Recommendations of the Expert Committee for the Selection and Inclusion of Medicines in the Pan American Health Organization's Strategic Fund 2015

Pan American Health Organization

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Contents

Acronyms

ACCIb-CCIb	Asociación Colaboración Cochrane Iberoamericana – Centro Cochrane Iberoamericano
AIDS	Acquired immune deficiency syndrome
AphA	American Pharmacist Association
ART	Antiretroviral therapy
ATZ/r	Atazanavir/ritonavir
CHAI	Clinton Health Action Initiative
CHA/HT	PAHO Communicable Diseases and Health Analysis - HIV, Hepatitits, Tuberculosis and Sexual Transmitted Infections Unit
CHA/VT	PAHO Communicable Diseases and Health Analysis - Neglected and Vector Borne Disease Unit
CI	Confidence interval
DALY	Disability-Adjusted Life Year
DR-TB	Drug-Resitant Tuberculosis
DRV/r	Darunavir/ritonavir
EC	Expert Committee
EML	Essential Medicine List
FDCs	Fixed-dose combinations
GDF	Global Drug Facility
rGLC	Regional Green Light Committee
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HSS/MT	Health Systems and Services/ Medicines and Health Technologies Unit
HIV	Human Immunodeficiency Virus
IATT	Interagency Task Team
LPV/r	Lopinavir/ritonavir
MDR-TB	Multi-drug resistant tuberculosis
NID	Neglected infectious diseases
NRTI	Nucleoside Reverse Trascriptase Inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitors
OBT	Optimized background therapy
OR	Odds ratio
PI	Protease inhibitor
PMTCT	Prevention of mother-to-child transmission
PPPY	Price per patient per year
QALY	Quality-adjusted life year
QT interval	Not an acronym. Measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle.
RCT	Randomized control trial
RNA	Ribonucleic acid
RR	Relative risk

STHs	Soil-transmitted helminthiases
UNITAID	Not an acronym. Organization cooperating with WHO and other organizations on the WHO Millennium Goals.
USD	United States dollar
USFDA	United States Food and Drug Administration
VL	Viral load
WHO	World Health Organization
WHO EML	World Health Organization Essential Medicine List
XDR-TB	Extensive drug-resistant tuberculosis

Executive Summary

The second meeting of the PAHO Expert Committee for the Selection and Inclusion of Medicines in the Pan American Health Organization Strategic Fund was held at Pan American Health Organization Headquarters in Washington, D.C. (USA) on 7–9 July 2015.

The goal of the meeting was to review and update the current Strategic Fund Medicine List, last updated in August 2013. Ten experts from the Region of the Americas were convened to issue recommendations to the Director of PAHO for the potential inclusion or exclusion of twenty medicines in the Strategic Fund Medicine List.

In accordance with approved procedures based on the concept of "Essential Medicines," the PAHO Expert Committee reviewed applications for twenty medicines for the treatment of HIV/AIDS, multi-drug resistant tuberculosis, malaria, and neglected infectious diseases. It considered scientific evidence regarding the clinical effectiveness, safety, and cost for these medicines compared to those alternative treatments already included in the Strategic Fund's Medicine List when available. Seven applications for treatment of HIV/AIDS and drug-resistant tuberculosis were previously reviewed by the 20th WHO Expert Committee for the Selection and Use of Essential Medicines, held in Geneva in April 2015, and thirteen applications were evaluated based only on evidence presented by PAHO and its collaborators.

The PAHO Expert Committee issued the following recommendations to the Director of PAHO for updating the Strategic Fund Medicine List:

- Inclusion of six medicines:
  - bedaquiline, darunavir, etravirine, ivermectin, linezolid, and raltegravir
- Inclusion of four new indications and two additional dose presentations:

  New Indications:
  - ofloxacin, niclosamide, pentamidine, and praziquantel

  New dose presentations:
  - nevirapine, and primaquine
- Deletion of five medicines:
  - fixed-dose combination of abacavir/lamivudine/zidovudine, didanosine, indinavir, nelfinavir, and stavudine
- Reject inclusion of three medicines:
  - clofazimine, clarithromycin, and imipenem/cilastatin

PAHO, acting as the secretariat of the PAHO Expert Committee, prepared the medicine dossiers at the request of Member States and/or PAHO technical units. The medicine dossiers and the expert reviews are available for public consultation.[1]

[1] Medicines dossiers and consolidated expert reviews are available at www.paho.org/strategicfund

The PAHO Expert Committee worked exclusively on evaluating the applications for potential deletion or inclusion of medicine in the Strategic Fund Medicine List, which enabled PAHO to adequately respond to the needs of PAHO Member States. Due to this specific function and objective, this committee does not seek to replace or complement the work performed by WHO in developing the Essential Medicine List or by Member State pharmacotherapeutic committees who decide to include or exclude medicines from national essential medicine lists. As a result, the recommendations issued by this committee should not be utilized as references for the development of other essential medicine lists or treatment guidelines.

List of Participants

Chair

Dr. Lisa Bero, Chair of the Expert Committee, Professor, Chair of Medicines Use and Health Outcomes, Faculty of Pharmacy, Charles Perkins Center, The University of Sydney, Australia

Co-chair[2]

Dr. Perla M. de Buschiazzo, Co-Chair of the Expert Committee, Director, Centro Universitario de Farmacología (CUFAR), Facultad de Ciencias Médicas, Universidad Nacional de La Plata (UNLP), Medical Doctor, Full Professor of Pharmacology (Retired) and Extraordinary Professor of School of Medicine, UNLP, La Plata, Argentina

Experts

Dr. Joaquin Barnoya, Director of Reasearch, Cardiovascular Unit of Guatemala (UNICAR), Guatemala City, Guatemala

Dr. Facundo García Bournissen, Associate Researcher, Argentine National Science and Technology Research Council (Consejo Nacional de Investigaciones Científicas y Técnicas – CONICET), Buenos Aires, Argentina

Dr. Carlos Alberto Cuello-García, Director, Center for Evidence-Based Practice and Knowledge Translation, Tecnológico de Monterrey School of Medicine and Health Sciences, Monterrey, Mexico

Mr. Damian Francis Keith, Assistant Lecturer in Nutrition and Epidemiology, Tropical Medicine Research Institute, University of West Indies, Mona, Kingston, Jamaica

Dr. Albín Chaves Matamoros, Director of Pharmacoepidemiology, Costa Rican Social Security Fund (Caja Costarricense de Seguro Social), San José, Costa Rica

Dr. Edgard J. Narváez Delgado, Analyst, Reproductive Health Commodity Security Programme, United Nations Population Fund, Managua, Nicaragua

Dr. Gabriela J. Prutsky, Lead Investigator and Founder, Unidad de Conocimiento y Evidencia (CONEVID), Universidad Peruana Cayetano Heredia, Lima, Peru

Dr. Lenita Wannmacher, Associate Professor (Retired), Department of Pharmacology, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, Brazil

PAHO Secretariat

This report and the medicine dossiers were prepared by Miss Alexandra Guta, International Consultant for PAHO Health Systems and Services/ Medicines and Health Technologies (HSS/MT) Unit in Washington, D.C. The project was supervised by Mr. Adrian Barojas, Specialist, Strategic Fund, and Dr. José Luis Castro, Advisor, Rational Use of Medicines for the HSS/MT Unit.

[2] Co-Chair Dr. Perla de Buschiazzo was unable to attend the final Expert Committee meeting due to unforseen circumstances ; however, her reviews and comments where included in the final recommendations Dr. Lisa Bero, chair of the Expert Committee, acted as the sole chair of the Committee.

Collaborators

The evidence presented in the product dossiers not reviewed at the 20th WHO Expert Committee was obtained in collaboration with the Asociación Colaboración Cochrane Iberoamericana – Centro Cochrane Iberoamericano (ACCIb-CCIb), Barcelona, Spain.

Others

Advisors and Specialists from PAHO Communicable Diseases and Health Analysis - HIV, Hepatitits, Tuberculosis and Sexual Transmitted Infections Unit (CHA/HT): Dr. Giovanni Ravasi (Advisor HIV/AIDS), Dr. Anna Volz (Advisor Tuberculosis) and Dr. Mirtha Del Granado (Advisor Tuberculosis).

Advisors and Specialists from PAHO Communicable Diseases and Health Analysis - Neglected and Vector Borne Disease Unit (CHA/VT): Dr. Ana Nilce Elkhoury (Advisor Neglected Infectious Diseases), Dr. Laura Catala Pascual (Specialist Neglected Infectious Diseases), Dr. Steven Ault (Advisor Neglected Infectious Diseases), Dr. Martha Saboya (Specialist Neglected Infectious Diseases), Dr. Ana Lucianez (Specialist Neglected Infectious Diseases), Dr. Ruben Santiago Nicholls (Advisor Neglected Infectious Diseases) and Dr. Maria Paz Ade (Specialist Malaria Prevention and Control).

The aforementioned advisors and specialists have provided input for the development of the clinical PICO questions and dossiers. Additional comments were also provided along the process.

Declaration of Interests of Members of the PAHO Expert Committee for the Selection and Inclusion of Medicines in the PAHO Strategic Fund

All Expert Committee members have submitted written disclosures of competing interests that could cause a conflict of interest for the review and final recommendations of medicines to be included in or deleted from the Strategic Fund Medicine List. During the final meeting, the PAHO Expert Committee Members reported no additional conflict of interests to those previously mentioned.

Members reported the following interests:

Dr. Lisa Bero reported being a member of the WHO Expert Committee for the Selection of Essential Medicines since 2005 and co-chair of the Cochrane Collaboration since 2013

Dr. Perla M. de Buschiazzo reported no conflict of interest

Dr. Joaquin Barnoya reported no conflict of interest

Dr. Facundo Garcia Bournissen reported no conflict of interest

Dr. Carlos Alberto Cuello-Garcia reported having received research financial support as a scholarship amounting to $US 3,000 and paid travel expenses at one occasion from McMaster University and World Allergy Organization within the past three years

Mr. Damian Francis Keith reported no conflict of interest

Dr. Albin Chaves Matamoros reported no conflict of interest

Dr. Edgard J. Narváez Delgado reported no conflict of interest

Dr. Gabriela J. Prutsky reported no conflict of interest

Dr. Lenita Wannmacher reported no conflict of interest

The PAHO Strategic Fund and the PAHO Expert Committee

The PAHO Regional Revolving Fund for Strategic Public Health Supplies (hereinafterreferred to as the PAHO Strategic Fund or the Strategic Fund), was created in 1999 by the then Director of PAHO at the request of Member States of the Organization.

This regional mechanism primarily aims at strengthening the supply and management of essential public health supplies in Member States by providing technical cooperation and procuring quality, safe, and effective supplies at affordable prices by leveraging the advantages of economies of scale. To this end, the Strategic Fund publishes a list of medicines available for procurement in behalf of the Organization's Member States. The list utilizes the World Health Organization (WHO) Essential Medicines List (EML) as a foundation.

Recently, the Strategic Fund has received requests from Member States regarding medicines that are not included in the WHO EML. In response, the Director of PAHO established an external committee charged with reviewing requests for inclusion of medicines not currently listed in the WHO EML and making recommendations to the Director of PAHO based on its objective and independent review and analysis.

This committee's main objective is to allow PAHO to implement a decision making process for the selection of medicines based on comparative efficacy, safety, and, when information is available, on the value added by the medicine in comparison to its cost. Recommendations will be based on reviews of evidence that support the efficacy and safety of the presented medicines, and will provide an analysis of the therapeutic and economic advantages with respect to the medicines already incorporated on the PAHO Strategic Fund Medicine List. The Director of PAHO will review the committee's recommendations and make a final decision for inclusion or not into the PAHO Strategic Fund Medicine List.

The committee works exclusively on requests to update the Strategic Fund Medicine List, in order to enable PAHO to adequately respond to the needs of PAHO Member States. Given this specific function and objective, the committee does not seek to replace or complement the work performed by WHO in developing the EML or by Member State pharmacotherapeutic committees who decide to include or exclude medicines from national essential medicine lists (formularies). As a result, the recommendations issued by this Expert Committee should not be utilized as references for the development of other essential medicine lists or treatment guidelines.

Applications for inclusions or deletions of medicines for the treatment of communicable diseases, such as HIV/AIDS (abacavir/lamivudine/zidovudine, didanosine, darunavir, etravirine, indinavir, nevirapine, nelfinavir, raltegravir, stavudine) and multi-drug resistant tuberculosis (bedaquiline, clarithromycin, clofazimine, imipenem/cilastatin, linezolid) were requested and supported by the PAHO Communicable Diseases and Health Analysis - HIV, Hepatitits, Tuberculosis and Sexual Transmitted Infections Unit (CHA/HT). The applications for inclusion of medicines for the treatment of malaria (primaquine) and neglected infectious diseases such as leishmaniasis (pentamidine) and strongyloidiasis (ivermectin), along with a request for an additional indication for medicines already present on the Strategic Fund Medicine List such as ofloxacin 400mg tablets (second line treatment of leprosy), niclosamide 500mg chewable tablets (anticestodes), and praziquantel 600mg tablets (anticestodes) were requested and supported by the PAHO Communicable Diseases and Health Analysis - Neglected and Vector Borne Disease Unit (CHA/VT).

Applications were submitted to the Strategic Fund, which is within the HSS/MT Unit and functions as the secretariat of the Expert Committee. Strategic Fund staff prepared the product dossiers with the corresponding evidence regarding efficacy, safety, and cost of the requested medicine, compared to alternative treatments already included in the Strategic Fund Medicine List. The product dossiers also provide information on the public health relevance of the medicine, its pharmacotherapeutic characteristics, the regulatory status of the product in the Region of the Americas, and other relevant information.

The indications specified in the clinical questions for each product dossier were developed with input from the PAHO technical units supporting the applications. Prior to conducting the evidence search, each proposed clinical question was reviewed by the chair and co-chair of the Committee and three Expert Committee members. The evidence search for the developed clinical questions was conducted in collaboration with the Asociación Colaboración Cochrane Iberoamericana–Centro Cochrane Iberoamericano (ACCIb-CCIb). The evidence summaries contained the corresponding Grading of Recommendations Assessment, Development and Evaluation (GRADE) and, when relevant, characteristics of the critically reviewed clinical trials.

Prior to the meeting all product dossiers were submitted to the PAHO Expert Committee members for review. The Committee consists of ten members, including the chair and co-chair. Each expert was assigned five-to-six dossiers, resulting in three expert reviews per application.

PAHO compiled the reviews received for each application and circulated the consolidated reviews to all Committee members prior to the meeting. PAHO then communicated any additional comments received from the consolidated reviews to the original three experts.

