing capabilities towards escape mutants produced in RV infected animal models treated with either antibody alone. As a mixture, their neutralization capabilities were equivalent or superior to RIG against 10 North American street RV isolates in vitro and against 15 prevalent Chinese RV isolates in animal models. This cocktail has been shown to confer protection equal to a standard dose of human RIG at 0.03 mg/kg in Syrian hamsters and 0.1 mg/kg in beagles (Chao et al., 2017; Chao et al., 2020). Investigation of SYN023 interference with vaccine-induced immunity in these animal studies found reductions in RVNA titers at doses at and above 0.1 mg/kg that were similar to reductions observed with RIG. A phase I study conducted in China found the ARV MAbs to be safe, with no serious adverse events reported (Ding et al., 2020). A Phase 2b study of this biologic is underway.

Given recent technical progress that has made MAbs potentially cost-competitive with traditional blood-derived polyclonal antibodies, while contributing towards an improved supply at a global level, these biologics fill a critical need in LDC compared to RIG (Sparrow et al., 2019). However, this particular class of biologics remains absent in the current WHO Essential Medicines List (EML), because although they are similar in action to RIG, they are produced in vitro, rather than as a classical polyclonal, plasma-derived product. Moreover, at least two ARV MAb products are now licensed for human use during PEP and others are in the final phases of clinical testing. This application proposes the addition of ARV MAbs to the EML and the Essential Medicines List for Children (EMLc) for use during human PEP, for all populations at risk after RV exposure.

During October 2017, the Strategic Advisory Group of Experts (SAGE), WHO's principal advisory group for vaccines and immunization, reviewed its recommendations regarding rabies vaccines and immun e globulins (WHO, 2017). Among other issues, RIG use was reviewed and the inclusion of ARV MAbs was discussed. The updated WHO position paper on rabies vaccines was published during April 2018 and now include ARV MAbs in its recommendations stating that, if available, the use of such MAb products instead of RIG is encouraged (WHO, 2018a).

2. Relevant WHO technical department and focal point

Bernadette Abela-Ridder, Neglected Tropical Diseases, WHO.

Erin Sparrow, Immunization, Vaccines and Biologicals, WHO.

3. Name of organization(s) consulted and/or supporting the application

Beyond the support in concept of the WHO SAGE Working Group (2017) and the WHO Expert Consultations (2018), no other organizations have been consulted in relation to this application.

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine

There is no INN for the ARV MAbs. The ATC code for the ARV MAbs, for the relevant indication in comparison to RIG during human PEP as an anti-infective for systemic use, is J06BB05.

5. Dose forms(s) and strength(s) proposed for inclusion

Anti-rabies virus monoclonal antibodies (murine)	Injection: 600 IU/mL; 1500 IU/2.5 mL in vial
Anti-rabies monoclonal antibody (human)	Injection: 100 IU/2.5 mL; 250 IU/2.5 mL in vial

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class

This application covers the group of medicines designated as ARV MAbs, including branded medicinal products and any biosimilars, whether homologous (i.e., human MAbs), heterologous MAbs (i.e., murine) or those produced by other technical methods (e.g., in plants). We propose a square box indication, highlighting the therapeutic equivalence of biosimilars to these A RV MAbs. Any biosimilars would be expected to have a similar overall structure and function in RV neutralization. Such MAbs are considered once they have been assessed to confirm that there are no meaningful clinically differences regarding effectiveness and safety. This proposition will provide choice to nations to ensure that critical biologics are affordable and practical. The choice of RIG or MAb for use during human PEP should be determined by consultation between the medical professional, knowledgeable SMEs and the patient.

□ Anti-rabies virus monoclonal antibodies	Solution for injection (infiltration or IM)

* includes homologous, heterologous products, and quality-assured biosimilars

7. Treatment details (including requirements for diagnosis, treatment and monitoring)

Similar to RIG, ARV MAbs are to be used after WHO category 3 exposures by suspected rabid animals (WHO, 2018a, b). In combination with thorough wound cleansing and the first application of modern tissue culture-based ARV vaccines, these MAbs are to be used only once at the initiation of PEP (Day 0), infiltrated into and around the wounds, in the anatomical localities where RV concentrations are highest after a bite. In cases of non-bite, mucosal exposures, MAbs should be given IM. The maximum dose may be 20 IU/kg, 40 IU/kg or at a dose specified per each product, in line with label requirements.

