A RESOURCE MANUAL

FOR THE

MANAGEMENT

OF

RETINOBLASTOMA

IN

LOW & MIDDLE RESOURCE SETTINGS

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Retinoblastoma Network, ICEH, LSHTM

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INTRODUCTION

1. Retinoblastoma (Rb) is a cancer of children which if treated early is curable.

2. Rb affects young children mostly under the age of 5 years.

3. The incidence of retinoblastoma is 1:15,000-20,000 live births and with birth rates varying between 10,000 – 45,000 / million population in different countries that equates with approximately <1-3 cases / million total population. (See page 7 for estimating number of cases graph).

4 . There is no known gender or racial predilection.

5 . Retinoblastoma is curable if detected and treated early.

6 . The aim of treatment is:
   - Survival of the child
   - Salvage of the eye
   - Salvage of useful vision
   - Improve quality of life for child and caregiver.

7 . Treatment of Rb is best delivered in Rb centres staffed with multi-disciplinary teams.

TEMPLATE FOR PLANNING A NATIONAL RETINOBLASTOMA SERVICE

RATIONALE

If untreated, retinoblastoma is a lethal childhood cancer of the eye; however, with early diagnosis, referral and appropriate specialist treatment, the child's life and vision can be saved.

This template aims to provide information on what is required to develop a national retinoblastoma service for affected children and their families.

ASSESSING NEED

Most (>95%) children present in the first 5 years of life.

Birth Rate and Incidence of New Cases

The incidence of retinoblastoma is reasonably constant at about 1/16,000 births. The birth rate however varies between countries, being lower in high income countries (HIC), and higher in lower income populations (LIC).
The number of new cases per million total population therefore varies between about 1 (HIC) and 3 (LIC) cases per million population per year.
Figure 1 on page 7 provides a chart to estimate the expected number of new cases per year for countries of different population size and different birth rates.

Prevalence aged 0-5 years

If referral and diagnosis is made early and good timely treatment is provided, then most children with retinoblastoma can survive. Specialist follow-up is required for these children.
Therefore, in planning a National service for retinoblastoma, both new and follow-up cases need to be considered.
The number of children in a population with new retinoblastoma or undergoing retinoblastoma treatment with follow-up is likely to be between 5-15 cases / million population (based on an incidence of 1-3 new cases / million pop. / year). So, for a country with a population of 10 million people, with an average birth rate (i.e. 2 cases per million population), one can expect about 20 new cases of retinoblastoma per year; and if the survival rate is 50 – 100% then at any one time there will be about 50- 100 children with retinoblastoma between the ages of 0 and 5 (new and follow-up).

SERVICES FOR RETINOBLASTOMA - DIAGNOSIS AND MANAGEMENT

In order to save the lives and vision of children with retinoblastoma it is essential that:

1. **Parents and carers of children** are aware that a white pupil, or a squint, in the eye of a baby, infant or child is serious and requires urgent examination by an eye specialist.

2. **All health workers** know that:
    a. a white pupil, or a squint, maybe due to retinoblastoma,
    b. that parents who say their child has something white (or opaque) in the eye should be taken seriously,
    c. that all suspected cases should be referred URGENTLY to an eye specialist for diagnosis.

3. **General ophthalmologists** know:
    a. how to examine a child with suspected retinoblastoma and perform an examination under anaesthesia where indicated;
    b. how to perform a safe enucleation on appropriate cases including excision of a long portion of optic nerve;
    c. which cases to refer to a tertiary retinoblastoma centre.

4. **Tertiary retinoblastoma diagnostic and treatment services** are available, particularly for all bilateral cases, familial cases and cases with spread beyond the globe.
    These services should include ophthalmology, paediatric oncology (including chemotherapy), ophthalmic pathology, radiotherapy and counselling.

Community / Population Level

Health education about the need for a baby / infant / child with a white pupil (leucocoria) to be seen by an eye specialist urgently.

Primary Health Care

Health education about the need for a baby / infant / child with a white pupil to be seen by an eye specialist urgently.
Health workers should be able to examine the child's eye with a torch and look for leucocoria.
If possible, health workers should be trained to examine a child's eye for a red reflex and make a preliminary diagnosis of leucocoria.