The experts convened in person to review each application, present any additional evidence, obtain consensus on the Committee's recommendations, and approve this report.

General Items

1. Meeting Proceedings

The Expert Committee meeting took place at the Pan American Health Organization Headquarters in Washington, D.C. (USA) on 7–9 July 2015. Nine Expert Committee members, the Unit Chief of the PAHO Medicines and Health Technologies Unit, the regional staff of the PAHO Strategic Fund (the Committee Secretariat), the PAHO Regional Advisor on Rational Use of Medicines, the PAHO Regional Advisor for Tuberculosis Prevention and Control, PAHO Regional Advisor, and Specialists for Neglected Infectious Diseases attended the meeting. Other PAHO staff was present as observers.

Dr. Analía Porrás, Unit Chief for the Medicine and Health Technologies Unit, opened the meeting on behalf of the Director of PAHO, Dr. Carissa Etienne, who supported the establishment of this Committee. The PAHO Expert Committee members were asked to declare any real or potential conflicts of interest and the PAHO Secretariat provided an update of the Strategic Fund and a summary of the purpose, the objectives, and the methodology for the convening of the second PAHO Expert Committee. The Committee chair then reviewed the applications taken up at the WHO 20th Expert Committee on the Selection and Use of Essential Medicines in April, 2015, and shared with the PAHO Expert Committee WHO's final recommendations. Subsequently, the PAHO Expert Committee reviewed and provided final recommendations for the remaining thirteen applications exclusively requested by PAHO. The recommendations have been provided to the Director of PAHO, who will make a final decision for inclusion, deletion, or other determination.

2. General Recommendations

In the afternoon of the second day of the meeting, the PAHO Expert Committee met to discuss policies, procedures, and general recommendations for the PAHO Secretariat to consider. This session led to the following recommendations:

1. Include more robust pricing and, if available, cost-effectiveness analysis for the Region's context in the medicine dossiers. In noting these recommendations, the PAHO Secretariat will aim to include more price data from Member States and explore the inclusion of formal cost-effectiveness studies with help from RedETSA, the Network of Health Technology Assesment in the Americas.
2. Prevent the overlap of reviews by the WHO Expert Committee on the Selection and Use of Essential Medicines and the Strategic Fund Expert Committee. To that end, PAHO will aim to organize a meeting of the Strategic Fund Committee in 2016. This would stagger the meetings of the PAHO and the WHO Committees, thus preventing an overlap of reviews. If discrepancies arise between the WHO EML and the Strategic Fund Medicine List, the PAHO Secretariat will review the WHO Expert Committee recommendations and determine whether these discrepancies are due to efficacy and/or safety issues, and will notify the PAHO Expert Committee.
3. Establish a procedure and criteria to remove medicines from the Strategic Fund Medicine List even if there has not been an application for deletion from the corresponding PAHO Technical Unit. This item was considered to ensure that the PAHO Secretariat can remove medicines that are no longer relevant to Member States and/or that have not been recently procured. The PAHO Secretariat will draft criteria for this process and will submit it to the PAHO Committee for consideration.

4. Explore the possibility of submitting requests for deletion to the WHO Expert Committee on the Selection and Use of Essential Medicines. The applications for these requests would be based on dossiers previously reviewed and deleted by the Strategic Fund Expert Committee. This process would aim to assist WHO in removing medicines no longer relevant from the EML.
5. Require applications to include, when supported by public health need, evidence supporting use in pediatric populations.
6. The PAHO Secretariat would ensure that PICO (Population-Intervention-Comparison-Outcome(s)) questions developed would restrict the search to human studies. If the evidence summaries developed by the corresponding Cochrane collaborating center yield only data from animal studies, the PAHO Secretariat will communicate these results to the Expert Committee, which will review the medicine upon availability of efficacy and safety data from humans.
7. PAHO technical units sponsoring applications should not be present during the deliberations of the final recommendation. The technical units requesting that a medicine be included or deleted will be provided an opportunity to present any additional information and answer questions. This approach will allow the Expert Committee to maintain consistency with general practices of other selection committees.
8. The PAHO Secretariat should ensure that a list of the clinical studies included in the systematic reviews that supportmedicine dossiers are is also included in the medicine dossier.

Applications

The PAHO Expert Committee reviewed and made recommendations on 20 applications related to four therapeutic categories (HIV/AIDS, drug-resistant tuberculosis, malaria, and neglected infectious diseases). Seven applications initially requested by PAHO's technical units were subsequently reviewed at the WHO 20th Expert Committee on the Selection and Use of Essential Medicines in April 2015 in Geneva—five antiretrovirals (darunavir, didanosine, indinavir, nevirapine and stavudine) and two drug-resistant tuberculosis medicines (bedaquiline and linezolid). The remaining 13 applications included medicines that were solely requested by PAHO for potential deletion or inclusion in the PAHO Strategic Fund Medicine List. The supporting evidence dealing with the efficacy, safety, and cost of the reviewed medicines, including the corresponding references, is included in medicine dossiers prepared for expert review and available on the PAHO Strategic Fund website.

To support the evaluation of the applications and deliver their recommendations, the Committee provided reviews of the dossiers and included additional evidence for efficacy, safety, and cost when applicable and relevant. The expert reviews are also available on the PAHO Strategic Fund website. This report contains an overview of the clinical evidence comprised in the dossiers and the reviews, which serve as the foundation of the Expert Committee's final recommendations.

1. WHO Applications Reviewed by the WHO 20th Expert Committee for the Selection and Use of Essential Medicines

The WHO Expert Committee for the Selection and Use of Essential Medicines meets every two years to review the latest scientific evidence regarding the efficacy, safety, and cost-effectiveness of medicines for adults and children requested for inclusion or deletion in the WHO Essential Medicine List (EML). In April 2015, five antiretrovirals (darunavir, didanosine, indinavir, nevirapine, and stavudine) and two medicines for drug-resistant tuberculosis (bedaquiline and linezolid) that had been initially requested by PAHO's Unit of Communicable Diseases and Health Analysis/HIV, Hepatitis, Tuberculosis, and Sexually Transmitted Infections (CHA/HT) for deletion or inclusion in the Strategic Fund Medicine List were subsequently reviewed at WHO's 20th Expert Committee in April 2015 in Geneva.

The deletion or inclusion of medicines in the Strategic Fund Medicine List is based primarily on decisions taken by the WHO Expert Committee for the Selection and Use of Essential Medicines and the subsequent inclusion or deletion of medicines in the WHO List of Essential Medicines. Nonetheless, in this case, the request for deletion or inclusion of these seven medicines was submitted before the publication of the applications to be reviewed by the WHO 20th Expert Committee. Consequently, the PAHO Secretariat recommended that dossiers for those medicines be developed, based on the evidence and references provided by WHO and including supplementary information specific to the context of the Region of the Americas. The following section outlines the summary of evidence presented at the WHO 20th Expert Committee and the respective deletions or inclusions in the PAHO Strategic Fund Medicines List. The remaining thirteen applications not reviewed by the WHO 20th EC are listed in section 2 of this report.

1.1 HIV/AIDS Medicines

Over the last decade, the Region of the Americas has made important progress in reducing the mortality and morbidity associated with HIV/AIDS, becoming a leader worldwide in providing access to treatment, particularly among low- and middle-income countries. A 2014 public health analysis in Latin America and the Caribbean showed that 795,000 persons had received antiretroviral therapy (ART) in the Americas, representing 44% of all persons living with HIV and 56% of eligible patients based on currently implemented guidelines for eligibility criteria (*1*). In 2013, approximately 71% of patients on ART were treated with first-line antiretrovirals, 24% were using second-line therapies, and 5% received third-line regimens. Despite the Americas' lower burden and higher coverage rates compared to other regions, the gap between patients in need of treatment and those receiving treatment is widening in the Region. It is estimated that the number of patients in need of ART in the Region will reach 1.4 million persons, according to new treatment criteria (*2*). Consequently, the report on the status of the millennium development goals presented to the 53rd Meeting of the PAHO Directing Council in 2014 reiterated the need to increase efforts to further expand ART coverage in the Region (*3*).

In order to help Member States promote access to the most effective and safe HIV/AIDS medicines in accordance with the latest WHO HIV/AIDS treatment guidelines, the CHA/HT Unit submitted and supported the applications for the deletion of five antiretrovirals (abacavir/lamivudine/zidovudine, didanosine, indinavir, nelfinavir, stavudine) for efficacy and/or safety reasons, and for the inclusion of four antiretrovirals (darunavir, etravirine, nevirapine, raltegravir) in the Strategic Fund Medicine List.

Below is a summary of the evidence and corresponding recommendations for the HIV/AIDS medicines reviewed by the WHO 20th Expert Committee in April: darunavir, didanosine, indinavir, nevirapine, and stavudine.

1.1.1 HIV/AIDS Medicines requested for inclusion in the WHO 19th Model List of Essential Medicines (WHO EML)

1.1.1.1 Darunavir

The dossier presented to the PAHO Expert Committee for its review incorporates the available evidence in regards to efficacy, safety, and cost of darunavir, compared to other protease inhibitors (PIs) such as atazanavir and lopinavir (used in combination with ritonavir) presented in the WHO application. The evidence was presented as Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system tables that summarized the relevant studies. A summary of the evidence included in the GRADE tables is presented below. For more information please refer to the darunavir dossier available on the Strategic Fund website.

- Efficacy evidence for darunavir:

  Comparative evidence of darunavir/ritonavir versus lopinavir/ritonavir derived from two main randomized controlled trials (RCTs) POWER (2007, 2009) and TITAN (2007, 2012) is summarized in the GRADE tables and included in the darunavir dossier. Low quality evidence showed that at 48 weeks the mortality rate was 1.6% for darunavir/ritonavir (DRV/r) and 0.95% for lopinavir/ritonavir (LPV/r) or a boosted protease inhibitor (RR1.7 (0.5 to 5.81). A difference was also noted in the virologic response defined as <50 copies/ml at 96 weeks, where darunavir/ritonavir showed a rate of 53.8%, whereas lopinavir/ritonavir had a rate of 41.6% (RR 1.31 (1.14 to 1.5)). The quality of the evidence was moderate for the later outcome (*4, 5*).

A second GRADE table ATZ/r or DRV/r in first-line regimens that compares ATZ/r or DRV/r to LPV/r showed mortality rates at 192 weeks of 1.2% for DRV/r and 2% for LPV/r (RR 0.58 (0.17 to 1.95)). The quality of the evidence was considered very low. Additionally, the virologic response defined as <50 copies/ml at 192 weeks was 68.8% for DRV/r and 57.2% for LPV/r (RR 1.2 (1.07 to 1.35)). The quality of evidence was moderate. After 192 weeks, the increase in CD4 cells/mm3 for DRV/r was 343 and 346 for LPV/r, with no RR reported and moderate quality of evidence (*4*, *5*).

Supplementary data regarding the use of darunavir in treatment-naïve and treatment-experienced adolescent patients (DIONE study), treatment-naïve adults (ARTEMIS study), and treatment-experienced adults (ODIN study) also were provided by the Committee. The DIONE study reported no significant differences in virologic responses and phamacokinetic/pharmacodynamic results between adolescent and adult populations (ARTEMIS study) (*6–10*).

The overall available evidence showed superiority of darunavir over lopinavir for virologic responses but no such conclusions were reached for the mortality outcome because of the low to very low quality of evidence.

- Safety evidence for darunavir:

  The safety outcomes reported in the GRADE tables showed a 48-week difference in severe adverse events between DRV/r (12.6%) and LPV/r or a boosted protease inhibitor (11.4%) (RR 1.1 (0.76 to 1.58)). The on-treatment retention reported at 96 weeks was 79% for DRV/r and 55.8% for LPV/r (RR 1.42 (1.29 to 1.57)) (*4*, *5*).

  The second GRADE table results show the rate of patients experiencing one or more adverse events of grade 3 or 4 for DRV/r was 30% and 31.8% for LPV/r. The quality of evidence was low. The table also shows a higher rate of adherence defined as >95% adherence for DRV/r compared to 83.3% for LPV/r, with a rate of 78.3% after 192 weeks of treatment. The quality of this evidence was moderate (*4, 5*).

  The safety profile of darunavir appears to be of comparable frequency and severity to other therapeutic options such as LPV/r or ATZ/r, notwithstanding the low level of the quality of evidence. Additionally, no significant differences in discontinuation of medicines and adherence outcomes were reported.

- Cost:

  No specific studies of cost-effectiveness have been reported in the WHO application for darunavir and no information was available for the Region of the Americas. Limited cost-related information with a focus on Sub-Saharan Africa was provided in the application. Janssen has signed a royalty fee and a partnership agreement with the generic company Aspen Pharmacare to provide access to co-branded darunavir in Sub-Saharan Africa. In November 2012, Janssen stated their intention not to enforce their patent and limit darunavir access provided their product is used in resource-limited settings (*4, 5*).

  An additional cost-utility analysis shared by the Committee reported higher costs (i.e, lifetime National Health Service costs) for darunavir when compared to atazanavir or lopinavir. The cost differences were small, no significant differences regarding efficacy and tolerance outcomes were reported, and the differences in quality-adjusted life years (QALYs) were not statistically significant. Nonetheless, clinical experts consulted in the study suggested darunavir may be more tolerable and the difference can support the case for cost-effectiveness (*11*).

- Additional comments discussed at meeting:

  While the original application was for the 600mg and 800mg dose, the Committee recommended the inclusion of doses suitable for the pediatric population (75mg and 400mg), as were included in the WHO 19th EML.

- Recommendation:

  Following the review of the WHO-presented evidence and the inclusion of darunavir on the WHO 19th EML, the PAHO Expert Committee decided to include darunavir 75mg, 400mg, 600mg, and 800mg tablets, while taking into account the age restrictions in the Strategic Fund Medicine List for the treatment of HIV/AIDS.

1.1.1.2 Nevirapine

The dossier presented to the PAHO Expert Committee for review incorporates the available evidence in regards to efficacy, safety, cost, and advantages of nevirapine 50mg dispersible tablets presented in the WHO application for inclusion of nevirapine in the WHO EML. A summary of this evidence is outlined below. For more information please refer to the nevirapine dossier available on the Strategic Fund website.

- Efficacy of nevirapine in HIV-positive pediatric patients:

  Considering that nevirapine has been included in the WHO EML since 2002, its efficacy and safety have already been reviewed. For this review, WHO emphasized studies assessing nevirapine as a first-line treatment in pediatric patients, considering that the 50mg dispersible is mainly used in infants and young children. The WHO application includes two main reviews.