8. Information supporting the public health relevance

Globally, an estimated 29.2 million people globally undergo PEP annually. Current WHO PEP recommendations include thorough wound washing, rabies vaccination, and infiltration of ARV RIG. Historically, human PEP failures are rare, when these components are performed promptly and properly, even after severe exposures (Habel and Koprowski, 1955; Selimov et al., 1959; Lin et al., 1988). Since the advent of modern cell culture vaccines and RIG during the late 1970s, no failures were reported within enzootic developed countries, such as in Europe and North America. When PEP failures are reported in LDC, the majority of reports are related to the lack of the use of RIG among bite victims.

Historically, the WHO recognized three classes of biological products as currently available for the passive immunization component of PEP: hRIG, intact eRIG and highly purified F(ab´) 2 fragments produced from equine RIG. Production capacity and cost limit the availability of these serum-derived polyclonal RIGs, with most high disease burden LDC reporting negligible use. Understandably, in LDC, cost is an important factor in the lack of RIG use during PEP (Fang et al., 2010). For example, one study in India found only 21 of 783 (2.7%) patients with RV-prone bites were prescribed hRIG, and only 10 could afford to obtain the product (Gogtay et al., 2014). The survival outcome of these patients was not provided in this study. Other studies from India and Thailand have also shown that only 2%–3% of patients with severe animal bites receive RIG (Sudarshan et al., 2006; Kamoltham et al., 2003). Therefore, it is not surprising that mortality from rabies remains high.

The inclusion of ARV MAbs into human PEP represents an opportunity for large scale production of safe, effective, well-characterized, dependable, and uniform biologics, with anticipated lower long term manufacturing costs (Sparrow et al., 2019).

9. Review of benefits: summary of evidence of comparative effectiveness

To date, based upon review of the peer-reviewed literature, ARV MAbs have demonstrated comparative effectiveness to RIG (Table 9.1). For example, in studies using a cocktail of 2 human ARV MAbs, results were comparable to the RIG regimen in simulated PEP studies (Bakker et al., 2008). In another phase I simulated PEP study performed in India among adults, a single ARV MAb induced RV neutralizing activity (RVNA) activity comparable with an RIG-containing regimen (Gogaty et al. 2012). Thereafter, a phase 2/3, randomized, single-blind, noninferiority study was conducted in India among 200 participants (adults and children > age 5) with WHO category III suspected RV exposures. Participants received either ARV MAb or RIG (1:1 ratio) in wounds and, if required, intramuscularly on day 0, along with 5 doses of rabies vaccine on days 0, 3, 7, 14 and 28. The primary endpoint was the ratio of the day 14 geometric mean concentration (GMC) of RVNA, as measured in MAb recipients relative to RIG recipients. One hundred ninety-nine participants received MAb (n = 101) or RIG (n = 98) and at least 1 dose of vaccine.

The day 14 GMC ratio of RVNA for the MAb group relative to the RIG group was 4.23 (97% confidence interval [CI], 2.59–6.94) with a GMC of 24.9 IU/mL (95% CI, 18.94–32.74) for MAb recipients and 5.88 IU/mL (95% CI, 4.11–8.41) for RIG recipients. No deaths from rabies were reported. Based upon these collective findings (Table 9.1), a PEP regimen containing ARV MAbs is considered noninferior to RIG, as concerns RVNA elicitation, non-interference with active vaccination and survivorship after RV exposure.

Table 9.1 Comparative effectiveness of ARV MAbs

ARV MAb (reference)	STUDY TYPE	LOCALITY	PAITENTS	ANTIBODY RESPONSE	COMMENTS
17C7 (Gogtay et al., 2012)	Phase 1, randomized, open label, dose-escalation comparison of MAb or RIG plus vaccine, in a simulated PEP study, over 365 days	Large tertiary care, referral, public hospital in India	Healthy adults (n=74; 18-39 years of age, median 22; majority male subjects)	Day 14 MAb GMC, 23.4 IU/ml (95% CI 14.3-38.2); RIG GMC 15.3 IU/ml (95% CI 7.7-30.3)	Significantly higher passive antibody concentrations were detected in the MAb group than the RIG group, on days 3 and 7
17C7 (Gogtay et al., 2018)	Phase 2/3, randomized, single-blind, noninferiority study conducted in participants with World Health Organization category III rabies virus exposures to suspected rabid animals, over 84 days, of MAb or RIG, plus vaccine	5 hospitals across India	MAb (n = 101; mean age=34.3 years; 90.1% male) or RIG group (n = 98; mean age=32.2; 90.8% male)	Day 14 MAb GMC, 24.9 IU/mL (95% CI, 18.9–32.7); RIG GMC 5.9 IU/mL (95% CI, 4.1–8.4)*	No deaths or rabies cases reported
M777-16-3 & 62-71-3 (Kansagra et al., unpublished)	Randomized, double-blind, placebo controlled Phase I study	India	Healthy adults, both genders, n=18, MAbs only, IM (10, 20 or 40 IU/kg;	Passive antibody detected by Day 1, peaking by Day 3 and declining by	