Secondary Health Care

Eye specialists working at the secondary level should be able to make a clinical diagnosis of retinoblastoma.
They should know to urgently refer to a tertiary retinoblastoma treatment centre ALL cases of suspected retinoblastoma, especially those that are:

- Bilateral
- Familial
- Have extraocular spread

If urgent referral to a tertiary centre for management is difficult and likely to cause delays in treatment, then for unilateral, non-familial cases, confined to the globe, they should be able to treat by performing a safe enucleation with a long section of optic nerve. There should be a referral pathway to send the enucleated eye for pathological examination, in particular to check for extraocular spread through sclera or along the optic nerve. If there is any evidence of extraocular spread on pathological examination the child should be referred to a tertiary centre for further management.

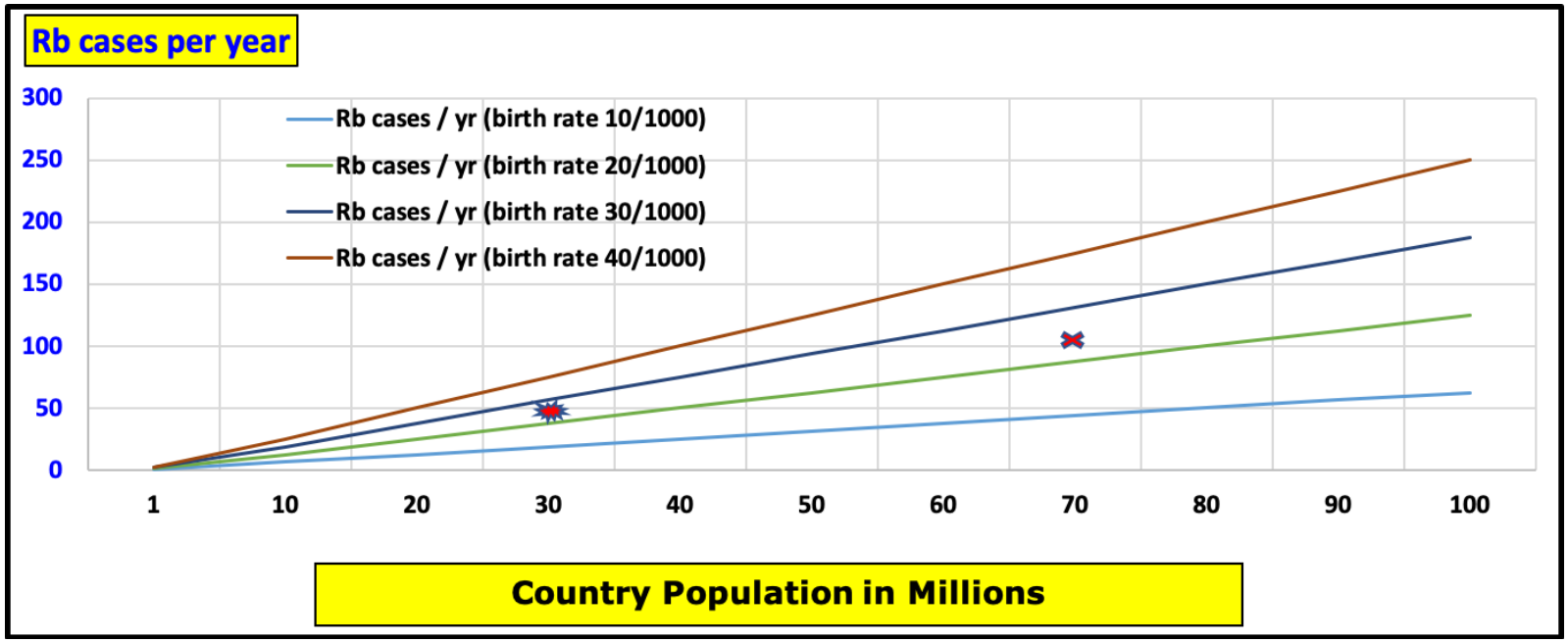
Tertiary Health Care

A specialist retinoblastoma service with a multi-disciplinary management team should be available for every 10 to 20 million population to provide treatment for new cases and long-term follow-up services including:

- Counselling (including genetic counselling),
- Ophthalmology (including eye surgery and non-invasive interventions)
- Oncology (appropriate for children)
- Pathology (preferably with expertise in ophthalmic pathology)
- Imaging (preferably MRI)
- Radiotherapy services may also be required in some cases
- Prosthesis services

Figure 1: Estimated number of new Retinoblastoma cases per year:

For different birth rates, assuming an incidence of 1 / 16,000 cases of Rb / 1000 births.



