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XIX Curso de Actualización en el Diagnóstico y Tratamiento de la Tuberculosis en el Niño y el Adulto

TUBERCULOSIS

Tratamiento propuesta de diferentes esquemas

Dr. Paris Cerecer Callu
Clinica de Tb Pediatrica
Hospital General Tijuana

Hospital General de Mexico, 10 de JUNIO de 2015

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Antecedentes

- La mayoría de los casos ocurren en niños pequeños **(<5 años de edad)**
- La mayor parte de la enfermedad se produce dentro de 2 años después de la exposición / infección (mas **< 1 año)**
- **Factores de riesgo** para infección y para enfermedad
- La mayoría de los casos de TB en niños es **pulmonar BK/cultivo negativos (o no disponible)**
- Enfermedad pulmonar dependiendo de la edad, y BK + (tipo adulto) en los adolescentes

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Antecedentes

- Principalmente Resistencia **Primaria (transmitida)**: importancia de la evaluación de los contactos de casos de TB-MDR.
- Se desarrolla mas frecuentemente **<1 año de la infección**
- Es más difícil de adquirir debido a la naturaleza de la enfermedad **paucibacilar** primaria en los niños (posible TB pulmonar cavitaria)
- Buena fuente para la **vigilancia de la TB Resistencia**. (refleja la transmisión de cepas resistentes en la comunidad)
- **No hay diferencia clínica o radiológica** entre TB sensible y TB resistencia.
- Las **reacciones adversas a las drogas son muy poco frecuentes en los ninos**, incluso con SLD.
- Resultados positivos en niños tratados por TB-MDR

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Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study

Peter J Dodd, Elizabeth Gardiner, Renia Coghlan, James A Seddon

Summary

Background Confirmation of a diagnosis of tuberculosis in children (aged <15 years) is challenging; under-reporting can result even when children do present to health services. Direct incidence estimates are unavailable, and WHO estimates build on paediatric notifications, with adjustment for incomplete surveillance by the same factor as adult notifications. We aimed to estimate the incidence of infection and disease in children, the prevalence of infection, and household exposure in the 22 countries with a high burden of the disease.

Methods Within a mechanistic mathematical model, we combined estimates of adult tuberculosis prevalence in 2010, with aspects of the natural history of paediatric tuberculosis. In a household model, we estimated household exposure and infection. We accounted for the effects of age, BCG vaccination, and HIV infection. Additionally, we tested sensitivity to key structural assumptions by repeating all analyses without variation in BCG efficacy by latitude.

Findings The median number of children estimated to be sharing a household with an individual with infectious tuberculosis in 2010 was 15 319 701 (IQR 13 766 297–17 061 821). In 2010, the median number of *Mycobacterium tuberculosis* infections in children was 7 591 759 (5 800 053–9 969 780), and 650 977 children (424 871–983 118) developed disease. Cumulative exposure meant that the median number of children with latent infection in 2010 was 53 234 854 (41 111 669–68 959 804). The model suggests that 35% (23–54) of paediatric cases of tuberculosis in the 15 countries reporting notifications by age in 2010 were detected. India is predicted to account for 27% (22–33) of the total burden of paediatric tuberculosis in the 22 countries. The predicted proportion of tuberculosis burden in children for each country correlated with incidence, varying between 4% and 21%.

Interpretation Our model has shown that the incidence of paediatric tuberculosis is higher than the number of notifications, particularly in young children. Estimates of current household exposure and cumulative infection suggest an enormous opportunity for preventive treatment.

Funding UNITAID and the US Agency for International Development.

Lancet GlobHealth 2014; 2:453–59

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See Comment page e432

See Online for an audio interview with James Seddo

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Neonatal Outcome of Children Born to Women with Tuberculosis

Background. As the incidence of tuberculosis (TB) has increased worldwide, it is expected that pregnant women will acquire this infection more frequently. *M.TB* infection during pregnancy may represent a risk for maternal and neonatal complications.