	of MAb only, over 42 days		compared to 6 subjects receiving placebo	Day 42; highest activity in the 40 IU/kg group	
M777-16-3 & 62-71-3 (Kansagra et al., unpublished)	Randomized, double-blind, placebo-controlled Phase II study of MAb plus vaccine	India	12 healthy adult volunteers received MAbs (40 IU/kg) on day 0 plus 5 doses of vaccine on days 0, 3, 7, 14 and 28; 6 healthy volunteers received placebo on day 0 plus 5 doses of vaccine on days 0, 3, 7, 14 and 28	Passive antibody detected at 0.5 IU/ml by days 2 and 3 in the MAb group compared to controls	Active induction of antibodies >0.5 IU/ml from vaccination in the placebo group were not detected until after day 7, compared to early detection of passive MAbs
M777-16-3 & 62-71-3 (Kansagra et al., 2020)	Randomized, open label, comparator controlled, multicentric, Phase III study of MAb plus vaccine compared to RIG and vaccine, conducted in participants with World Health Organization category III rabies virus exposures to suspected	10 centers across India	MAb (n = 154; mean age=33.5; 75.3% male) or RIG (n = 154; mean age=34.7; 75.9% male); both groups included children >5 and adults >65 years of age	130 (90.3%) patients in the MAb arm and 134 (94·4%) patients in the RIG arm had an antibody titer ≥0·5 IU/ml by Day 14, with a GMT of 4.4 and 4.9 IU/ml, respectively	MAbs found to be non-inferior to RIG, as assessed by antibody titer and no deaths or rabies cases reported

	rabid animals, over 84 days				
CTB011 & CTB012 (Ding et al., 2020)	An open, parallel, single dose, phase 1 bridging study	China	Adult subjects received MAbs (0.3 mg/kg) alone (n = 8; mean age 37.5 years, 50% male) or in combination with rabies vaccine (n = 24; mean age 38.5 years, 38% male)	Recipients achieved adequate levels of detectable passive antibody (≥0.5 IU/mL) on day 3 post injection, with MAbs detected for ~ 43 days	The elimination half-life of the MAbs was ~ 14-24 days

*The GMCs of antibody activity were not significantly different between the groups on days 28, 42, and 84.

Breadth of viral neutralization

As one potential disadvantage, polyclonal antibodies are conceived to neutralize more lyssavirus variants than MAbs (WHO 2018b). To date, researchers have attempted to address the reactivity of these biologics by using in vitro neutralization tests and various experimental animal models with a broad number of viral isolates to help provide reassurance of the breadth of protection given by MAbs compared to polyclonal antibodies. All ARV MAbs considered for human use have been shown to neutralize RV in the region under study, most significantly related to canine rabies virus variants which cause the majority of human fatalities at a global level (Dietzschold et al., 1990; Bakker et al., 2005; Mueller et al., 2009; Wang et al., 2011; Chao et al., 2017). Enhanced surveillance and pathogen discover activities continue to characterize local viruses and coverage by available products to ascertain the public health relevance of lyssavirus antigenic diversity and neutralization coverage by existing MAbs.

10. Review of harms and toxicity: summary of evidence of safety

Compared to RIG, no unusual adverse events were detected in recipients of ARV MAbs, which were generally mild, and resolved without complications (Table 10.1).