Examples:

- For a country with a population of **30 million population** and a **birth rate of approx. 30 births /1000 pop**. There will be about **60** new cases of Rb/yr.
- For a country with a population of **70 million population** and a birth rate of approx. 25 births /1000 pop. There will be about **110** new cases of Rb/yr.

Comments:

Figures are based on an incidence of 1 Rb case /16,000 births. The actual **incidence may vary +/- 20%** of this figure.
This is the estimated **new cases per year** and does not take into account the need to follow-up cases for further treatment.

Table 1: Services for Retinoblastoma – Who does what? - Community to Tertiary Centre

Level	Person	Knowledge and Skill	What to do?
Community	Parents / carers	Recognise white pupil, squint	Seek advice of eye specialist urgently
Primary	All health workers	Recognise white pupil, squint	Refer all suspected cases to an eye specialist urgently
Secondary	General ophthalmologists	Diagnose Rb and refer ALL cases urgently to a tertiary Rb treatment centre. If urgent referral is not possible then for unilateral, non-familial cases confined to the globe perform a safe enucleation and send the specimen for pathology to check for extraocular spread.	Refer ALL cases to a Rb tertiary treatment centre URGENTLY. If the child has UNILATERAL Rb which is confined to the globe and urgent referral is NOT possible then perform a safe enucleation including a long section of optic nerve and send for pathological examination.
Tertiary	Specialist multi-disciplinary team of ophthalmologist, oncologist, pathologist, counsellor, radiotherapist and prosthetist	Paediatric ophthalmology Genetic counselling Paediatric oncology Ophthalmic pathology Radiotherapy Imaging Prosthesis services	Diagnose, manage, counsel and follow up all referred cases of Rb.

Table 2: Services for Retinoblastoma – Required Resources

Level	Knowledge and Skill	Equipment, Medicines etc
Community	Recognise white pupil or squint	Information about leukocoria – poster, video etc
Primary	Recognise white pupil or squint	Information about leukocoria – poster, video etc Torch to examine pupil.
Secondary	Diagnose Rb. Perform safe enucleation on unilateral cases confined to globe	Facilities and equipment for safe examination under anaesthetic (EUA). Instruments for safe enucleation of the globe. Access to pathology services if enucleation is performed.
Tertiary	Paediatric ophthalmology Genetic counselling Paediatric oncology Ophthalmic pathology Radiotherapy Prosthesis services	Facilities and equipment for safe examination under anaesthetic (EUA). Ultrasound RetCam to image the retina MRI Focal therapy, including laser, cryotherapy and intra-vitreous injection of chemotherapy. Systemic chemotherapy External beam radiotherapy (rarely used) Available pathology services Prosthesis fitting.

SCREENING

Early diagnosis and referral of Retinoblastoma is critical.

Mothers and other family members may notice a white pupil (leukocoria) or an abnormal red reflex or a squint.

Health workers can be trained to screen infants and small children by checking for **a retinal red reflex** particularly if the family members have a concern.

The following groups should be targeted for screening:

- All children with siblings or parents with a history of retinoblastoma or enucleation
- All newborn babies after delivery and before discharge
- All children attending Reproductive and Child Health (RCH) clinics
- All children less than 5 years attending immunization or other health campaigns.

All infants should also be checked for strabismus (squint) and any child with strabismus must have their retina examined after dilating the pupils.

EARLY DIAGNOSIS & MANAGEMENT

1. Any child with no retinal red reflex, a white pupil or strabismus should be referred to an ophthalmologist as soon as possible.

2. Any child with no red reflex, a white pupil or strabismus should receive from an ophthalmologist a full retinal examination after dilating the pupils of both eyes.

3. The common differential diagnoses of a white pupil include:
   - Retinoblastoma
   - Congenital cataract
   - Coats' disease
   - Intraocular inflammation e.g. toxocariasis
   - Persistent hyperplastic primary vitreous
   - Retinopathy of prematurity.