  A first review concludes that nevirapine has demonstrated a favorable pharmacokinetic profile allowing twice daily dosing, a child-appropriate formulation, and no major adverse reactions, all of which make nevirapine a promising alternative in the pediatric population, especially in children with lower baseline viral loads (*12*).

  The second review compares two randomized control trials that assessed the role of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the treatment of HIV-infected children (*13*).

  The first trial (PENPACT1) concludes that there are no significant differences at 4 years between virologic, immunologic, and clinical outcomes between NNRTIs and protease inhibitors (PIs) when used as a first- or second-line antiretrovirals. On the other hand, the second trial (IMPAACT P1060) concludes that infants younger than 36 months are more at risk of treatment failure with nevirapine compared to lopinavir/ritonavir based regimens. Consequently, the WHO recommended PI-based regimens for infants and young children as initial HIV treatment (*14*).

  Nevertheless, in resource-limited settings, where lopinavir/ritonavir pediatric formulation is expensive, unavailable, or requires cold chain storage, nevirapine remains an available, affordable, and feasible alternative to lopinavir/ritonavir or NNRTIs in children older than 3 years of age *(15)*.

  Furthermore, additional references provided by the PAHO Expert Committee show that among HIV-infected children previously exposed to nevirapine, switching to nevirapine-based therapy after achieving viral suppression with a ritonavir-boosted lopinavir regimen resulted in lower rates of viremia greater than 50 copies/mL than did maintaining the primary ritonavir-boosted lopinavir regimen (*16*).

  Overall, the majority of studies show that nevirapine had a similar effectiveness to lopinavir/ritonavir and could be used as an alternative to protease inhibitors in the pediatric population.

- Safety of nevirapine in HIV-positive pediatric patients:

  In regards to the safety profile of nevirapine, the WHO application concluded that nevirapine has been widely studied in clinical trials as a first-line antiretroviral, a maternal prophylaxis for the prevention of mother-to-child transmission (PMTCT), and as infant prophylaxis for PMTCT. Nevirapine is the only NNRTI used in more than half of the first-line pediatric regimens in children under 3 years old in resource-limited settings.

  Nonetheless, concerns related to viral resistance to nevirapine in infants previously treated with NNRTIs through PMTCT or maternal treatments with nevirapine have been raised. An observational study and a recent randomized controlled trial report that nevirapine-based, first-line treatments could be compromised in infants who acquire HIV despite the use of prophylactic nevirapine intrapartum and peripartum. When patients have been exposed to nevirapine or another NNRTI used for PMTCT or maternal treatment, it is recommended that treatment be started with a PI containing regimen. Nonetheless, the safety profile showed nevirapine is still recommended when PIs are not available or affordable in resource-limited settings (*17*).

- Cost:

  No cost studies were available in the WHO application. Nonetheless, cost results were reported and the application included prices from various sources, such as UNITAID-CHAI pediatric project, International Reference Prices, WHO Global Price Reporting Mechanism, and Médecins Sans Frontières (Doctors without Borders). Price sources indicate an average price per patient per year (PPPY) of US$ 61 for nevirapine 50mg dispersible tablets formulation, representing approximately 50% of the PPPY for nevirapine 10mg/ml syrup formulation of US$ 109.40. In addition to a reduction in waste associated with the use of dispersible tablets compared to the syrup formulation, this formulation offers a significant cost advantage for patients.

- Additional comments discussed at meeting:

  The PAHO Expert Committee reiterated the need to confirm the bioequivalence of this formulation compared to the formulations currently available in the Strategic Fund Medicine List to ensure that efficacy is maintained in the pediatric population. The Secretariat confirmed that there are products readily available that already have undergone an evaluation by the WHO Prequalification Program and by the United States Food and Drug Administration (USFDA), which ensure that nevirapine 50mg dispersible tablets are of adequate efficacy, safety and quality.

- Recommendation:

  Following a review of WHO's presented evidence and the inclusion of nevirapine in the WHO 19th Model EML, the PAHO Expert Committee decided to include nevirapine 50mg dispersible tablets in the Strategic Fund Medicine List for treatment of HIV/AIDS in pediatric populations.

1.1.2 HIV/AIDS Medicines requested for deletion from the WHO 19th Model List of Essential Medicines (WHO EML)

1.1.2.1 Didanosine

The dossier presented to the PAHO Expert Committee for review includes the rationale for deletion of didanosine presented in the WHO application. A summary of the evidence included is presented below. For more information please refer to the didanosine dossier available on the Strategic Fund website.

- Rationale for deletion from the WHO EML

  The rationale supporting the request for deletion of didanosine from the WHO EML for adults and children was classified in two categories (*18*):

  i. deletion based on antiretroviral dosage

  ii. deletion of products from the EML for children due to the exclusion of the adult formulation in order to promote full alignment of both documents.

  The latest WHO 2013 HIV treatment guidelines restrict the use of didanosine in the adult population to special situations (as an alternative to second-line regimens) based on its toxicity profile, unfavorable formulation, and/or administration characteristics. Similarly, didanosine is no longer recommended in the pediatric population.

  In addition, the use of didanosine has significantly declined following a fragmentation of volumes that led to significant supply delays of these antiretrovirals.

  Finally, the need for additional antacid buffers, the increased gastrointestinal side effects such as diarrhea, and the mitochondrial toxicities associated with the use of didanosine were also listed as reasons to exclude didanosine from the WHO EML.

- Additional comments discussed at meeting:

  N/A

- Recommendation:

  Following the review of the WHO presented evidence and the deletion of didanosine from the WHO 19th EML, the PAHO Expert Committee decided to delete the following didanosine presentations from the Strategic Fund Medicine List:

  - 100mg, 167mg, 250mg packets of buffered powder for oral solution;
  - 250mg, 400mg un-buffered enteric coated capsules;
  - 25mg, 50mg, 150mg, 200mg buffered chewable dispersible tablets.

1.1.2.2 Indinavir

The dossier presented to the PAHO Expert Committee for review includes the rationale for the deletion of indinavir presented in the WHO application. A summary of the evidence included is presented below. For more information please refer to the indinavir dossier available on the Strategic Fund website.

- Rationale for deletion from the WHO EML

  The rationale supporting the request for deletion of indinavir from the WHO EML is based on the availability of newer fixed-dose combinations. Additionally, indinavir is no longer considered a preferred protease inhibitor due to a lack of its availability as a fixed-dose combination; the increasing resistance due to its low genetic barrier to resistance, particularly when boosted and replaced by newer antiretrovirals; and its toxicity profile (*18*). Consequently, the WHO 2013 HIV treatment guidelines no longer recommend the use of indinavir due to increased resistance. Furthermore, the PAHO Expert Committee provided additional references showing a higher frequency of severe adverse reactions and toxicities (i.e, nephrotoxicity) with indinavir than with other protease inhibitors (*19*).

- Additional comments discussed at meeting:

  N/A

- Recommendation:

  Following the review of the WHO presented evidence and the deletion of indinavir from the WHO 19th EML, the PAHO Expert Committee decided to delete indinavir 400mg tablets from the Strategic Fund Medicine List.

1.1.2.3 Stavudine

The dossier presented to the PAHO Expert Committee for review includes the rationale for deletion of stavudine single presentations and stavudine-based fixed-dose combinations from the WHO List of Essential Medicines (adults and children) presented in the WHO application. A summary of the evidence included is presented below.

Additionally, supplementary evidence was provided from a search conducted by the Asociación Colaboración Cochrane Iberoamericana–Centro Cochrane Iberoamericano (ACCIb-CCIb), focusing particularly on the efficacy and safety of higher versus lower doses of stavudine. The evidence search considered that stavudine remains one of the nucleoside reverse transcriptase inhibitors still used as first-line antiretroviral therapy in resource-limited settings. A summary of the evidence included is presented below. For more information please refer to the stavudine dossier available on the Strategic Fund website.

- Rationale for deletion from the WHO EML

  With the intention of aligning the WHO EML with the formulary developed by the WHO Interagency Task Team (IATT) on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Their Children, WHO requested that single formulations of stavudine be deleted from the adult and the children WHO EML (*18*). This would favor the use of stavudine-based fixed-dose combinations (FDCs) and maintain consistency with the IATT guidelines.

  Moreover, a request was put forward to delete the stavudine/lamivudine/nevirapine 12mg/60mg/100mg tablets FDC from the Essential Medicine List for children (EMLc), since it was not included in the WHO 2013 pediatric dosing schedule, and the 30mg/150mg/200mg FDC was requested to be deleted because it was only recommended in patients with body weight >25kg.

  WHO has recommended that countries phase out stavudine as a preferred initial antiretroviral option in adults and does not recommend its use in children, except in rare situations.

  Nonetheless, the application stated that despite the recommendation to discontinue its use for well-recognized metabolic toxicities, stavudine remains one of the main NRTIs used in first-line regimens in various resource-limited settings due to its availability as generic, low-cost, and easy-to-use, fixed-dose combinations. Therefore, the PAHO Expert Committee evaluated additional information specifically applicable to the Americas in the dossier.

  After reviewing the evidence presented, expert members reported additional information and references that showed that stavudine toxicity causes increased regimen substitution, treatment interruption, and suboptimal adherence, and that it requires expert clinical supervision (*20*).

  Moreover, drug-related toxicity represented a leading cause of treatment interruption, accounting for more than one-third of all treatment interruptions (*21*).

Citing Brazil as an example in the Region, the Committee reported that the country has already phased-out the use of stavudine in HIV patients, with the exception of the pediatric formulation, mainly because of a lack of pediatric formulations (*22*).

A Cochrane review also reported that the use of thymidine analogs, such as stavudine and zidovudine, yield considerable toxicity without significant differences between both in terms of severe adverse events and adherence, tolerance, or treatment retention *(23*) and should be switched to newer NRTIs such as tenofovir or abacavir (*24*).

- Cost:

  No cost studies were available.

- Additional comments discussed at meeting:

  - The final recommendation of the WHO 20th Expert Committee stated that stavudine will be automatically deleted in two years without additional review on the next iteration of the WHO EML. The WHO Expert Committee concluded that although the evidence supports deletion, it will be postponed because of current stocks in the countries.
  - The PAHO Secretariat clarified that Member States have not procured any stavudine formulation through the Strategic Fund since 2012, and there are no barriers for Member States to access alternative NRTI antiretrovirals.

- Recommendation:

  Following the review of WHO's presented evidence and the absence of barriers to procuring alternatives NRTIs in the Region of the Americas, the PAHO Expert Committee decided to delete the following stavudine presentations from the Strategic Fund Medicine List:

  - Stavudine 15mg; 20mg and 30 mg tablets
  - Stavudine 1mg/ml powder for oral solution
  - Stavudine+lamivudine+nevirapine6mg/30mg/50mg,12mg/60mg/100mgand30mg/150mg/200mg tablets
  - Stavudine + lamivudine 30mg/150mg tablets

1.2 Drug-Resistant Tuberculosis

Drug-resistant tuberculosis (DR-TB) is a growing public health concern that prevents adequate scale-up in tuberculosis diagnosis and control worldwide (*25*). In the Americas, multi-drug resistant tuberculosis (MDR-TB) continues to pose an important public health challenge, despite the lower incidence compared to other high burden countries elsewhere in the world (*26*). The rising number of multi-drug resistant tuberculosis (MDR-TB) in the Region represents 6% of total TB cases, and in high-burden countries such as Peru or Brazil, this figure can be as high as 19% and 35%, respectively. Moreover, many countries continue to have low diagnosis rates, low cure rates, and high mortality rates, as well as multiple MDR-TB cases evolving to extensive drug-resistant tuberculosis, which have important effects in the resistance to current treatments (*26*).

As a way to address the rising challenge around multi-drug and extensive-drug-resistant tuberculosis, PAHO launched the Regional Strategic Plan for TB Control, an initiative that engages and supports

countries to scale-up diagnosis, drug-susceptibility testing, and patient treatment. To this end, PAHO aims at increasing access to effective and safe quality drugs to contain the emerging trend of DR-TB, which represents an priority for tuberculosis control.

Following the re-purposed use of Group 5 tuberculosis medicines by WHO in the latest published tuberculosis guidelines, the Region's countries have expressed an interest in obtaining these medicines through the Strategic Fund. To respond to the needs of Member States, the PAHO CHA/HT Unit has submitted and supported the application for inclusion of five new antituberculosis medicines in the PAHO Strategic Fund Medicine List: bedaquiline, clarithromycin, clofazimine, imipenem/cilastatin, and linezolid.

A summary of the PAHO Expert Committee's review and recommendations for the medicines reviewed by the WHO 20th Expert Committee—bedaquiline and linezolid—is presented below. The recommendations for the medicines reviewed solely by PAHO Expert Committee (clarithromycin, clofazimine, imipenem/cilastatin) are included in section 2 of this report.

1.2.1 Multi-Drug Resistant Tuberculosis Medicines Requested for Inclusion in the WHO 19th Model List of Essential Medicines

1.2.1.1 Bedaquiline

The dossier presented to the PAHO Expert Committee includes evidence regarding the efficacy and safety of bedaquiline from the WHO applications for inclusion of the medicine on the WHO EML. The evidence was presented as GRADE system tables that summarize the use of bedaquiline in the treatment of MDR-TB. A summary of the evidence is presented below. For more details, please refer to the bedaquiline dossier and the corresponding GRADE tables available on the Strategic Fund website.

- Efficacy of bedaquiline for MDR-TB

The efficacy and safety information available was mainly derived from two randomized clinical trials, both sponsored by Janssen Pharmaceuticals (innovator) (*27*, *28*). Results from the two trials report that adding bedaquiline to a preferred background regimen for 24 weeks resulted in faster culture conversion and significantly more culture conversions at 120 weeks, when compared to placebo. There were more deaths in the bedaquiline group than in the placebo group.

A first randomized control trial (C-208) showed that sputum culture conversion after 24 weeks of treatment was 52/66 (78.8%) in the bedaquiline group and 38/66 (57.6%) in the placebo group. In subgroups of patients with pre-extensive drug resistant tuberculosis (pre-XDR-TB) and XDR-TB, the conversion rates were lower than in MDR-TB patients, but bedaquiline still demonstrated higher conversion rates compared to placebo. A second randomized control trial (C-209) showed similar results.

The PAHO Expert Committee furthered commented that available efficacy data was based on a small group of patient results, and the primary endpoint of measure of sputum conversion rates was not as clinically relevant as survival or clinical improvement. Furthermore, the evidence was considered of low quality because of the risk of bias/limitations, indirectness, and imprecise clinical trials. The Committee finally reiterated the need to conduct additional robust studies with bedaquiline.