Table 10.1 Reactogenicity in patients receiving ARV MAbs

ARV MAb (reference)	Severity	Adverse event
17C7 (Gogtay et al., 2018)		Pain=14(14.1%) Redness=15(15.2%) Swelling=13(13.1%) Fever=2(2%) Headache=20(20.2%) Nausea=7(7.1%) Fatigue=12(12.1%)

		Chills=4(4.0%) Myalgia=15(15.1%) Arthralgia=13(13.1%)
M777-16-3 & 62-71-3 (Kansagra et al., 2020)	Mild=63(40.9%) Moderate=2(1.3%) Severe=0	Pain=18(11.7%) Pyrexia=13(8.4%) Swelling=7(4.6%) Tenderness=3(1.9%) Hyperbilirubinaemia=2(1.3%) Urinary tract infection=4(2.6%) Myalgia=2(1.3%) Haematuria=4(2.6%) Erythema=6(3.9%)
CTB011 & CTB012 (Ding et al., 2020)	No severe nor serious reactions reported	Hypertriglyceridemia=2(25%) Alanine aminotransferase increase=2(25%) Aspartate aminotransferase increase=2(25%) CPK increase=2(25%) Creatinine increase=1(12.5%) Anemia=1(12.5%)

To date, ARV MAbs have demonstrated comparative safety to RIG in human clinical trials (Table 10.2).

Table 10.2 Comparative safety of ARV MAbs

ARV MAb (reference)	STUDY TYPE	LOCALITY	PAITENTS	ADVERSE EVENTS, LOCAL	ADVERSE EVENTS, SYSTEMIC
17C7 (Gogtay et al., 2012)	Phase 1, randomized, open label, dose-escalation comparison of MAb or RIG plus vaccine, in a simulated PEP study, over 365 days	Large tertiary care, referral, public hospital in India	Healthy adults (n=74; 18-39 years of age, median 22; majority male subjects)	The MAb was well tolerated, with a similar frequency of local injection site reactions (e.g., pain) to RIG, usually resolving within 3 days	Solicited systemic reactions were comparable between the study groups, the majority were mild, resolving without sequelae, and no anti-drug antibodies were detected
17C7 (Gogtay et al., 2018)	Phase 2/3, randomized, single-blind,	5 hospitals across India	MAb (n = 101; mean age=34.3;	MAb (n=30; 30.3%) or RIG (n=21; 21.4%).	MAb (n=28; 28.3%) or RIG (n=20; 20.4%).

	noninferiority study conducted in participants with World Health Organization category III rabies virus exposures to suspected rabid animals, over 84 days, of MAb or RIG plus vaccine		90.1% male) or RIG (n = 98; mean age=32.2; 90.8% male)	Signs included pain, redness or swelling*	Signs included fever, headache, nausea, fatigue, chills, myalgia, or arthralgia*
M777-16-3 & 62-71-3 (Kansagra et al., unpublished)	Randomized, double-blind, placebo controlled, Phase I study	India	Healthy adults, both genders, n=18, MAbs only, IM; compared to 6 subjects receiving placebo	None reported	None reported
M777-16-3 & 62-71-3 (Kansagra et al., unpublished)	Randomized, double-blind, placebo controlled, Phase II study	India	12 healthy adult volunteers received MAbs (40 IU/kg) on day 0 plus 5 doses of vaccine on days 0, 3, 7, 14 and 28; 6 healthy volunteers received placebo on day 0 plus 5 doses of vaccine on days 0, 3, 7, 14 and 28	1 subject in the study group reported a skin lesion and pain, compared to none in the placebo group	1 patient in the study group reported fever and another with fever plus burning micturition compared to none in the placebo group
M777-16-3 & 62-71-3 (Kansagra et al., 2020)	Randomized, open label, comparator controlled, multicentric,	10 centers across India	MAb (n = 154; mean age=33.5; 75.3% male) or RIG (n =	65 mild to moderate signs in the MAb group compared	No serious adverse events reported

	Phase III study of MAb plus vaccine compared to RIG and vaccine		154; mean age=34.7; 75.9% male); both groups included children >5 and adults >65 years of age	to 57 in the RIG group	
CTB011 & CTB012 (Ding et al., 2020)	An open, parallel, single dose, phase 1 bridging study	China	Adult subjects received MAb (0.3 mg/kg) alone (n = 8; mean age 37.5 years, 50% male) or in combination with rabies vaccine (n = 24; mean age 38.5 years, 38% male)	From 8.3-25% of subjects developed temporary adverse events and adverse drug reactions, all of Grade 1 or 2 and both transient and self-limiting, particularly in the group with vaccine co-administration	No serious or severe events were reported, but a few subjects developed temporary anti-drug antibodies, which did not affect the MAb pharmacokinetics

* All solicited reactions were of mild to moderate severity, except for 3 events of redness, 1 event of pain, and 1 case of fever (41.3°C) assessed as severe, all in the RIG group. Seventy-five unsolicited events were reported from 57 participants during the 84-day study period. All were assessed as unrelated to study treatment except for 2: itching at the wound site from 1 participant in the MAb group and injection site pain from a participant in the RIG group. The mean changes in hematology and chemistry parameters from day 0 to day 28 were comparable between the 2 study groups. No antidrug antibodies were detected in any of the study participants.