4. The following cases of Rb should be referred to a tertiary centre for management of Rb as soon as possible; any child:
   - having a small tumour with potential to save the eye
   - with bilateral or multifocal tumours
   - after enucleation for further management
   - with extra-ocular disease.

RADIOLOGY & IMAGING

1. All suspected cases of retinoblastoma should have an ocular ultrasound if available.

2. All cases of Rb with probable extra-ocular extension should have a MRI if available to evaluate the extent of the disease. If MRI is not available CT scan can be considered. This should be done as soon as possible, preferably within a week of diagnosis.

3. The standard CT and MRI scan protocol should be used which includes less or equal to 2mm slice thickness. In cases of CT, reconstructed coronal and axial planes should be provided.

4. The radiologist should report on the following in CT scan/MRI:
   - Presence of mass
   - Presence of calcification
   - Extra-ocular extension
   - Status of optic nerve, orbit and adnexa.

STAGING AND CLASSIFICATION

Establishment of the correct diagnosis and staging of the disease is important before embarking on any specific treatment for Rb.

The International Retinoblastoma Staging system (IRSS) incorporates intraocular and extraocular disease and is used to stage the patient in order to plan appropriate treatment.

International Retinoblastoma Staging System	
Stage	**Definition**
0	Eye can be salvaged with focal treatment or systemic chemotherapy
I	Enucleation with no tumour residue (low risk features on pathology)
II	Enucleation with tumour residue (high risk features on pathology: (tumour at optic nerve cut end or scleral or extra-scleral extension)
III	Regional extension
IIIA	Overt orbital disease with optic nerve extension or extraocular extension
IIIB	Regional lymph node extension
IV	Metastatic disease
IVA	Haematogenous metastases
IVB	CNS extension

In cases of Rb confined to the globe the **International Intraocular Retinoblastoma Classification (IIRC**) is used to classify the intraocular tumour. Both eyes are classified on the day of presentation (i.e. an eye is **not** reclassified to a higher grade if it progresses)

International Intraocular Retinoblastoma Classification (IIRC)

Group A
Small tumours (<3 mm) that are only in the retina and are not near the optic disc or the fovea.

Group B
All other tumours (>3 mm or close to the optic disc or fovea) that are still only in the retina.

Group C
Well-defined tumours with small amounts of sub-retinal seeding or vitreous seeding.

Group D
Large or poorly defined tumours with widespread vitreous or sub-retinal seeding+/- retinal detachment of greater than a quarter.

Group E
The tumour is very large, extends near the front of the eye, is bleeding or causing glaucoma or has other features that mean there is almost no chance that the eye can be saved.

TREATMENT MODALITIES

Focal treatment

Cryotherapy for small peripheral Rb.
Diode laser therapy for small posterior Rb.

Enucleation

The ophthalmologist should try and obtain at least 17mm of optic nerve length, and comment on the length and pliability of the optic nerve.
See surgical technique:
https://www.youtube.com/watch?v=FgGtw6oyHl8&t=53s
A primary orbital implant should be inserted if available. It is important to fit a good prosthesis as soon as possible.

Chemotherapy

This may be given systemically as first line treatment (see protocols later) or by intravitreal injection (usually Melphalan or Topotecan) if vitreous seeds are present after systemic chemotherapy.
In specialised centres it is occasionally given via the ophthalmic artery.

Radiotherapy

Occasionally a radiotherapy plaque is placed on the sclera over the tumour.
External beam radiotherapy may be used to salvage the only remaining eye or in patients with extra ocular disease or for palliation in metastatic disease.

Extraocular disease

Decide if treatment is to cure or to palliate.
Cure may be possible if there are no systemic metastases or involvement of the brain.

TREATMENT PROTOCOLS

Children with Rb should be managed by a multidisciplinary team (MDT) consisting of a Counsellor, Ophthalmologist, Oncologist, Pathologist (COOP) and if available radio-oncologist in specialised centres.