- Safety of bedaquiline for MDR-TB

In regards to the safety profile of bedaquiline, the randomized control trial (C-208) results included in the WHO application showed a higher mortality with bedaquiline treatment. There were ten deaths in the bedaquiline group and two in the placebo group. This difference in mortality (10.2%) was statistically

significant. Five deaths in the bedaquiline group and two in the placebo group were related to tuberculosis progression (*27*, *28*).

Furthermore, bedaquiline produced a higher rate of adverse effects, mainly QT interval prolongation and hepatic and pancreatic disorders, among others.

The PAHO Expert Committee reported that the quality of evidence was very low, and any estimate of the effect was very uncertain. No clinical data on treatment with bedaquiline was available for periods longer than 24 weeks in the available evidence and no clinical data was available in regards to treatment of extra-pulmonary tuberculosis (bone, central nervous system). The overall effect was considered very uncertain.

- Cost:

  A tiered pricing strategy has been proposed by the innovator, Janssen Pharmaceuticals, for access to bedaquiline. The range of costs for a 24 week treatment varies from US$ 900 for low-income countries, to US$ 3,000 for middle-income countries, and up to US$ 30,000 for high-income countries. Additionally, based on the assumption of the translation of trial results to current practice, studies in low- and middle-income settings showed that bedaquiline is very likely to be cost-effective in most environments while displaying a favorable cost-saving ratio *(27, 28)*.

- Additional comments discussed at meeting:

  - The PAHO Expert Committee recognized the limited evidence available; however, as there are very few viable treatment options for MDR/XDR-TB patients, the Committee concluded that bedaquiline's efficacy and safety profile supported the inclusion.
  - The Committee reiterated the need to monitor and review further evidence from upcoming clinical trials in supporting of this inclusion. The review should take place during the next WHO Expert Review for the Selection and Use of Essential Medicines (2017) or during the third meeting of the PAHO Expert Committee (date to be determined).
  - The Committee also suggested that patients receiving MDR-TB regimens, including bedaquiline, should be monitored for potential adverse events or related toxicities through national pharmacovigilance programs and data from the WHO Programme for International Drug Monitoring (Uppsala, Sweden).

- Recommendation:

  Following the review of the WHO presented evidence and the inclusion of bedaquiline on the WHO 19th EML, the PAHO Expert Committee decided to include bedaquiline 100mg tablets in the Strategic Fund Medicine List for treatment of MDR-TB.

1.2.1.2 Linezolid

The dossier presented to the PAHO Expert Committee includes evidence regarding the efficacy and safety of linezolid available in the WHO application for inclusion on the WHO EML. The evidence was presented as GRADE system tables. A summary of this evidence is presented below. For more details, please refer to the linzolid dossier and the corresponding GRADE tables available on the Strategic Fund website.

- Efficacy of linezolid for MDR-TB

  Data regarding the efficacy and safety of linezolid in MDR-TB patients were very limited, in that its use remains restricted to patients with extensive drug-resistance and intolerance to other treatments. In terms of efficacy, a total of 23 studies were analyzed for the review of linezolid treatment for MDR-TB.

Of these, two were randomized control trials and only one assessed efficacy. In eight studies describing treatment outcomes in series where patients received linezolid, 67% (116/172) patients achieved cure. In five studies reporting comparative results, treatment success was achieved in 48% (42/88) of patients receiving linezolid, compared to 39% (159/404) who did not receive it. The quality of the evidence was very low and all studies were observational (*29*).

A systematic review provided adequate evidence that linezolid is effective for the treatment of MDR-TB. The review reported a treatment success rate with linezolid higher than 80% (<600mg or > 600mg), compared to treatment with no linezolid, with no difference in efficacy in the subgroup analysis that explored dose response at <600mg or > 600mg linezolid regimen (*30*).

Another systematic review that included one randomized controlled trial and four multi-centric studies showed that 83% (95% CI 75-90; I2: 62.8%) of patients treated with linezolid had a favorable outcome, defined as cure or treatment completion. The pooled rate of culture conversion was 89% (95%CI 83-95%; I2: 49.6%) (*31*).

Overall, the efficacy evidence presented was of very low quality and the studied outcomes were weak, with a main focus on culture conversion and treatment completion as a result for treatment success. Furthermore, the included studies were observational, many of which did not include a comparative group; this, in turn, highlighted the need to conduct additional randomized control trials to define stronger efficacy outcomes.

- Safety of linezolid for MDR-TB

In regards to the safety profile of linezolid, data included five observational studies assessing death as a safety outcome, resulting in no rate difference between patients receiving linezolid (11%; 10/88) and patients receiving no linezolid (11%; 46/404). In studies comparing toxicity, discontinuation of treatment resulting from toxicity was higher in the linezolid group (22%) compared to the no linezolid group (13%); however, the quality of the evidence was considered very low, mainly because of methodological weaknesses (*29*).

Another systematic review showed that mortality was considerably lower with doses of linezolid below 600mg per day. Additionally, out of 367 patients for whom data on safety was available, peripheral neuropathy (31%, 95% CI, 19-42%; I2=81.7%) and anemia (25%, 95% CI, 15-34%; I2=76.6%) were the main adverse effects. Conversely, patients receiving less than 600 mg/day were more likely to experience nervous system adverse events (p <0.01) *(32).*

In addition, the PAHO Expert Committee reported on a systematic review mentioned in the WHO application that demonstrated significant adverse events of linezolid with one-half of patients experiencing an adverse event and more than two-thirds experiencing serious adverse events that required the cessation or interruption of treatment. The main adverse events were reported as anemia and peripheral neuropathy (*30*).

Overall, the evidence showed that linezolid presented important safety issues due to the presence of serious adverse events and toxicities that led to the discontinuation of the medicine. However, the quality of the evidence was very low, with data retrieved from non-randomized trials. Weak methodology was employed to ascertain and define safety outcomes. Additionally, well-designed studies and subsequent systematic reviews including non-heterogenous data are needed to reach stronger conclusions about the safety profile of linezolid.

- Cost:

  No cost-effectiveness studies were available. Nonetheless, the PAHO Expert Committee noted the important disparity in prices for linezolid tablets across the Region, with cost ranging from US$ 25 to US$ 74 for a 600 mg tablet of linezolid.

- Additional comments discussed at meeting:

  - The PAHO Expert Committee recognized the limited evidence available; however, as there are very few viable treatment options for MDR/XDR-TB patients, the Committee concluded the efficacy and safety profile supported linezolid's inclusion.
  - The Committee reiterated the need to monitor and review further evidence from upcoming clinical trials supporting this inclusion. This upcoming review should take place during the next WHO Expert Review for the Selection and Use of Essential Medicines (2017) or the third meeting of the PAHO Expert Committee (date to be determined).
  - The Committee also suggested that patients receiving MDR-TB regimens including linezolid should be monitored for potential adverse events or related toxicities through national pharmacovigilance programs and data from the WHO Programme for International Drug Monitoring (UPPSALA).
  - Regarding concerns about the irrational use of this medicine and increasing antimicrobial resistance, the Committee stated that linezolid procurement through the Strategic Fund should be used as part of a WHO recommended M/XDR-TB regimen in patients for whom there are few or no other treatment alternatives. The PAHO Secretariat clarified that all MDR-TB medicine procurement requires Member States to complete the Global Drug Facility (GDF) procurement request form. Prior to procurement this form is reviewed by the Regional Green Light Committee (rGLC).

- Recommendation:

  Following the review of WHO's presented evidence and the inclusion of linezolid on the WHO 19th EML, the PAHO Expert Committee decided to include linezolid 600mg tablets in the Strategic Fund Medicine List for treatment of MDR-TB.

2. PAHO Applications Reviewed

2.1 HIV/AIDS Medicines

The section that follows summarizes the evidence presented and the corresponding recommendations for HIV applications requested solely by PAHO and reviewed by the PAHO Expert Committee (abacavir/lamivudine/zidovudine, etravirine, nelfinavir, raltegravir). For more public health information, please refer to section 1.1 HIV/AIDS Medicines of this document.

2.1.1 Inclusion

2.1.1.1 Etravirine

The dossier presented to the PAHO Expert Committee for review incorporates the available evidence in regards to the efficacy, safety, and cost of etravirine added to an optimized background combination therapy, compared to an optimized background combination therapy without etravirine in treatment-experienced, HIV-positive adult patients who failed second-line ARV therapy. A summary of the evidence is presented below.

Dr. Facundo Garcia Bournissen, Dr. Carlos Cuello García, and Dr. Lenita Wannmacher were the three experts who reviewed this application.

- Efficacy evidence for adding etravirine to an optimized background therapy:

  The evidence summary presented in the reviewed dossier is of high quality and was based on one Phase II study and two main Phase III studies (randomized, double-blinded, placebo-controlled trials) for the requested indication. The two main Phase III studies (DUET 1 and DUET 2) compared etravirine 200mg and a placebo in addition to a background therapy including darunavir/ritonavir and an investigator-selected optimized background therapy (OBT). Both Phase III studies were sponsored by Tibotec Pharmaceuticals, Ireland.

  The primary efficacy outcome measured was treatment response. The evidence showed that when etravirine was added to an OBT it resulted in higher treatment response at 24, 48, and 96 weeks, compared to an OBT alone. The quality of the reported evidence was high. The reviewed results are presented below (*33*, *34*).

  At 24 weeks in both studies, etravirine added to an OBT was associated with a higher rate of treatment response, compared to OBT alone (non pooled results):

  - DUET-1 treatment response as HIV-1 RNA level ≥50: etravirine 56% (170/304); placebo 39% (119/308) ($p<0.05$). Treatment response as HIV-1 RNA level ≥400: etravirine 74% (224/304); placebo 51% (158/308) ($p<0.05$).
  - DUET-2 treatment response as HIV-1 RNA level ≥50: etravirine 62% (183/295); placebo 44% (129/296) ($p<0.05$). Treatment response as HIV-1 RNA level ≥400: etravirine 75% (221/295); placebo 54% (159/296) ($p<0.05$).

  Furthermore, the superiority of etravirine compared to placebo in DUET 1 and 2 studies was consistent at 48 weeks according to the following reported results (pooled from DUET 1 and 2):

  - Treatment response as HIV-1 RNA level ≥50: etravirine 61% (363/599); placebo 40% (240/604) ($p<0.0001$). Treatment response as HIV-1 RNA level ≥400: etravirine 72% (428/599); placebo 47% (286/604) ($p<0.05$).

  Finally, at 96 weeks of treatment, both studies reported that etravirine was still associated with a higher rate of treatment response compared to placebo (pooled results from DUET 1 and 2) *(35)*:

  - Treatment response as HIV-1 RNA level ≥50: etravirine 57% (344/599); placebo 36% (219/604) ($p<0.0001$). Treatment response as HIV-1 RNA level ≥400: etravirine 68% (407/599); placebo 43% (260/604) ($p<0.05$).

  Virological load was the second efficacy outcome measured in studies. The evidence demonstrated that etravirine added to an OBT reduced HIV viral load at 48 and 96 weeks, compared to optimized background therapy without etravirine. The quality of the reported evidence was high (*33*).

  - Overall mean change in log10 HIV-1 RNA copies / mL at week 48 was −2.25 (SE: 0.057) in the etravirine group and −1.49 (SE: 0.061) in the placebo group ($p<0.05$). This reduction was maintained at 96 weeks: −2.16 in the etravirine group and −1.42 in the placebo group ($p<0.05$)
  - Regarding immunological responses, mean increases in CD4(+) T-cell count from baseline at week 96 were 128 cells/mm(3) with etravirine, versus 86 cells/mm(3) with placebo ($p<0.0001$).

Additional efficacy outcomes, such as the confirmed AIDS-defining clinical events or death, were measured and reported in studies. The presented evidence showed that etravirine may have a similar rate of AIDS-defining clinical events to the OBT. The quality of evidence reported was considered low (*33*).

- At week 48, the AIDS-defining clinical events or death occurred in 35 / 599 patients (6%) in the etravirine group and 59 / 604 patients (10%) in the placebo group ($p<0.05$).
- At week 96, results showed 48 / 599 patients (8%) in the etravirine group and 66 / 604 patients (11%) in the placebo group ($p>0.05$)

Additional information from a double-blind placebo controlled trial evaluating the efficacy and safety of etravirine compared to efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI), was also reported by the PAHO Expert Committee. The study showed the non-inferiority of etravirine and significant lower incidence of adverse reactions (neuropsychiatric effects) in the etravirine arm (*35*).

The Committee also mentioned another study: a multicenter study assessing the efficacy of etravirine in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) in patients without virologic failure on non-nucleoside reverse transcriptase inhibitors (NNRTIs) or NNRTI-experiences switched due to adverse events (group A) or patients switched after virologic failure on efavirenz or nevirapine-based regimens (group B). The primary endpoint was efficacy at 52 weeks, analyzed by intention-to-treat. Treatment efficacy rates in groups A and B were 88.0% and 77.4%, respectively. The study concluded that etravirine plus two nucleoside analogs is a suitable, well-tolerated combination both as a switching strategy and after failure with first generation NNRTIs (*36*).

Furthermore, although not in the scope of this review, additional information regarding the use of etravirine in HIV-1 in children and adolescents was included in the expert reviews. The additional reference focused on a pediatric phase II study of 101 treatment-experienced pediatric (6 to 18 years old) patients that showed 59% virological response at 48 weeks for the etravirine group (*37*).

In conclusion, the efficacy evidence demonstrates the superiority of etravirine when added to an OBT, in comparison to the OBT alone in regards to treatment response defined by virologic load and AIDS-related events and related complications. Similarly, other studies support the efficacy of etravirine when compared to other treatment regimens.

- Safety evidence for adding etravirine to an optimized background therapy:

In regards to safety, the moderate quality evidence presented in the reviewed dossier showed a similar rate of adverse events leading to therapy discontinuation for etravirine when compared to the OBT alone. Additionally, the evidence demonstrated a similar rate of serious adverse events for both groups, with the exception of rash, which proved to be higher in the etravirine group compared to the OBT alone. The quality of this evidence was considered high (*33*).

- At 96 weeks, the two Phase III studies (DUET 1 and 2) showed similar rates of adverse events leading to discontinuation: etravirine 9% (51/599); placebo 6% (37/604); and similar rates of serious adverse events: etravirine 26% (157/599); placebo 26% (156/604). Rash was the only adverse event to occur significantly more frequently with etravirine 21% (123/599) than with placebo 12% (71/604) ($p<0.0001$).