To date, no serious adverse events were reported from the use of ARV MAbs in humans. A majority of reactions were mild to moderate in severity, resolving without sequelae (Gogtay et al., 2012, 2018; Kansagra et al., 2020; Ding et al., 2020). For example, in one comparative clinical trial in India, a total of 461 adverse events were reported, of which 83.7% were solicited events and 16.3% were unsolicited events. (Gogtay et al., 2018). Of the 386 solicited events reported within the first 7 days of PEP, 250 (64.8%) were injection site reactions (n = 112 at the wound site, n = 40 at another site of any remaining RIG or MAb volume injection, and n = 98 at the site of rabies vaccine injection), and 136 (35.2%) were solicited systemic reactions, with 85 from 28 participants in the MAb group and 51 from 20 participants in the RIG group. All solicited reactions were of mild to moderate severity, except for 3 events of redness, 1 event of pain, and 1 case of fever (41.3°C) assessed as severe, all in the RIG group. Seventy-five unsolicited events were reported from 57 participants during the 84-day study period. All were assessed as unrelated to study treatment except for 2: itching at a wound site from 1 participant in the MAb group and injection site pain from a participant in the RIG group. The mean changes in hematology and chemistry parameters from day 0 to day 28 were comparable between the two groups. No antidrug antibodies were detected in any of the study participants.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine

Overall, PEP is a highly cost-effective strategy to directly prevent deaths in persons with a WHO Category 3 exposure (Anothaisintawee et al., 2019). Unfortunately, as an emerging technology, there are very few data on the comparative costs and effectiveness of MAbs per se. To date, only 2 ARV MAb products have been licensed and marketed in India, so prices from a broader range of settings is not available. Moreover, similar to RIG, the use of ARV MAbs occurs only once in a person's lifetime, after exposure but before illness onset, so any cost effectiveness estimate is in the form only of the cost per case, in the light of the clinical event prevented, which is considered lifesaving with timely and appropriate PEP.

Although PEP should be free to patients, supported by local governments, the ability to pay varies widely across the globe. Studies on willingness-to-pay PEP thresholds of $1,400 to $2,953 USD were found in Tanzania and the Philippines, respectively (Shim et al., 2009; Quiambao et al., 2020).

In most LDCs in Africa and Asia, RIG is extremely limited in availability and varies greatly in price from $15-70 USD/vial (Sreenivasan et al., 2019). The ARV Mabs are anticipated to be intermediate in price in comparison to hRIG and eRIG. For example, in India, an estimate for a routine course of antibody during PEP in a LDC for an average sized adult varies from ~$285 USD for hRIG, $55 USD for MAb and $ 13USD for eRIG. Hence, any potential increase over 2% uptake in passive immunization that MAbs might offer in the market for RV-exposed individuals would save additional lives otherwise lose to this highly virulent disease.

12. Summary of regulatory status and market availability

The summary of the regulatory status and market availability of each biologic in various settings is presented in Table 12.1. To date, none of the MAbs have been approved yet by the Australian Government, EMA, FDA, Health Canada or the Japanese Pharmaceuticals and Medical Devices Agency, as they are intended for use primarily in LDC. Additional licensing agreements are under discussion.

Table 12.1 Regulatory Status and Market Availability of the Anti-Rabies Virus MAbs

NAME	TYPE	PEDIATRIC	ADULT	Registration
M777-16-3 & 62-71-3/ Docaravimab & Miroravimab / Twinrab	Heterologous (cocktail of 2 murine MAbs)	✓	✓	India (licensed)
17C7/SII RAB1 Rabishield	Homologous (single human MAb)	✓	✓	India (licensed). Also registered in Uzbekistan, Tajikistan, Georgia, Kyrgyzstan, Bahrain, Kenya, Mozambique, Nepal, Kazakhstan,

				Tanzania, Chad, DR Congo, Ethiopia, and Oman (and supplied to several other countries, without formal registration)
CR 57/rhRIG	Homologous (single human Mab)	✓	✓	Phase 3 clinical findings submitted to the Chinese FDA
CTBO11 & CTBO12/SYN023	Homologous (cocktail of 2 human MAbs)	✓	✓	Phase 2b clinical trial underway

13. Availability of Pharmacopoeia standards

As of yet, none of the ARV MAbs are listed in the British, European, U.S. or International Pharmacopeia.