Intraocular Retinoblastoma

International Classification of Intraocular Retinoblastoma		
	Definition	**Treatment**
A	Small tumours <3 mm outside macula	Focal treatment. If no focal treatment available either: • Send to a site with focal treatment • If no focal treatment is available in country seek expert guidance
B	Bigger tumours >3 mm or tumours in the macula or tumours with sub-retinal fluid	Focal treatment +/- systemic chemotherapy up to 6 cycles
C	Localized (within 3 mm from the tumour) vitreous or sub-retinal seeds	**Unilateral**: Enucleate **Bilateral:** Attempt 'Second Eye' Salvage: Systemic chemotherapy 6 cycles +/- focal treatment
D	Diffuse (> 3 mm away from the tumour) vitreous or sub-retinal seeds **If Enucleated** look for: **High Risk Histopathological Features**: • Retrolaminar optic nerve involvement • Choroidal Invasion >3mm	**Unilateral:** Enucleate **Bilateral:** Attempt 'Second Eye' Salvage: Systemic chemotherapy +/- focal treatment. IF EYE SALVAGE FAILS: enucleation. **Post Enucleation**: If low risk histopathological features present – no further treatment If high risk histopathological features present: 6 cycles of chemotherapy
E	Any of the following: Tumour touching the lens; neovascular glaucoma; tumour in the anterior chamber; opaque media due to vitreous hemorrhage; aseptic orbital cellulitis; phthisis bulbi	Enucleation. If low risk – no further treatment. If high risk histopathological features present (as for Group D): 6 cycles of chemotherapy

Standard dose systemic chemotherapy given every 3 weeks for Intraocular Rb

Drug	**Dose: Mg/m^2**	**Rate of infusion**	**Diluent**
Vincristine	1.5 mg/m^2 body surface area (BSA D1) *(to a max. of 2mg/ dose)*	Slow Bolus	Not less than 10mls of 0.9% NaCL. **Note: RISK of EXTRAVASATION**
Etoposide	300 mg/m^2 BSA D1	4-hour infusion	0.4mg/ml in 0.9% NaCl
		Note: Rapid infusion will lead to hypotensive crisis	
Carboplatin	600 mg/m2 BSA D1	1-hour infusion	0.5mg/ml in D5% or DNS
Requirements before each cycle			
ANC > 1; Platelets > 100; Check Hb, Renal profile, LFT's and Magnesium level are adequate.			
Age	**Dose Modifications**		
< 6 mth	Give 50% of the dose for each drug		
6-12 mths	Give 75% of the dose for each drug		
12+ mths	No modification		

Retinoblastoma with Extraocular Extension

International Retinoblastoma Staging System		
Stage	**Definition**	**Standard of care**
0	Eyes salvaged with focal treatment or systemic chemotherapy	See Intraocular Protocol
I	Enucleation with no tumour residue	See Intraocular Protocol
II	Enucleation with microscopic tumour residue: • Scleral • Extrascleral extension • Tumour at optic nerve cut end	Enucleation done so histopathology informs treatment. Confirm CSF/MRI (or CT) Brain/ BMA are all normal (i.e. no brain involvement or metastases). Chemotherapy: 12 cycles for tumour at optic nerve cut end or extraocular extension; 6-12 cycles for scleral involvement. (Clinical review & CSF analysis following every 3 cycles). Then EBRT if available.
III	Regional extension	If child has ophthalmitis give 3 days of steroids. If child responds and globe appears normal consider second EUA and decide if to downstage. Confirm CSF/MRI (or CT) Brain/ BMA are all normal (i.e. no brain involvement or metastases). 6 cycles of chemotherapy then Enucleation (or exenteration) then EBRT (45 Gy) then 6 more cycles of chemotherapy (Total of 12 cycles). Do clinical review & CSF analysis following every 3 cycles.
III A	Overt orbital disease with optic nerve extension or extraocular extension	
IIIB	With regional lymph node extension	
IV	Metastatic disease	**Palliative care** May include: Oral Etoposide, limited courses of IV chemotherapy, or other treatments depending on resources at each site.
IVA	Haematogenous metastases	
IVB	CNS extension	