Methods. We studied the perinatal events of 35 consecutive pregnancies complicated by TB from **March 1990 to June 1998**; 105 apparently healthy pregnant women were included as controls, matched in age, gestational age upon arrival at the Institute, and socioeconomic status. Frequency and type of neonatal complications were recorded..

Results. Seventeen (48.5%) TB mothers had a pulmonary infection and 18 (51.5%), an extrapulmonar localization of TB. The **neonatal morbidity rate in children born to women with TB was 23% against 3.8%** of the children of the control cohort (p <0.05). Average weight of newborn infants of tuberculous mothers was 2,859 ± 78.5 g, while average weight at birth of control neonates was 3,099 ± 484 g (p = 0.03). Newborns of women with TB had a higher risk of **prematurity (RR 2.1;** 95% CI 1–4.3), **perinatal death (RR 3.1**; 95% CI 1.6–6), and **weight at birth less than 2,500 g (RR 2.2**; 95% CI 1.1–4.9). **Pulmonary localization of TB and late start of the treatment in the mothers increase the risk of perinatal death and neonatal morbidity.**

Children born to women with TB have an increased risk of morbidity and mortality in the neonatal period.

Figueroa-Damián R, Arredondo-Garciá JL ***Archives of Medical Research Vol.32, Issue 1, 2001***

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Tuberculosis in Children Exposed to MDR-TB

- Retrospective cohort study of child and adult household contacts of patients treated for MDR-TB in Lima, **Peru**, in **1996** to **2003**.
- Among **1299** child contacts, 67 were treated for TB TB prevalence was **1771 per 100,000 children**.
- In **4362** child-years of follow-up, TB incidence rates per 100,000 child-years were:
- **2079 in year 1**
- **315** in year 2
- **634** in year 3
- **530** in year 4.
- **Seven (87.5%) of 8 children tested had MDR-TB**.
- Child contacts had TB disease rates approximately **30 times higher** than children in the general population.
- Children were at high risk for TB disease when the index case started MDR-TB treatment and during the following year.

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Tuberculosis in children

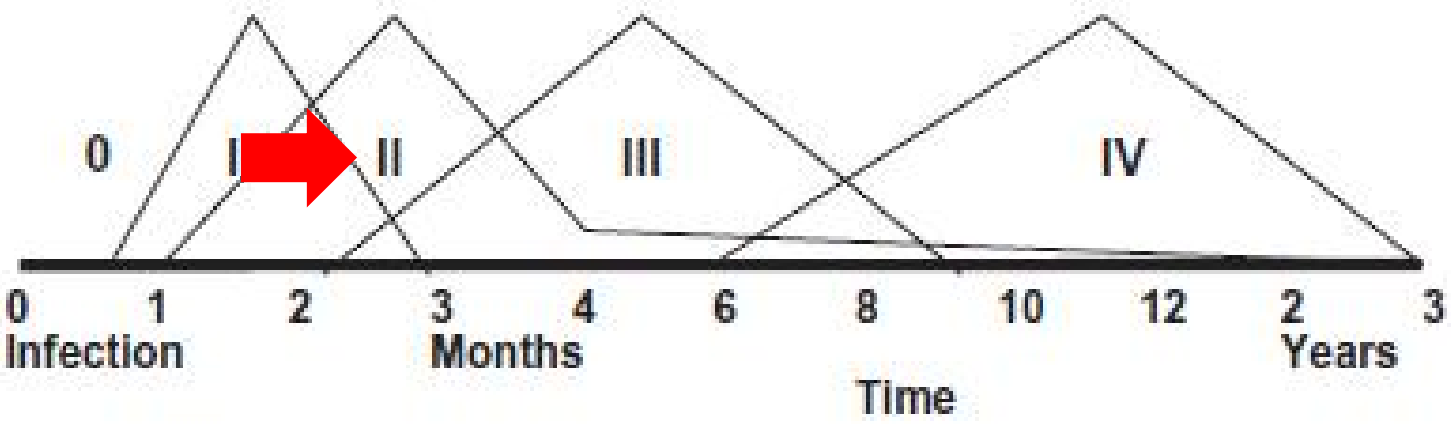

Fig. 1 Schematic timeline following primary pulmonary infection with *Mycobacterium tuberculosis*.
Adapted timeline of tuberculosis,[13] first described by Wallgren. 0, incubation; I, tuberculin skin test conversion; II, Ghon focus and/or disseminated (miliary) disease; III, lymph node disease (<5 years of age)/pleural effusion (>5 years of age); IV, adult-type disease (>10 years of age).