14. References

Anothaisintawee T, Julienne Genuino A, Thavorncharoensap M, Youngkong S, Rattanavipapong W, Meeyai A, et al. Cost-effectiveness modelling studies of all preventive measures against rabies: A systematic review. Vaccine. 2019 Oct 3;37 Suppl 1:A146-A153.

Bakker AB, Marissen WE, Kramer RA, Rice AB, Weldon WC, Niezgoda M, et al. Novel human monoclonal antibody combination effectively neutralizing natural rabies virus variants and individual in vitro escape mutants. J Virol. 2005 Jul;79(14):9062-8.

Bakker AB, Python C, Kissling CJ, Pandya P, Marissen WE, Brink MF, et al. First administration to humans of a monoclonal antibody cocktail against rabies virus: safety, tolerability, and neutralizing activity. Vaccine. 2008; 26(47):5922-7.

Chao TY, Ren S, Shen E, Moore S, Zhang S-F, Chen Li, et al. SYN023, a novel humanized monoclonal antibody cocktail, for post-exposure prophylaxis of rabies. PLoS Negl. Trop. Dis. 2017; 11(12).

Chao TY, Zhang SF, Chen L, Tsao E, Rupprecht CE. In Vivo Efficacy of SYN023, an Anti-Rabies Monoclonal Antibody Cocktail, in Post-Exposure Prophylaxis Animal Models. Trop Med Infect Dis. 2020 Feb 21;5(1):31.

de Kruif J, Bakker AB, Marissen WE, Kramer RA, Throsby M, Rupprecht CE, et al. A human monoclonal antibody cocktail as a novel component of rabies postexposure prophylaxis. Annu Rev Med. 2007;58:359-68.

Dietzschold B, Gore M, Casali P, Ueki Y, Rupprecht CE, Notkins AL, et al. Biological characterization of human monoclonal antibodies to rabies virus. J Virol. 1990 Jun;64(6):3087-90.

Ding Y, Wu M, Zhang H, Zhu X, Hu Y, Li X, et al. Safety, pharmacokinetics and pharmacodynamics of SYN023 alone or in combination with a rabies vaccine: An open, parallel, single dose, phase 1 bridging study in healthy Chinese subjects. Antiviral Res. 2020 Oct 19;184:104956.

Fang LX, Ping F, Ping du Y, Hui BG, Yan YX. Socioeconomic status is a critical risk factor for human rabies post-exposure prophylaxis. Vaccine 2010; 28:6847–51.

Gogtay N, Thatte U, Kshirsagar N, Leav B, Molrine D, Cheslock P, et al. Safety and pharmacokinetics of a human monoclonal antibody to rabies virus: a randomized, dose-escalation phase 1 study in adults. Vaccine. 2012 Nov 26;30(50):7315-20.

Gogtay NJ, Nagpal A, Mallad A, et al. Demographics of animal bite victims & management practices in a tertiary care institute in Mumbai, Maharashtra, India. Indian J Med Res 2014; 139:459–62.

Gogtay NJ, Munshi R, Ashwath Narayana DH, Mahendra BJ, Kshirsagar V, et al. Comparison of a Novel Human Rabies Monoclonal Antibody to Human Rabies Immunoglobulin for Postexposure Prophylaxis: A Phase 2/3, Randomized, Single-Blind, Noninferiority, Controlled Study. Clin Infect Dis. 2018;66(3):387-39.

Habel K, Koprowski H. Laboratory data supporting the clinical trial of anti-rabies serum in persons bitten by a rabid wolf. Bull World Health Organ 1955; 13:773–9.

Hampson K, Coudeville L, Lembo T, Sambo M, Kieffer A, Attlan M, et al. Estimating the global burden of endemic canine rabies. PLoS Negl Trop Dis. 2015 Apr 16;9(4):e0003709.