Another study investigated stable patients co-infected with hepatitis B and/or C virus (HBV/HCV) enrolled in DUET trials. The study concluded that the incidence and severity of adverse events with etravirine were generally comparable to placebo, irrespective of co-infection status (*38*).

The PAHO Expert Committee also reported results from two additional studies comparing etravirine to efavirenz, showing a significantly lower incidence of neuropsychiatric effects for etravirine (*35*, *39*).

The Committee also noted that there have been reports to the United States Food and Drug Administration of severe and potentially life-threatening fatal skin reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis and erythema multiforme associated to etravirine use. Although very rare, these adverse reactions need to be taken into consideration when treatment with etravine is initiated in patients (*40*).

In conclusion, in the short term etravirine demonstrates an acceptable safety profile with no significant differences in the rate of serious adverse reactions occurring compared to placebo, other than rash. Nonetheless, there is a lack of safety data on the long-term basis.

- Cost:

  Regarding cost studies, one Canadian cost-effectiveness study used data from the DUET 1 and 2 trials and national databases to model the cost per QALY lifetime using Canadian dollars cost in 2009, considering direct costs from a Canadian healthcare system perspective. The study concluded that the addition of etravirine to an optimized background therapy containing darunavir/ritonavir, at least two NRTIs, and optional enfuvirtide for HIV-1 positive treatment-experienced adults, resulted in an incremental 1-year cost per additional individual with a viral load <50copies/ml (at 48 weeks) of $23,862, and an incremental life-time cost of $49,120 per QALY gained (*41*).

- Additional comments discussed at meeting:

  - The PAHO Secretariat clarified that six Member States have requested that PAHO procure etravirine (100mg or 200mg) since 2012.
  - The PAHO Expert Committee noted the cost-effectiveness studies reviewed included data from middle- and high-income countries. The Committee reiterated the need to obtain cost-effectiveness studies relevant to Member States who utilize the Strategic Fund as a procurement mechanism.
  - The PAHO Secretariat clarified the request for inclusion of etravirine as third-line therapy in treatment-experienced HIV adults who failed second-line antiretroviral therapy.
  - The PAHO Expert Committee mentioned that etravirine is considered a costly last resort alternative for HIV/AIDS treatment and that the Strategic Fund could contribute to lowering price for access to this medicine.
  - The PAHO Expert Committee recommends patients receiving HIV/AIDS regimens including etravirine should be monitored for potential adverse events or related toxicities through national pharmacovigilance programs and data from the WHO Programme for International Drug Monitoring (Uppsala, Sweden).

- Recommendation:

  The PAHO Expert Committee decided to include 100mg and 200mg tablets of etravirine in the Strategic Fund Medicine List for use as a third-line therapy in adults who have failed second-line therapy. The PAHO Expert Committee recognized the limited evidence available; however, as there are very few viable treatment options for HIV patients failing on second-line therapy, the Committee concluded that the efficacy and safety profile supported the inclusion. Additionally, the PAHO Expert Committee emphasized that the PAHO Secretariat should establish an internal mechanism to monitor Member States procurement

requests for etravirine. This mechanism should ensure that requested quantities are aligned with estimated prevalence of patients failing second-line therapies.

2.1.1.2 Raltegravir

The dossier presented to the PAHO Expert Committee for review incorporates available evidence on the efficacy, safety, and cost of raltegravir added to an optimized background combination therapy, compared to an optimized background combination therapy without raltegravir in treatment-experienced HIV-positive patients. A summary of the evidence is presented below.

Dr. Lisa Bero, Dr. Perla de Buschiazzo, and Dr. Edgard Narváez Delgado were the experts who reviewed this application.

- Efficacy evidence for raltegravir:

The evidence reviewed in the dossier reported efficacy outcomes from two PHASE III studies (BENCHMRK 1 and BENCHMRK 2). The quality of the evidence ranged from low to high, varying depending on the efficacy outcomes measured (treatment response, virological failure, HIV viral load, confirmed AIDS-defining clinical events). These studies were funded by Merck (innovator) (*42*).

The primary efficacy outcome measured in the studies was the treatment response (viral load) measured at 16 weeks, and subsequently at 48 and 96 weeks. In both studies, high quality evidence showed that raltegravir demonstrated superior rates of treatment response to placebo when added to an optimized background therapy at 16 weeks, with results remaining consistent at 48 and 96 weeks with moderate quality evidence (*42*).

At 16 weeks, the non-pooled results from both studies showed:

- BENCHMRK 1 treatment response as HIV-1 RNA level <400: raltegravir 78.4% (178/227); placebo 41% (48/117) (p<0.001). Treatment response as HIV-1 RNA level <50: raltegravir 62.1% (141/227); placebo 33.3% (39/117) (p<0.001).
- BENCHMRK 2 treatment response as HIV-1 RNA level <400: raltegravir 78.3% (177/226); placebo 43.2% (51/118) (p<0.001). Treatment response as HIV-1 RNA level <50: raltegravir 62.8% (142/226); placebo 36.4% (43/118) (p<0.001).

At 48 weeks, an open-label phase of the study, pooled results from both studies showed:

- Treatment response as HIV-1 RNA level <400: raltegravir 73.1% (332/454); placebo 37.4% (88/235) (p<0.001). Treatment response as HIV-1 RNA level <50: raltegravir 62.8% (185/454); placebo 33.2% (78/235) (p<0.001).

Finally, at 96 weeks, results showed:

- Treatment response as HIV-1 RNA level <400: raltegravir 61% (282/462); placebo 28% (66/237) (p<0.001). Treatment response as HIV-1 RNA level <50: raltegravir 57% (262/462); placebo 26% (62/237) (p<0.001).

Results from BENCHMRK 1 and BENCKMRK 2 studies showed raltegravir may also reduce the number of confirmed AIDS-defining clinical events. Nonetheless, the reported difference in the rate of events between raltegravir and placebo at week 48 was very small (3.7% and 4.6%, respectively) and the quality of evidence was low due to lack of blinding *(42)*. In a long-term efficacy analysis, raltegravir also showed a lower virological failure rate when added to an optimized background regimen (33%) compared to placebo (62%) at week 96 *(43)*.

During the plenary session, the PAHO Expert Committee also reviewed an additional reference outlining the long-term follow-up of the BENCHMRK studies (*44*). The study concluded that at week 156, 51% in the raltegravir group versus 22% in the placebo group (non-completer classed as failure) had viral loads of less than 50 copies per mL, and 54% versus 23% had viral loads of less than 400 copies per mL. Mean CD4 cell count increase (analyzed by an observed failure approach) was 164 cells per µL versus 63 cells per µL. After week 156, 251 patients (54%) from the raltegravir group and 47 (20%) from the placebo group entered the open label raltergravir phase; 221 (47%) versus 44 (19%) completed the entire study. Data from a longer follow-up was at high-risk of bias due to lack of blinding and high attrition. This study provided additional support for the efficacy and safety profile of raltegravir after a longer treatment period.

Additional references provided by the PAHO Expert Committee evaluated the use of raltegravir as a first-line combination in a comparative double-blind "non-inferiority" trial comparing raltegravir + tenofovir + emtricitabine versus efavirenz + tenofovir + emtricitabine in 566 patients. They concluded that after 48 weeks, approximately 84% of patients in both groups had undetectable viral load. Thus, no significant superiority in terms of efficacy was reported for raltegravir when used as a first-line treatment (*45–47*).

Nonetheless, another open-label study showed that at a 96-week follow-up, raltegravir and control groups had efficacy greater than 75%, defined by viral load (VL) <200 copies/mL (raltegravir 80.4%, control 76.0% (difference: 4.4 [95%CI -2.6, 11.3])) and met non-inferiority criteria. Both groups also demonstrated similar safety profiles, thus supporting the use of raltegravir in combination with lopinavir/ritonavir as an option following failure of first-line NNRTI + two NRTIs (*48*).

Based on the available efficacy studies, the PAHO Expert Committee concluded that the efficacy data remains limited to very few trials and the long-term efficacy of raltegravir remains uncertain.

- Safety evidence for adding raltegravir to an optimized background therapy:

  In terms of the safety of raltegravir, moderate-quality evidence compiled from the Phase III studies showed similar rates of drug-related clinical adverse events between raltegravir (58.4%) and placebo (58.6%). Furthermore, the risk of serious adverse events was also similar in both groups (raltegravir 25.3%; placebo 22.4%).

  The PAHO Expert Committee stated that there was limited evidence regarding the safety profile of raltegravir. Consequently, additional relevant studies were provided by the Committee to support the safety evidence of raltegravir when compared to other available treatments rather than placebo. A study comparing efavirenz to raltegravir concluded adverse reactions were generally comparable between the two regimens, with fewer drug-related clinical adverse events (49% vs. 80%; $P < 0.001$) occurring in raltegravir than in efavirenz recipients, while discontinuations due to adverse events occurred in 5% and 7%, respectively (*45-47*). Another trial comparing efavirenz to raltegravir also showed similar results after 96 weeks of treatment, with no statistical differences observed in the rate of serious adverse events or withdrawals between both groups (*49*). Furthermore, another trial reported a comparable overall incidence of adverse reactions between a raltegravir- and tipranivir-based regimen (*50*).

  The PAHO Expert Committee then concluded that the safety profile of raltegravir is very similar to other treatment options available, and that no significant differences were observed based on the studies available.

- Cost:

  One cost-effectiveness study evaluated data from the Phase III studies and national databases from Spain, Switzerland ,and the UK to model the cost per QALY up to 5 years, using the costs in 2007 Euro and 2010 exchange rates from a health-system perspective and considering direct costs. The available evidence concluded that in treatment-experience patients, raltegravir added to an OBT showed an incremental cost per QALY of €19,117 for the UK, €31,431 for Spain, and €33,107 for Switzerland *(51)*.

- Additional comments discussed at meeting:

  - The PAHO Secretariat informed that six Member States have requested that PAHO procure raltegravir 400mg since 2011.
  - The PAHO Secretariat clarified the request for inclusion of raltegravir as third-line therapy in treatment-experience HIV-adults who failed second-line antiretroviral therapy.
  - The PAHO Expert Committee mentioned that raltegravir is considered a costly last resort alternative for HIV/AIDS treatment and the Strategic Fund could contribute to lowering price for access to this medicine.
  - The PAHO Expert Committee recommends that patients receiving HIV/AIDS regimens including raltegravir should be monitored for potential adverse events or related toxicities through national pharmacovigilance programs and data from the WHO Programme for International Drug Monitoring (Uppsala, Sweden).

- Recommendation:

  The PAHO Expert Committee decided to include raltegravir 400mg tablets in the Strategic Fund Medicine List for use as a third-line therapy in adults who have failed second-line therapy. The PAHO Expert Committee recognized the limited evidence available; however, as there are very few viable treatment options for HIV patients who fail second-line therapy, the Committee concluded that the efficacy and safety profile supported the inclusion. Additionally, the PAHO Expert Committee emphasized that the PAHO Secretariat should establish an internal mechanism to monitor Member States procurement requests for raltegravir. This mechanism should ensure that requested quantities are in line with estimated prevalence of patients failing second-line therapies.

2.1.2 Deletion

2.1.2.1 Abacavir/lamivudine/zidovudine

The dossier presented to the PAHO Expert Committee for review incorporates the available evidence about the efficacy, safety, and cost of the three NRTIs fixed-dose combination abacavir/lamivudine/zidovudine in comparison with other preferred combinations including 2 NRTIs (e.g. tenofovir + lamivudine or tenofovir + emtricitabine or zidovudine + lamivudine) and 1 NNRTI (efavirenz or nevirapine), for the treatment of HIV-positive adults and adolescents. A summary of the evidence is presented below.

Dr. Perla de Buschiazzo, Dr. Edgard Narváez Delgado and Mr. Damian Francis were the experts who reviewed this application.

- Efficacy evidence for abacavir/lamivudine/zidovudine:

  The evidence results provided to the PAHO Expert Committee in the dossier for the treatment of HIV-positive adults and adolescents with three nucleoside-reverse transcriptase inhibitors (NRTIs) were

based on a systematic review that included four randomized clinical trials evaluating the effectiveness and tolerability of the three NRTIs combinations compared with other antiretroviral therapy based on protease inhibitors (PIs) and/or non nucleoside reverse transcriptase inhibitors (NNRTIs) (*52)*.

The results reported in the dossier suggest that in HIV-positive adults and adolescents, virological failure of antiretroviral initial therapy based on three NRTIs (ABC/3TC/AZT) or including a PI or NNRTI may be similar (RR 1.14; 95%CI 0.56 to 2.31) (*53–55*).

Additionally, the virological suppression showed no differences between groups in four studies using a cut-off of <400 copies/mL (RR 0.73; 95%CI 0.39 to 1.36) or a cut off of <50 copies/mL (RR 0.97; 95%CI 0.75 to 1.25) (*50–53*). CD4 cell counts were not different between the groups at the end of study (SMD -0.01; 95%CI -0.11 to 0.09) *(53–55)*. The quality of the evidence for these results was low.

Study results showed that the CD4+ cell count of antiretroviral initial therapy based on three NRTIs (ABC/3TC/AZT) or including a PI or NNRTI was similar, and that co-formulated abacavir-lamivudine-zidovudine remains a viable option for initiating antiretroviral therapy, especially in HIV-infected patients with pre-existing hyperlipidemia. The quality of this evidence was moderate (*52*).

The PAHO Expert Committee also discussed a randomized controlled trial (RCT) that was initially excluded by the main systematic review incorporated in the dossier. This study evaluated the antiretroviral equivalence and safety of an abacavir/lamivudine/zidovudine regimen, compared to an indinavir/lamivudine/zidovudine regimen. The results showed that the proportion of patients who met the end point of having an HIV RNA level of 400 copies/mL or less at week 48 in the abacavir group (51%) was equivalent to that in the indinavir group (51%), with a treatment difference of −0.6% (95% confidence interval [CI], −9% to 8%). In patients with baseline high viral load (HIV RNA levels > 100 000 copies/mL); the proportion of patients achieving less than 50 copies/mL was greater in the PI group than in the NRTI with treatment difference of -14%; 95% CI, -27% to 0%). This should raise concerns about the efficacy of this combination in patients starting treatment later in the course of the disease. The study also showed similar effects on CD4 cell count in both groups. Finally, the authors concluded the three NRTI combination was equivalent to the indinavir/lamivudine/zidovudine regimen (*56*).