Systemic chemotherapy given 3 weekly for Orbital Rb

Drug	**Dose: Mg/m^2**	**Rate of infusion**	**Diluent**
Vincristine	1.5 mg/m^2 body surface area BSA D1 *(to a max. 2mg/dose)*	Slow Bolus	Not less than 10mls of 0.9% NaCL **Note: RISK of EXTRAVASATION**
Etoposide	300 mg/m^2 BSA D1	4-hour infusion	0.4mg/ml in 0.9% NaCl
		Note: Rapid infusion will lead to hypotensive crisis	
Carboplatin	600 mg/m2 BSA D1	1-hour infusion	0.5mg/ml in D5% or DNS
Requirements before each cycle			
ANC > 1; Platelets > 100; Also check Hb, Renal profile, LFT's and Magnesium level are adequate.			
Age	**Dose Modifications**		
< 6 months	Give 50% of the dose for each drug		
6-12 months	Give 75% of the dose for each drug		
12+ months	No modification		

PATHOLOGY REPORTING

After an enucleation the histopathology contributes to the staging of the Rb that determines further treatment.
The main high-risk factor (HRF) is extension of the tumour in the optic nerve to the margin of the surgical resection.
Other risk factors include:

- post laminar optic nerve invasion;
- involvement of anterior segment;
- massive invasion of choroid $\geq$ 3mm;
- invasion of sclera;
- extra scleral tumour extension.

FOLLOW-UP

Children with unilateral Rb need to be seen every 3 months up to the age of 3 years and every 6 months up to the age of 5 years and thereafter annually for life.
For children at high risk of developing new Rb tumours (*Rb1* germ line mutation, family history of disease or bilateral Rb) continue with EUAs as often as every month depending on the child's age.
Rb survivors treated with chemotherapy or EBR, require oncology clinic follow-up at 6-monthly intervals for 5 yrs. Survivors of Rb should receive individualised lifelong follow-up with counselling and treatment for late effects of disease.

GENETIC COUNSELLING

1. Retinoblastoma can be hereditary or sporadic.

2. Hereditary forms are often bilateral and multifocal.

3. Hereditary Rb has up to a 50% chance of being passed on to offspring. Siblings and first cousins are also at an increased risk.

4. Children with hereditary Rb should be frequently examined under general anesthetic in the first 3 years of life.

5. Relatives of children affected by Rb (siblings, cousins, and offspring) should be screened for Rb as soon as possible after birth.

6. Parents and other relatives of children with Rb should be given counselling from someone well trained in Rb counselling.

7. Children with Rb should be offered genetic counselling as they grow up.

8. If *Rb1* gene mutation identification is available then test the first affected person in each Rb family, and if the *Rb1* gene mutation is found offer genetic testing for all at-risk relatives.

9. If *Rb1* gene mutation identification is NOT available, then the following guidelines may be used:

Bilateral case with no Family History

- Siblings have 5% risk; screen all siblings to age 18 months
- Offspring have a 50% risk; screen all offspring to age 3 years

Unilateral case with no Family History

- Siblings have 1% risk; screen all siblings to age 12 months
- Offspring have a 5-10% risk; screen all offspring to age 18 months

COUNSELLING

For the Parent or Guardian: Counselling is a very important part of their Rb journey. By giving the parents time and a chance to talk and ask questions, it allows them to help understand the illness and treatment required. It gives the team a chance to correct any misconceptions. It gives the parents opportunities to express feelings and to help build up a rapport; trust and a relationship with the hospital staff and team involved in their child's care. By giving them the time and chance to talk, it allows them to feel listened to, which can make a huge difference to their experience and journey.

For the child: Preparation through play helps the child understand the reasons behind their treatment and gives them an opportunity, if they are old enough, to ask questions. Using play allows children to cope with anxieties and feelings and has been found to help with speeding the recovery process. Play and preparation also helps with many other things such as to helping to reduce the psychological effects of a hospital admission, and to help cope with treatment and the effects of it.

PSYCHOSOCIAL SUPPORT

Ongoing psychosocial support from a trained social worker or clinical psychologist with expertise in Rb counselling is important for all Rb children and their families.

RETINOBLASTOMA NETWORK, ICEH

This Resource manual is a product of the work of the Retinoblastoma Network, initially supported by the Commonwealth Eye Health Consortium at the International Centre for Eye Health, LSHTM, London.

The Retinoblastoma Network currently consists of a partnership of many individuals and institutions from a number of African, Asian and European countries involved in improving the management of retinoblastoma with an emphasis on low and middle income countries.