Kamoltham T, Singhsa J, Promsaranee U, Sonthon P, Mathean P, Thinyounyong W. Elimination of human rabies in a canine endemic province in Thailand: five-year programme. Bull World Health Organ 2003; 81:375–81.

Kansagra K, Parmar D, Mendiratta SK, Patel J, Joshi S, Sharma N, et al. A Phase 3, Randomised, Open-Label, Non-inferiority Trial Evaluating Anti-Rabies Monoclonal Antibody Cocktail (TwinrabTM) Against Human Rabies Immunoglobulin (HRIG). Clin Infect Dis. 2020 Jun 17:ciaa779.

Lin FT, Chen SB, Wang YZ, Sun CZ, Zeng FZ, Wang GF. Use of serum and vaccine in combination for prophylaxis following exposure to rabies. Rev Infect Dis 1988; 10(suppl 4):S766–70.

Müller T, Dietzschold B, Ertl H, Fooks AR, Freuling C, Fehlner-Gardiner C, et al. Development of a mouse monoclonal antibody cocktail for post-exposure rabies prophylaxis in humans. PLoS Negl Trop Dis. 2009 Nov 3;3(11):e542.

Quiambao B, Varghese L, Demarteau N, Sengson RF, Javier J, Mukherjee P, et al. Health economic assessment of a rabies pre-exposure prophylaxis program compared with post-exposure prophylaxis alone in high-risk age groups in the Philippines. Int J Infect Dis. 2020 Aug;97:38-46.

Schumacher CL, Dietzschold B, Ertl HC, Niu HS, Rupprecht CE, Koprowski H. Use of mouse anti-rabies monoclonal antibodies in postexposure treatment of rabies. J Clin Invest. 1989 Sep;84(3):971-5.

Selimov M, Boltucij L, Semenova E, Kobrinskij G, Zmusko L. The use of antirabies gamma globulin in subjects severely bitten by rabid wolves or other animals. J Hyg Epidemiol Microbiol Immunol 1959; 3:168–80.

Shim E, Hampson K, Cleaveland S, Galvani AP. Evaluating the cost-effectiveness of rabies post-exposure prophylaxis: a case study in Tanzania. Vaccine. 2009 Nov 27;27(51):7167-72.

Sparrow E, Torvaldsen S, Newall AT, Wood JG, Sheikh M, Kieny M-P, et al. Recent advances in the development of monoclonal antibodies for rabies post exposure prophylaxis: A review of the current status of the clinical development pipeline. Vaccine. 2019;37 Suppl 1:A132-A139.

Sreenivasan N, Li A, Shiferaw M, Tran CH, Wallace R, Blanton J, et al. Overview of rabies post-exposure prophylaxis access, procurement and distribution in selected countries in Asia and Africa, 2017-2018. Vaccine. 2019 Oct 3;37 Suppl 1:A6-A13.

Sudarshan MK, Mahendra BJ, Madhusudana SN, et al. An epidemiological study of animal bites in India: results of a WHO sponsored national multi-centric rabies survey. J Commun Dis 2006; 38:32–9.

Tarantola A, et al. Rabies Vaccine and Rabies Immunoglobulin in Cambodia: Use and Obstacles to Use. J Travel Med. 2015 Sep-Oct;22(5):348-52.

Wang Y, Rowley KJ, Booth BJ, Sloan SE, Ambrosino DM, Babcock GJ. G glycoprotein amino acid residues required for human monoclonal antibody RAB1 neutralization are conserved in rabies virus street isolates. Antiviral Res. 2011 Aug;91(2):187-94.

WHO. Rabies Working Group Report, SAGE meeting, October 2017. Available at http://www.who.int/immunization/sage/meetings/2017/october/1_Background_paper_WG_RABIES_final.pdf?ua=1.

World Health Organization. Rabies vaccines: WHO position paper, April 2018 - Recommendations. Vaccine. 2018a;36(37):5500-3.

World Health Organization, Expert Consultation on Rabies, Third report. Geneva: World Health Organization; 2018b (WHO Technical Report Series, No. 1012). License: CC BY-NC-SA 3.0 IGO. Available at: https://www.who.int/rabies/resources/who_trs_1012/en/

Wiktor TJ, Koprowski H. Monoclonal antibodies against rabies virus produced by somatic cell hybridization: detection of antigenic variants. Proc Natl Acad Sci U S A. 1978 Aug;75(8):3938-42.