Furthermore, the PAHO Expert Committee reported efficacy and safety results from an additional systematic review, including eight RCTs with a total of 1610 patients virologically suppressed after a successful treatment with a PI containing antiretroviral therapy that assessed the abacavir-based triple nucleoside treatment regimen. Overall, there was no significant difference between the participants on triple nucleoside combination and controls (RR 0.88, 95% CI 0.74 to 1.04), either PI-based (RR 0.80, 95% CI 0.62 to 1.03) or NNRTI-based (RR 0.99, 95% CI 0.79 to 1.24) for overall failure. Eight trials with 1,587 participants reported on virologic failure. Triple nucleoside combination (689 participants) was compared to PI continuation (461 participants) or to NNRTI simplification (437 participants). This review found that there was no significant difference between the participants on triple nucleoside combination and controls (RR 1.39, 95% CI 0.95 to 2.02), either PI-based (RR 1.49, 95% CI 0.72 to 3.08) or NNRTI-based (RR 1.32, 95% CI 0.89 to 1.97), though the test for overall effect (p=0.09) was closed to the level of significance, thus suggesting a weak evidence of higher incidence of virologic failure in the 3NRTI group compared to controls (*57*).

In conclusion, the PAHO Expert Committee stated that no significant difference was reported for the measured efficacy outcomes (virological failure, virological suppression, CD4+ counts), and that the NRTIs fixed-dose combination demonstrated similar efficacy to alternative treatments wit PI or NNRTI. The overall quality of the evidence was low, with a high heterogeneity reported with the exception of CD4+ counts.

- Safety evidence for abacavir/lamivudine/zidovudine:

  In terms of safety, the results derived from the systematic review of the four randomized controlled-trials showed no differences in the rate of adverse events between fixed-dose of NRTIs and antiretroviral therapy (ART) with PI and NNRTI (RR 1.22; 95%CI 0.78 to 1.92); hypersensitivity cases were more frequent among patients receiving PI or NNRTI, but did not reach statistical significance (RR 4.04; 95% CI 0.41 to 40.02) (*53–55*, *58*). The quality of the evidence for these results was very low to low.

  Furthermore, the supplementary systematic review discussed by the Committee reported that, overall, for discontinuation due to adverse events there was no significant difference between the participants on triple nucleoside combination and controls (RR 0.68, 95% CI 0.44 to 1.07), either PI-based (RR 0.77, 95% CI 0.39 to 1.53) or NNRTI-based (RR 0.63, 95% CI 0.34 to 1.18); the test for overall effect (p=0.09) was closed to the level of significance, thus suggesting a weak evidence of lower incidence of side effects in the experimental group. There were also no differences between the groups for death and AIDS-related events, and the rates of patients with viral load levels below the detectability cut-off (*57*).

  Overall, the PAHO Expert Committee concluded that no significant differences had been reported regarding the safety profile of abacavir/lamivudine/zidovudine in comparison with other preferred antiretroviral therapies including PIs and NNRTIs.

  The Committee also noted that the use of NRTI fixed-dose combination was a viable alternative for initiating antiretroviral therapy in adult and adolescent HIV-infected patients that do not tolerate PI or NNRTI, or who living in settings where these ART options are not available. Nonetheless, the efficacy and safety outcomes aforementioned remain very uncertain in specific populations such as HIV patients co-infected with tuberculosis.

- Cost:

  Regarding cost studies, no relevant cost effectiveness studies or economic evaluations were available.

- Additional comments discussed at meeting:

  - The PAHO Secretariat clarified that only one Member State has procured this fixed-dose combination through the Strategic Fund since 2011.
  - The PAHO Expert Committee clarified that the application for potential deletion of the fixed-dose combination of abacavir/lamivudine/zidovudine 300mg/150mg/300mg focused on the adult and adolescent population, and that no studies regarding the pediatric population had been included.

- Recommendation:

  Based on the available evidence, the PAHO Expert Committee concluded that the efficacy and safety of this three NRTIs fixed-dose combination is comparable to other preferred regimens. Nonetheless, the PAHO Expert Committee decided to delete the fixed-dose combination abacavir/ lamivudine/ zidovudine 300mg/150mg/300mg from the Strategic Fund Medicine List due to a lack of demand for this three NRTIs fixed-dose combination and the availability of abacavir, lamivudine, and zidovudine as individual formulations on the list.

2.1.2.2 Nelfinavir

The dossier presented to the PAHO Expert Committee for review incorporates the available evidence about the efficacy and safety of nelfinavir compared to newer available protease inhibitors used as

preferred regimens for the treatment of HIV/AIDS, such as lopinavir/ritonavir. A summary of the evidence is presented below.

Dr. Facundo Bournissen, Dr. Albín Chaves, and Dr. Lenita Wannmacher were the experts who reviewed this application.

- Efficacy evidence of nelfinavir:

  The evidence assessing the efficacy outcomes of nelfinavir was retrieved from a randomized clinical trial conducted in 686 HIV-positive patients aged 12 years or older randomized to receive nelfinavir or lopinavir/ritonavir. High quality evidence demonstrated that virological response (<400 copies of HIV RNA/mL) at 24 and 48 weeks of treatment was greater for lopinavir/ritonavir than for nelfinavir. More patients had less than 400 copies of HIV RNA in the lopinavir group than in the nelfinavir group (79% vs. 71% and 75% vs. 63%, at 24 and 48 weeks, respectively). Results also remained consistent at 48 weeks when considering a baseline of <50 copies of HIV RNA/mL (67% vs. 52%) (*59*).

  The proportion of patients that maintained a virological response up to week 48 was higher in the lopinavir group (84%) than in the nelfinavir group (66%) (HR 2.0; 95%CI 1.5 to 2.7). Another review of the same study results concluded that the risk of loss of virological response at week 96 was significantly higher for nelfinavir-treated patients than for the lopinavir/ritonavir group (HR 2.2; 95%CI 1.7 to 3.0) (*60*). On the other hand, both groups were equally able to increase significantly the mean CD4+ cell count by week 48, and no significant difference was observed in regards to this efficacy outcome.

  The PAHO Expert Committee also cited another double-blind, randomized, phase III study that reported a higher rate of resistance with nelfinavir than with lopinavir/ritonavir. The low resistance rate observed with lopinavir/ritonavir demonstrated higher chances of durability of initial antiretroviral therapy and lower risk of treatment failure (*61*).

  In conclusion, the high quality evidence presented showed that lopinavir/ritonavir had a better virological response while significantly increasing CD4+ cell counts, which made it a better combination to reduce treatment failure and ensure appropriate efficacy of treatment for HIV-positive patients. The results remained consistent in the adolescent population, although with low quality data.

- Safety evidence of nelfinavir:

  In regards to the safety profile of nelfinavir, the low quality evidence showed that the risk of adverse events that could lead to treatment discontinuation was similar to that in lopinavir/ritonavir for both adolescent and adult HIV-positive patients. Results reported that drug–related adverse events led to discontinuation in 3.4% of patients treated with lopinavir–ritonavir and 3.7% of those treated with nelfinavir (*59*). Hence, the available studies reviewed by the experts could not determine a higher risk of adverse events or toxicities related to nelfinavir's use.

- Cost:

  A cost-effectiveness study evaluating the risk of HIV-related AIDS events from lopinavir/ritonavir compared to nelfinavir concluded that the incremental cost-effectiveness ratio of lopinavir/ritonavir was US$ 6,376 per life-year gained, and the incremental cost-utility ratio was US$ 6,653 per QALY gained, taking into account 2001 monetary values. The results showed that the use of lopinavir/ritonavir in the first antiretroviral regimen, as compared to nelfinavir, was cost-effective based on improved efficacy and resistance (*62*).

  Additionally, relevant data from the Region showed that lopinavir/ritonavir has a lower cost compared to nelfinavir.

- Additional comments discussed at meeting:

  The PAHO Secretariat clarified that Member States have not procured nelfinavir 250mg tablets through the Strategic Fund since 2011.

- Recommendation:

  Based on the evidence presented, the PAHO Expert Committee decided to delete nelfinavir 250mg tablets from the Strategic Fund Medicine List, considering that it does not demonstrate adequate efficacy, safety, or cost-effectiveness when compared to preferred regimens available on the list for treatment of HIV/AIDS.

2.2 Multi-Drug Resistant Tuberculosis Medicines

Below is a summary of the evidence and corresponding recommendations for the MDR-TB applications solely requested by PAHO and reviewed by the PAHO Expert Committee (clarithromycin, clofazimine, and imipenem/cilastatin). For additional public health information, please refer to section 1.2 Drug-resistant tuberculosis.

2.2.1 Inclusion

2.2.1.1 Clarithromycin

The PAHO Expert Committee reviewed the efficacy, safety, and cost of clarithromycin, a WHO-listed Group 5 antituberculosis medicine, added to an optimized standard regimen compared to an optimized standard regimen without clarithromyin for the treatment of multi/extensive-drug resistant tuberculosis. A summary of the evidence is presented below.

Dr. Facundo Garcia Bournissen, Dr. Gabriela Prutsky and Dr. Lenita Wannmacher were the experts who reviewed this application.

- Efficacy evidence of clarithromycin:

  There is very limited evidence available regarding the use of clarithromycin in humans for the treatment of drug-resistant tuberculosis. A recent review reported a lack of data evaluating the efficacy of clarithromycin in human clinical trials and only limited animal-model results. The authors reported that *Mycobacterium tuberculosis* is intrinsically resistant to clarithromycin, despite its antibacterial efficacy shown when treating other non-tuberculosis mycobacterial infections (*63*).

  Additionally, a pharmacokinetic, open-label, uncontrolled study evaluated the interaction between clarithromycin and linezolid in multi-drug resistant tuberculosis, showing that the co-administration of 500mg of clarithromycin and 300mg of linezolid increased linezolid exposure by a median of 44% (interquartile range 23 to 102%, p=0.043) compared with baseline. However, this effect was only observed in five patients, and no statistically significant effect was observed with clarithromycin 250mg (*64*). Furthermore, the systematic review included in the clarithromycin dossier reported that macrolides did not demonstrate any add-on benefit in MDR-TB or XDR-TB treated with linezolid (*65*).

  An additional cohort retrospective study presented by the PAHO Expert Committee evaluated the outcome of clarithromycin as salvage therapy in positive MDR-TB patients (n=44) that had failed standard and second-line regimens, and compared the frequency of culture conversion associated with other Group 5 drugs. No significant difference was observed in culture conversion by number of new drugs in the salvage regimen or by extent of resistance. Under clarithromycin treatment, the culture conversion occurred

in 32% (yes) versus 30% (no) (OR = 1.1; 95% CI: 0.5–2.2; P value: 0.83). Treatment allocation was not randomized and the reasons for Group 5 drug selection were not clearly explained in the manuscript (*66*).

Another systematic review referenced by the PAHO Expert Committee and published after the search for evidence also showed no in vitro susceptibility of MDR-TB strains to clarithromycin. On the other hand, clarithromycin resulted in the reduction of intracellular colony-forming unit counts (animal and human cells) (*67*).

In conclusion, the very limited evidence in the application review was not sufficient to determine the efficacy of clarithromycin when added to an optimized standard regimen or compared to other MDR-TB treatments.

- Safety evidence of clarithromycin added to an optimized standard regimen:

  There is presently no reported data on the safety of clarithromycin from randomized controlled trials related to the use of this medicine in tuberculosis patients. Result reported from the pharmacokinetic study state that clarithromycin was well tolerated and that no severe adverse events were reported (*64*).

  In conclusion, clarithromycin appeared to be a safe medicine but there is an important lack of safety evidence in regards to MDR-TB treatment and in combination with other therapies.

- Cost:

  No cost-effectiveness study search was considered in this review.

- Additional comments discussed at meeting:

  - The PAHO Technical Unit sponsoring the application (CHA/HT) reiterated the need for additional MDR-TB medicines, as there is a scarcity of viable treatments for MDR/XDR-TB patients.
  - The PAHO Expert Committee noted the need for additional medicines for MDR/XDR-TB; however, the available evidence on clarithromycin does not demonstrate the minimal standard for efficacy and safety, and stated that more robust studies are needed. The Committee agreed to re-evaluate this medicine in subsequent meetings once additional evidence is available.

- Recommendation:

  Based on the evidence presented, the PAHO Expert Committee decided to reject the inclusion of clarithromycin 250mg and 500mg tablets in the Strategic Fund Medicine List, considering that the available evidence is limited and does not support the efficacy and safety of clarithromycin in the treatment of MDR-TB.

2.2.1.2 Clofazimine

The dossier presented to the PAHO Expert Committee for review incorporates the available evidence about the efficacy, safety, and cost of clofazimine added to an optimized standard regimen in multi/extensive-drug resistant tuberculosis. A summary of the evidence is presented below.

Dr. Perla de Buschiazzo, Dr. Carlos Cuello-García and Dr. Joaquin Baronya were the experts who reviewed this application.

- Efficacy evidence of clofazimine added to an optimized standard regimen:

  Two systematic reviews, including uncontrolled observational studies, examined the efficacy and safety of clofazimine, but could not compare it to the optimized standard regimen. The first systematic review

assessed the treatment success as the main efficacy outcome, showing results pooled from 11 studies that gave a treatment success rate of 62% (95%-CI: 52.8% – 71.1%), with a very low quality in the GRADE assessment (*68*).

Furthermore, mortality was reported individually from studies, ranging from 3.2% (95%-CI: 1.1% - 6.4%) to 29.9% (95%-CI: 10.3%-54.7%), and results from eight studies showed treatment failure was experienced between 1.0% (95%-CI: 0.1%-2.6%) and 63.4% (95%-CI:38.3%-85.0%) of these studies' patients. The quality of the evidence for both outcomes is considered very low due to the high risk of bias, indirectness, and imprecision (*68*).

The second systematic review by Gopal and colleagues showed that treatment with clofazimine resulted in favorable outcomes, consisting of either cure or treatment completion for 65% (95%-CI: 52%-79%) of the MDR-TB patients and for 66% (95%-CI: 42%-89%) of the patients with XDR-TB. The quality of this evidence was considered very low (*69*). Nonetheless, sputum smear, culture conversion, and resistance have not been evaluated by the selected systematic reviews as efficacy outcomes.

Hence, the overall efficacy composite outcomes showed positive cure and treatment success rates up to 66%. On the other hand, mortality and treatment-failure rates showed important disparities, reaching important proportions in some studies. It was suggested that clofazimine represents an additional therapeutic option in the treatment of drug-resistant tuberculosis; however, the dose and duration of use require additional research (*68*).

Similarly, the second systematic review concluded that additional randomized control trials are required to determine the efficacy of clofazimine, in order to establish optimized doses and define the role of clofazimine drug-containing regimens in the treatment of drug-resistant tuberculosis (*70*).