Ben J Marais Journal of Paediatrics and Child Health **50** (2014) 759–767

Table 2. Risk of Progression from Tuberculosis (TB) Infection to Disease

Age at Primary Infection (yr)	No Disease (%)	Pulmonary Disease (%)	Miliary or Central Nervous System TB (%)
<1	50	30 to 40	10 to 20
1 to 2	75 to 80	10 to 20	2.5
2 to 5	95	5	0.5
5 to 10	98	2	<0.5
>10	80 to 90	10 to 20	<0.5

Adapted from Marais, et al. Childhood pulmonary tuberculosis: old wisdom and new challenges. *Am J Resp Crit Care Med*. 2006;173:1078–1090.

Pediatric Tuberculosis
Andrea T. Cruz and Jeffrey R. Starke
Pediatr. Rev. 2010;31;13-26
DOI: 10.1542/pir.31-1-13

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Resultados

- Antecedentes de contacto o convivencia con persona con tuberculosis activa

Contacto	Frecuencia
Madre	23 (22.55%)
Padre	12(11.76%)
Hermanos	11 (10.78%)
Tío (a)	18 (17.65%)

- Contacto Intradomiciliario en un **47.57%** (49)

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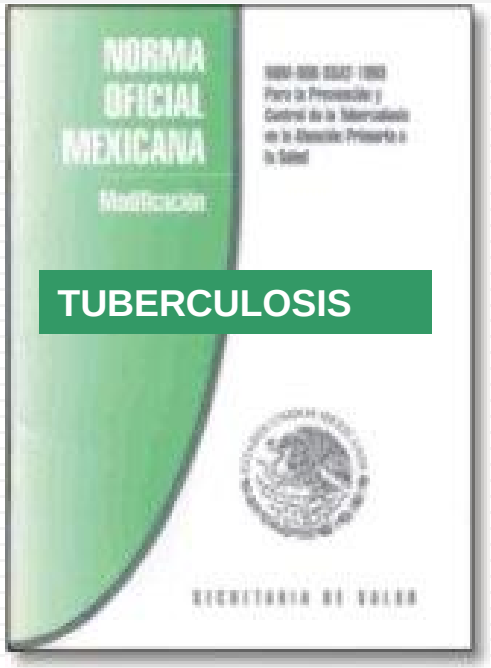

Guía práctica para la
ATENCIÓN de la **TUBERCULOSIS**
en **NIÑOS, NIÑAS** y **ADOLESCENTES**

Guidance for national tuberculosis programmes on the management of tuberculosis in children

Second edition

World Health Organization

Cuadro 9.2 Tratamiento en niños con tuberculosis pulmonar y extra pulmonar

Localización	Fase inicial Fármacos (meses)	Fase de sostén Fármacos (meses)	Duración
Pulmonar	HRZE (2)	HR (4)	6 meses
Pulmonar + VIH	HRZE (2)	HR (7)	9 meses
Extrapulmonar:			
Ganglionar	HRZE (2)	HR (7)	9 meses
Genitourinaria	HRZE (2)	HR (10)	9 - 12 meses
Meníngea	HRZE (2)	HR (10)	9 - 12 meses
Miliar o sistémica	HRZE (2)	HR (10)	12 meses
Ósea y articular	HRZE (2)	HR (10)	9 - 12 meses
Pleural	HRZE (3*)	HR (9)	9 - 12 meses
Pericárdica	HRZE (3*)	HR (9)	9 - 12 meses
Peritoneal	HRZE (3*)	HR (9)	9 - 12 meses
Congénita	HRZS o E (2)	HR (7)	9 meses
Cutánea, ótica y ocular	HRZE (2)	HR (10)	9 - 12 meses

(*) Por letalidad.