The PAHO Expert Committee also discussed a recently published randomized controlled trial evaluating the use of clofazimine for 21 months on patients 18–24 years old with MDR-TB (*71*). This multi-center, open, randomized controlled trial was reviewed by an expert using the GRADE approach for assessing two outcomes: a) "cure", defined as a patient who had completed treatment according to program protocol and had been consistently culture negative (with at least five results) for the final 12 months of treatment for tuberculosis; and b) "death" assessed and reported by clinicians.

The study showed that patients treated with clofazimine did not present more events of death when compared to control patients (RR, 0.99; 95%CI, 0.33 to 1.71); also, the rate of cured patients in the clofazimine group was not different from the control group (RR, 1.28; 95%CI, 0.84 to 1.90). The confidence in these estimates was low due to risk of bias (the study was not blind, no placebo was used, and the randomization sequence generation was not described as well as the allocation concealment), and imprecision (*71*).

Overall, the PAHO Expert Committee concluded that additional evidence is required to establish the efficacy of clofazimine for the treatment of MDR-TB, considering that there is a lack of data from randomized control trials, that data were poorly reported, and that there was a high risk of bias and imprecision.

- Safety evidence of clofazimine added to an optimized standard regimen:

  The systematic reviews did not include a meta-analysis or pooled assessment of the number of patients who had experienced adverse events. Safety results were retrieved from non-controlled observational studies.

The first systematic review assessed "adverse events" as a composite outcome defined by gastrointestinal disturbances (nausea, vomiting, and abdominal pain) and skin pigmentation, and concluded that adverse events ranged from 13.8% (95%-CI: 2.2% - 32.9%) to 87.8% (95%-CI: 76.8%-95.6%) *(68)*.

A second study review reported a low rate of major adverse events and no treatment discontinuation (*72*). Conversely, another study reported gastrointestinal intolerance in 40%-50% of patients, skin pigmentation in 75%-100% of patients, and icytosis along with skin dryness in 8%-28% of patients (*73*). Overall, the very low quality of the evidence showed adverse events may be frequent in MDR-TB and XDR-TB patients.

In regards to treatment interruption due to adverse events, the results from individual studies assessed in the systematic review reported 6.3% (95%-CI: 3.6%-9.7%) to 14.6% (95% CI: 0.7%-41.8%) of patients had to interrupt treatment (*68*). The same review also showed that treatment discontinuation ranged from 3.2% (95% CI: 0.1%-10.3%) to 10.4% (95% CI: 7.7%-13.4%).

Overall, the PAHO Expert Committee concluded that the safety data provided in the studies was of very low quality, due to its high risk of bias and indirectness. Hence, there is a need for more robust safety evidence related to clofazimine in MDR-TB treatment.

- Cost:

No relevant economic evaluation regarding the cost-effectiveness of clofazimine for the treatment of MDR-TB and XDR-TB was available. A systematic review of the cost-effectiveness of MDR-TB treatment in general, based on four studies, provided data on cost, effectiveness, and cost-effectiveness in Estonia, the Philippines, Peru, and the Russian Federation. The authors concluded that the reported cost per patient for MDR-TB treatment and the cost per DALY averted was: Estonia ((US$ 10,880/US$ 598 (I$960)), Peru (US$ 2,423/US$ 163 (I$291)), the Philippines (US$ 3,613/US$ 143 (I$255)), and the Russian Federation (US$ 14,657/US$ 745 (I$1,059)) (*74*).

The costs were extrapolated to other settings, leading to estimates between US$ 3,401 and US$ 195,018, which varied depending on the region and its model of care. The study concluded that for all WHO sub-regions, the cost of MDR-TB treatment per DALY averted was lower than the per capita GDP, and that it represented a cost-effective strategy in low- and middle-income countries, provided that an outpatient model of care was used.

- Additional comments discussed at meeting:

  - The PAHO Technical Unit sponsoring the application (CHA/HT) reiterated the need for additional MDR-TB medicines, as there is a scarcity of viable treatments for MDR/XDR-TB patients.
  - The PAHO Expert Committee noted the need for additional medicines for MDR/XDR-TB; however, the available evidence does not demonstrate the minimal standard for efficacy and safety of clofazimine, and stated that more robust studies are needed. The Committee agreed to re-evaluate this medicine in subsequent meetings once additional evidences are available.

- Recommendation:

Based on the presented evidence, the PAHO Expert Committee decided to reject the inclusion of clofazimine 100mg and 200mg capsules in the Strategic Fund Medicine List, considering that the available evidence is limited and does not support the efficacy and safety of clofazimine in the treatment of MDR-TB.

2.2.1.3 Imipenem/cilastatin

The dossier presented to the PAHO Expert Committee for review incorporates the available evidence about the efficacy, safety, and cost of imipenem/cilastatin added to an optimized standard regimen, compared to an optimized standard regimen alone in multi/extensive-drug-resistant tuberculosis. A summary of the evidence is presented below.

Dr. Lisa Bero, Dr. Carlos Cuello-García and Dr. Gabriela Prutsky were the experts who reviewed this application.

- Efficacy evidence of imipenem/cilastatin:

  No systematic reviews support the use of imipenem/cilastatin for the treatment of drug resistant tuberculosis. Moreover, no data from randomized clinical trials in humans were available. Therefore, the efficacy and safety results were based on a study including 10 patients with tuberculosis caused by a resistant strain to isoniazid and rifampcin.

  Imipenem/cilastatin was administered in addition to other antituberculosis agents at standard doses. The clinical isolates were resistant to 7±2 antituberculosis agents. Eight patients experienced a conversion of cultures to negative and seven remained negative without therapy. Additionally, two deaths were reported and one was due to active tuberculosis (*75*).

  Overall, the PAHO Expert Committee concluded that the available evidence was scarce; no randomized control trials were available and no significant outcomes have been assessed.

- Safety evidence of imipenem/cilastatin:

  The safety evidence is also very limited regarding the use of imipenem in MDR-TB patients. The study mentioned above also reported that the imipenem combination regimen was well tolerated, with the exception of rash in two patients and occasional diarrhea (*75*).

- Cost:

  Considering that no clinical studies have assessed the effectiveness of imipenem/cilastatin for the management of MDR-TB, no economic evaluations were searched for this purpose.

- Additional comments discussed at meeting:

  - The PAHO Technical Unit sponsoring the application (CHA/HT) reiterated the need for additional MDR-TB medicines, as there is a scarcity of viable treatments for MDR/XDR-TB patients.
  - The PAHO Expert Committee noted the need for additional medicines for MDR/XDR-TB; however, the available evidence does not demonstrate the minimal standard for efficacy and safety of imipenem/cilastatin, as no data from clinical trials in humans was available to support this application. The Committee stated that robust human studies are needed and agreed to re-evaluate this medicine in subsequent meetings once additional evidence is available.

- Recommendation:

  Based on the evidence presented, the PAHO Expert Committee decided to reject the inclusion of imipenem/cilastatin 500mg/500mg powder for injection in the Strategic Fund Medicine List, considering that the evidence available is limited to animal studies and does not support the efficacy and safety of this medicine for use in humans for MDR-TB treatment.

2.3 Malaria Medicines

The Americas is the second region of the world with the highest malaria transmission. Nonetheless, the Region has shown significant improvement in mortality and incidence rates, with a decrease of 79% and 65%, respectively, in the last decade. Results from 2014 reported that out of 21 endemic countries, 13 have reached more than 75% reduction in malaria incidence, while 5 are expected to reach the target by 2015. Seventeen countries still reported both *Plasmodium falciparum* and *P.vivax* cases, with *P.vivax* representing approximately 62% of all estimated cases. This situation demonstrates how urgent it is to increase access to anti-malarials in endemic countries and accelerate progress towards reducing and eliminating malaria in the Americas (*76*).

To assist Member States to achieve the goals of malaria reduction and elimination, the PAHO CHA/VT unit has requested and supported the application of a primaquine pediatric formulation for inclusion in the Strategic Fund Medicine List.

Below is a summary of the evidence and corresponding recommendation for the review of primaquine 5mg pediatric formulation.

2.3.1 Inclusion

2.4.1.1 Primaquine

The dossier presented to the PAHO Expert Committee for review incorporates the available evidence about the efficacy and safety of a lower dose presentation of primaquine (5mg) in comparison with existing dosages (7.5mg and 15mg) included in the Strategic Fund medicine list. A summary of the evidence is presented below.

Dr. Albín Chaves, Dr. Gabriela Prutsky and Mr. Damian Francis were the experts who reviewed this application.

- Efficacy and safety for low-dose primaquine

The main objective of a potential inclusion of a lower dose of primaquine is to ensure an accurate, effective, and safe weight-based pediatric dosing. A search was conducted to determine the comparative efficacy and safety of currently used dose presentations of primaquine (7.5mg or 15mg) and a low dose presentation of the medicine (5mg); however no clinical studies were retrieved. Instead, other references were accessed to support the rationale for inclusion of low-dose primaquine in the Strategic Fund medicine list.

A recent publication mentioned that one of the difficulties observed in the treatment of children with malaria with primaquine was that the lowest available pharmacological presentation of primaquine for the treatment of pediatric patients (i.e, 7.5mg) is physically too small to divide accurately (*77*).

Furthermore, another publication stated that in low-income settings, tablet splitting is commonly performed, but the practice and implications have rarely been discussed. The primary reason for tablet splitting is to increase dose flexibility, particularly for the elderly, children, and persons who require titrating or tapering doses. The accuracy of tablet splitting is influenced by tablet size, shape, hardness, splitting method, and human ability. Small, round, or oddly shaped tablets give rise to the greatest deviations, and harder tablets are most likely to fragment or powder, leading to drug loss (*78*).

In the light of the limited evidence presented, the PAHO Expert Committee stated that numerous studies that previously assessed the efficacy and safety of primaquine are available and should be consulted to further support this application. Additionally, among other referenced studies, a publication by the

American Pharmacist Association (APhA) was considered, which outlined criteria to determine whether tablet splitting was appropriate *(79)*.

- Additional comments discussed at the meeting:

  N/A

- Recommendation:

  Based on the presented evidence, the PAHO Expert Committee decided to include primaquine 5mg tablets in the Strategic Fund Medicine List for the treatment of *P.vivax* and *P.ovale* malaria in support adequate weight-based dosing schemes and to ensure efficacy and safety of this medicine in the pediatric population.

2.4 Neglected Infectious Diseases Medicines

Neglected infectious diseases (NIDs) include 17 infectious diseases and common causes of debilitating illnesses related to poverty in developing countries. The combined burden of disease related to NIDs and their health outcomes has been estimated to be almost as large as that of major diseases such as HIV, tuberculosis, and malaria (*80*). In Latin America and the Caribbean, the burden attributable to NIDs is approximately 5.5 million DALYs, or an estimated 9% of the total global burden (*81*). This section focuses on the three leading neglected infectious diseases in the Americas—strongyloidiasis, leishmaniasis, and leprosy.

- Strongyloidiasis

  Strongyloidiasis is considered one of the most neglected among neglected infectious diseases. In Latin America, only a very limited number of studies have assessed the prevalence of strongyloidiasis (*82*). In terms of treatment, it is essential to point out that the aim is to cure patients of *Strongiloides stercoralis*, not merely to lower the parasite burden. The risk of host re-infection is high, and the recommended drugs for large-scale chemotherapy interventions for soil-transmitted helminthiases (STHs) do not have a significant activity against this specific helminth, unless they include ivermectin (*83*). Therefore, mass treatment with appropriate doses and duration of ivermectin should be made a priority in countries with endemic prevalence of strongyloidiasis.

- Leishmaniasis

  In the Americas, cutaneous and mucosal leishmaniasis affects approximately 53,000 persons each year in 18 countries. More than 80% of cases of both forms of leishmaniasis in the Americas have been reported in Brazil (40%), Colombia (20%), Peru (16%), and Nicaragua (5%), all of them among the ten countries of the world with most reported cases (*84*). It is imperative to provide access to adequate treatment for various forms of leishmaniasis in order to further reduce the burden of this disease in the Americas. Hence, the increased availability of different anti-leishmaniasis medicines with different dosages and formulations will enable countries to provide adequate, effective, and quality treatments for various forms of leishmaniasis present in the Americas.

- Leprosy

  Leprosy, an infectious disease caused by the bacteria *Mycobacterium leprae*, is a neglected disease that still represents an important burden in the Americas, which ranks as the second region worldwide, with 33,084 new cases detected. Brazil sustains the highest burden in the Region, with 93.9% of the total number of cases in the Americas. Along with early diagnosis, multidrug therapy remains the backbone

of leprosy control and elimination. Hence, continuous and improved access to effective, safe, and quality leprosy medicines will help to prevent disabilities and reduce the burden associated with this disease in the Region (*85*).

Since 2009, the Pan American Health Organization's has urged Member States to implement the Resolution CD49.R19 on the Elimination of neglected diseases and other poverty-related infections and scale up public health interventions to reduce the burden of NIDs in the Americas and work toward the elimination of poverty-related diseases by promoting access to disease control tools and improving the acquisition of quality-assured affordable medicines to treat NIDs (*86*).

To this end, the PAHO CHA/VT unit has requested and supported the application of ivermectin for the treatment of strongyloidiasis, of ofloxacin as a second-line treatment of leprosy, and of pentamidine as a treatment alternative for leishmaniasis. Furthermore, niclosamide and praziquantel indications were reviewed without prior review of the dossier.

Below is a summary of the evidence and corresponding recommendation provided by the PAHO Expert Committee for the aforementioned reviews.

2.4.1 Inclusion

2.4.1.1 Ivermectin

The dossier presented to the PAHO Expert Committee for review incorporates the available evidence about the efficacy, safety, and cost of ivermectin, compared to albendazole, for the treatment of strongyloidiasis in adult and pediatric patients. A summary of the evidence is presented below.

Dr. Lisa Bero, Dr. Albín Chaves and Dr. Joaquin Barnoya were the experts who reviewed this application.

- Efficacy evidence for ivermectin:

No systematic review and meta-analysis was available for this review. Efficacy data were retrieved from five clinical trials, of which four were randomized trials that assessed parasitological cure as the main efficacy outcome of interest (*87*). The quality of the evidence presented was low to moderate for the adult studies and moderate for the studies on children.

The trial results showed that ivermectin may achieve higher rates of negative parasitological tests than albendazole in children and adults with chronic infection due to *S. stercoralis*. Some studies showed statistically significant differences in the rate of cure between ivermectin and albendazole treatments, reaching an average of 40% difference.

The following parasitological cure rate results were reported by different clinical trials:

- Parasitological cure rates: ivermectin (83%) and albendazole (38%) ($p<0.01$) (*88*).
- Coprological cure rates: ivermectin (97.0%), albendazole (77.4%) (*89*).
- Parasitological cure rates: ivermectin (76.2%), albendazole (38.1%), ($p=0.029$) in the intention-to-treat analysis; ivermectin (88.9%) and albendazole (50%), ($p=0.023$) in the per-protocol analysis (*90*).
- Parasitological cure rates: ivermectin double dose (93.1%), ivermectin single dose (96.8%), albendazole (63.3%) ($p=0.006$) in modified intention to treat analysis (*91*).
- Parasitological cure: ivermectin (89%), albendazole (45%) (*92*).

- Safety evidence for ivermectin:

  Limited safety data was available from clinical trials. The quality of the evidence presented was considered low to moderate. No very severe adverse reactions and treatment interruptions were reported. While adverse reactions were more frequent in children (32%; 109/301), the difference in rates between ivermectin and albendazole treatments were not considered significant. Common adverse events reported were abdominal distension, headache, nausea, dizziness/vertigo, etc. (*92*).

  Given these findings, the safety profile seems to be similar for ivermectin and albendazole, with no significant difference reported in studies.

- Cost:

  A cost-effectiveness study showed that any presumptive treatment strategy is cost-effective when compared with most common medical interventions. When the prevalence of *S. stercoralis* is greater than 2%, the incremental cost-effectiveness ratios of all presumptive treatment strategies were similar. Ivermectin is associated with an incremental cost-effectiveness ratio of US$ 1,700 per QALY gained for treatment with 12mg ivermectin, compared to five days of albendazole when the prevalence is 10% *(93)*.

- Additional comments discussed at the meeting:

  N/A

- Recommendation:

  Based on the presented evidence, the PAHO Expert Committee concluded that ivermectin demonstrated favorable efficacy and an acceptable safety profile compared to existing alternative treatments and decided to include ivermectin 3mg (scored) tablets in the Strategic Fund Medicine List for treatment of strongyloidiasis.

2.4.1.2 Niclosamide

No dossier was presented to the PAHO Expert Committee for the review of niclosamide indications. The PAHO CHA/VT Unit requested the addition of a supplementary indication for niclosamide 500mg tablets (chewable) in the Strategic Fund Medicine List under "anticestodes". The PAHO Expert Committee reviewed the WHO helminthiases classification submitted by PAHO's Secretariat as evidence for the proposed indication.

- Recommendation:
  Based on the information provided by the PAHO Secretariat, the PAHO Expert Committee decided to include the indication anticestodes in addition to intestinal anthelminthic for niclosamide 500mg tablet (chewable) in the Strategic Fund Medicine List.

2.4.1.3 Ofloxacin

The dossier presented to the PAHO Expert Committee for review incorporates the available evidence regarding the efficacy and safety of ofloxacin compared to WHO multi-drug therapy (rifampicin, clofazimine, dapsone) as a second-line therapy for the treatment of multibacillary and paucibacillary leprosy in adult patients. A summary of the evidence is presented below.

Dr. Carlos Cuello, Dr. Facundo García Bournissen and Mr. Damian Francis were the experts who reviewed this application.

- Efficacy evidence for ofloxacin:

  Three publications have mainly examined the efficacy and safety of ofloxacin used in combination with rifampicin as a combination treatment for leprosy. Two publications included previously untreated patients with multibacillary leprosy, and the third focused on previously untreated patients with paucibacillarry leprosy. The overall quality of the presented efficacy evidence was considered low.

  Results from studies regarding efficacy showed that treatment with ofloxacin 400mg and rifampicin 600mg administered for one month may present significantly higher rates of relapse compared to treatment with one year of WHO multi-drug therapy, and similar rates compared to treatment with six months of WHO multi-drug therapy in multibacillary and paucibacillary leprosy, respectively.

  After 12 years of follow up, the first study presented a relapse rate for one month of treatment with ofloxacin 400mg with rifampicin 600mg of 25%, compared to the one-year WHO multi-drug therapy relapse rate of 3%, with relapses occurring after five years of treatment (P< 0.05) (*94*). A second study showed a difference of 38% compared to 4.3% for ofloxacin-based treatment versus WHO regiment respectively for similar durations *(95*).

  In regards to paucibacilary leprosy, a third study demonstrated relapses in two patients in the ofloxacin group and in one patient in the WHO multi-drug therapy, with similar relapse rates in both groups (*96*).

  Nonetheless, disregarding the existing disparities between the efficacies of both regimens, the PAHO Expert Committee clarified that the indication requested for inclusion was the use of ofloxacin as a second-line treatment of leprosy in situations where the first line of treatment is not feasible, and took into account the lack of available evidence. The Committee stated that the efficacy evidence should have included a comparison of ofloxacin-based regimens and placebo. Additionally, to further support the effectiveness of ofloxacin containing therapies, the Committee provided additional references referring to studies based on regimens including rifampicin, ofloxacin, and minocycline. The Committee noted that minocycline is not included in the Strategic Fund Medicine List or the in WHO EML (*97*–*101*).

- Safety evidence for ofloxacin:

  For both multibacillary leprosy and paucibacillary leprosy, the safety profile of ofloxacine demonstrated a low and similar incidence of adverse reactions between as the WHO multi-drug therapy (*95*, *102*). Overall, treatment with ofloxacin seemed to be well tolerated by patients and no major adverse reactions or toxicities have been reported.

- Cost:

  No economic studies were found in the search performed.

- Additional comments discussed at meeting

  N/A

- Recommendation:

  Based on the available evidence presented, the PAHO Expert Committee concluded that ofloxacin demonstrated a favorable efficacy and acceptable safety profile when used in combination with rifampicine as a second-line treatment for multibacillary and paucibacillary leprosy. The Committee recommended the inclusion of ofloxacin 400mg tablets in the Strategic Fund Medicine List as a second-line therapy for leprosy to be used in combination with rifampicine.

2.4.1.4 Pentamidine

The dossier presented to the PAHO Expert Committee for review incorporates the available evidence about the efficacy and safety of pentamidine for the treatment of cutaneous and mucocutaneous leishmaniasis, compared with other recommended treatments such as pentavalent antimonials contextualized to the Region of the Americas. A summary of the evidence is presented below.

Dr. Lisa Bero, Dr. Edgard Narváez and Dr. Lenita Wannmacher were the experts who reviewed this application.

- Efficacy of pentamidine:

The evidence included in the dossier supporting the request for potential inclusion of pentamidine was derived from a recent PAHO publication summarizing the latest studies and reviews on the use of pentamidine isethionate compared with other alternative treatments for leishmaniasis. The overall quality of the efficacy evidence presented in the studies was low.

A systematic review identified one randomized control trial that concluded that the cure rate of meglumine antimoniate was superior to pentamidine (80 participants; RR 2.21; 95% IC; 1.41 to 3.49) in *Leishmania braziliensis* cutaneous leishmaniasis. However, another RCT found no difference for *L. guyanensis* infection. This systematic review also incorporated studies and results from a previous Cochrane systematic review which did not have data on pentamidine (*103*).

A previous systematic review evaluated pentamidine as a first-line therapy or as an alternative therapy in case of treatment failure. In the meta-analysis, a direct study of medicine efficacy showed similar efficacy results for pentamidine and for pentavalent antimonium (OR, 0.81; 95% CI, 0.64–1.10). A trial also showed that when used as an alternative following treatment failure with pentavalent antimonium, 87.2% of patients treated with pentamidine showed a favorable outcome, compared to 63.6% re-treated with pentavalent antimonium ($p < 0.05$) (*104*).

For mucocutaneous leishmaniasis, a systematic review concluded that pentamidine was as effective as meglumine antimoniate in terms of curing rates (p=0.68), thus leaving the choice of therapy to cost, availability, safety profile, and local experience (*105*).

An additional reference provided by the PAHO Expert Committee referred to a randomized control trial that compared meglumine antimoniate, pentamidine isethionate, and amphotericin B in terms of efficacy and tolerability when used for the treatment of American cutaneous leishmaniasis caused by *L. (Viannia) guyanensis*. The intention-to-treat analysis showed an efficacy of 58.1% for pentamidine and of 55.5% for meglumine (p=0.857). The quality of this evidence was not assessed in the review (*106*).

Overall, the PAHO Expert Committee stated that the pentamidine was shown to be effective as an alternative treatment or a second-line treatment and can be used in patients non-responsive or failing other treatments.

- Safety of pentamidine:

A systematic review performed an analysis of adverse events comparing pentavalent antimonials and pentamidine isethionate, providing safety information on 4,359 patients treated for cutaneous leishmaniasis. A table listing most common adverse events reported is available in the pentamidine dossier (p. 17). Overall, the most frequently reported clinical adverse effects of pentavalent antimonials and pentamidine were musculoskeletal pain, gastrointestinal disturbances (nausea, vomiting), and mild

to moderate headache. Nonetheless, no GRADE assessment was available for this review and the quality of the evidence was not rated (*107*).

- Cost:

  No cost studies were available for this review.

- Additional comments during the meeting:

  The evidence reviewed by the PAHO Expert Committee was retrieved from PAHO's 2013 publication on leishmaniasis in the Americas (*Leishmaniasis en las Américas: recomendaciones para el tratamiento*). This publication (Spanish only) was based on systematic reviews that gathered evidence on the efficacy and safety of treatments for leishmaniasis types relevant to the Americas.

- Recommendation:

  Based on the presented evidence, the PAHO Expert Committee concluded that pentamidine demonstrated adequate efficacy and safety as an alternative treatment for cutaneous and mucocutaneous leishmaniasis. The Committee recommended the inclusion of pentamidine isethionate 300mg powder for injection in the Strategic Fund Medicine List to be used in accordance to the recommendations outlined in the PAHO publication on leishmaniasis in the Americas (*Leishmaniasis en las Américas: recomendaciones para el tratamiento*) (*108*).

2.4.1.5 Praziquantel

No dossier was presented to the PAHO Expert Committee for the review of praziquantel indications. The PAHO CHA/VT Unit requested the addition of a supplementary indication for praziquantel 600mg tablets in the Strategic Fund Medicine List under "anticestodes". The Expert Committee reviewed the WHO helminthiases classification submitted by PAHO's Secretariat as evidence for the proposed indication.

- Recommendation:
  Based on the information provided by the PAHO Secretariat, the PAHO Expert Committee decided to include the indication anticestodes in addition to intestinal anthelminthic, antischistosomal, and antitrematode for praziquantel 600mg tablet in the Strategic Fund Medicine List.

Summary of Recommendations

The Director of PAHO will review the PAHO Expert Committee's recommendations and make a final decision to include, delete, or otherwise determine the status of these medicines in the PAHO Strategic Fund Medicine List. Upon receiving the Director's judgment, the Secretariat will publish an updated version of the PAHO Strategic Fund Medicine List.[3]

1. Inclusions

The PAHO Expert Committee recommended that six new medicines be included in the Strategic Fund Medicine List (bedaquiline, darunavir, etravirine, ivermectin, linezolid, and raltegravir). The Committee also recommended that a new indication be included for four medicines already in the list (ofloxacin, niclosamide, pentamidine, praziquantel) and additional dose presentations be included for another two medicines (nevirapine and primaquine). The PAHO Strategic Fund Medicine List will be updated as shown in Table 1.

[3] The updated 2015 PAHO Strategic Fund medicines list will be available at www.paho.org/strategicfund

Table 1. Updated Strategic Fund Medicine List 2015.

International Nonproprietary Name (INN) or Generic Name	Strength	Presentation	Indication(s)	Ref
ANTI-INFECTIVE MEDICINES				
Antituberculosis medicines				
Bedaquiline	100mg	Tablet	MDR-TB	[1]
Linezolid	600mg	Tablet		
Antiretrovirals				
Darunavir	75mg, 400mg, 600mg, 800mg	Tablet	HIV	[2]
Etravirine	100mg; 200mg	Tablet		[2]
Nevirapine	50mg	Tablet (dispersible)		
Raltegravir	400mg	Tablet		[3]
Anthelminthics				
Intestinal Anthelminthics				
Ivermectin	3mg	Tablet (scored)	Strongyloidiasis	
Niclosamide	500mg	Tablet (chewable)	Intestinal anthelminthic Anticestodes	
Praziquantel	600mg	Tablet	Intestinal anthelminthic; Antischistosomal; Antitrematode; Anticestode	
Antileprosy medicines				
Ofloxacin	400mg	Tablet	Leprosy (second-line)	[4]
Antiprotozoal medicines				
Antileishmaniasis medicines				
Pentamidine	300mg (isethionate)	Powder for injection	Leishmaniasis	[5]
Anti-malarials				
Primaquine	5mg	Tablet	As complement to malaria treatment (for radical cure of *P.vivax* and *P.ovale* and as gametocytocide for *P. falciparum*)	

[1] Procurement of this medicine through the Strategic Fund should be limited for use according to WHO recommended M/XDR-TB regimen in patients for whom there are few or no treatments available. Patients receiving this medicine should be monitored for potential adverse events or related toxicities through national pharmacovigilance programs and data from the WHO Programme for International Drug Monitoring (UPPSALA).

[2] Age restriction > 3 years old

[3] Procurement of this medicine through the Strategic Fund should be limited for use as third-line therapy in treatment-experienced HIV adults who failed second-line antiretroviral therapy. It is recommended patients receiving HIV/AIDS regimens including this medicine be monitored for potential adverse events or related toxicities through national pharmacovigilance programs and data from the WHO Programme for International Drug Monitoring (UPPSALA).

[4] To be used in combination with rifampicin as a second-line therapy for leprosy treatment.

[5] This medicine should be used in accordance to the recommendations outlined in the Leishmaniasis in the Americas: Recommendations for the treatment 2013 guide (*Leishmaniasis en las Américas: recomendaciones para el tratamiento*).

2. Reject inclusion

The PAHO Expert Committee concluded that there was not sufficient evidence to recommend the inclusion of three medicines (clofazimine, clarithromycin, and imipenem/cilastatin). While taking into account the public health implications and access limitations for multi-drug resistant tuberculosis medicines, the Committee recommended that a supplementary review for these applications should be considered in the future, when additional evidence regarding efficacy and safety for the aforementioned medicines would be available.

3. Deletion

The PAHO Expert Committee recommended the deletion of four medicines (didanosine, indinavir, nelfinavir, and stavudine) due to efficacy and/or safety reasons. The Committee also recommended the deletion of another medicine (fixed-dose combination abacavir/ lamivudine/ zidovudine), as it is no longer required by Member States.

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