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Example of a weight band table when using the most widely available FDC

Weight bands	Numbers of tablets		
	Intensive Phase		Continuation Phase
	RHZ	E	RH
	60/30/150	100	60/30
4-6kg	1	1	1
7-10kg	2	2	2
11-14kg	3	2	3
15-19 kg	4	3	4
20-24kg	5	4	5
25 kg+	Go to adult dosages and preparations		

Doses revisadas (WHO 2010) para ninos hasta 25 kgs:

Rifampicin 15 (10-20) mg/kg/day
Isoniazid 10 (7-15) mg/kg/day
Pyrazinamide 35 (30-40) mg/kg/day
Ethambutol 20 (15-25) mg/kg/day

Es algo difficil implementarlas con las FDC disponibles de momento

Example of a weight band table when using the "new" FDC being developed

Weight bands	Numbers of tablets		
	Intensive Phase		Continuation Phase
	RHZ	E	RH
	75/50/150	100	75/50
4-7kg	1	1	1
8-11kg	2	2	2
12-15kg	3	3	3
16-24 kg	4	4	4
25 kg+	Go to adult dosages and preparations		

International Union Against Tuberculosis and Lung Disease

World Health Organization

Toward Zero TB Death –WHO-The Union Childhood TB Training Modules (2014)

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Problemas

- Presentaciones pediatricas — **DOSIS FRACCIONADAS PRESENTACION DE ADULTOS**
- Dosis intermitente vs diaria — **USO DE DOSIS ALTAS RECOMENDACIONES?**
- Dosis fraccionadas — **BIODISPONIBILIDAD**
- Resistencias — **TRATAMIENTO DIAGNOSTICO OPORTUNO ESTUDIO DE CONTACTO TX PREVENTIVO?**
- Nuevos medicamentos — **RECOMENDACIONES?**

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Tratamiento de tuberculosis

Dosis intermitente vs diario

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Tuberculosis in childhood: a systematic review of national and international guidelines

Elettra Berti, Luisa Galli, Elisabetta Venturini, Maurizio de Martini, Elena Chiappini*

- **Background**: Paediatric tuberculosis (TB) represents a major public health concern worldwide. About 1 million children aged less than 15 years develop TB each year, contributing to 3-25% of the total TB caseload.

- **Methods**: A literature search of the Pubmed database was performed from January 2000 to August 2013, using the terms “tuberculosis” and “children”. The search was limited to guidelines and consensus conferences, human species and full text availability, with no language restrictions.

Berti et al. BMC Infectious Diseases 2014, 14(Suppl 1):S3

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Tuberculosis in childhood: a systematic review of national and international guidelines

Elettra Berti, Luisa Galli, Elisabetta Venturini, Maurizio de Martini, Elena Chiappini*

- **Results**:
  Twenty-seven national and international guidelines are identified. Several discrepancies on the diagnosis workup of TB are underlined.
- A general consensus exists, otherwise, on TB treatment and only minor discrepancies are evidenced, **such as the recommendations on daily or intermittent treatment regimens**.
- **Conclusions**
  Moreover, future studies should analyze the **drug metabolism and the efficacy of intermittent** dosing regimens in childhood, as well as new treatment regimens in order to improve the therapy compliance.

Berti et al. BMC Infectious Diseases 2014, 14(Suppl 1):S3

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Conclusiones

- Las recomendaciones del tratamiento de tuberculosis son homogeneas y solo una discrepancia menor es evidente en esta revision.

- **Punto principal de diferencias** es representado por los esquemas recomendados de tratamiento diario e intermitente(dos o tres veces por semana), que difiere en las diferentes guias clinicas.

- Necesaria evidencia del **metabolismo y eficacia de tratamiento intermitente** en niños.

- Necesarios realizacion de mas estudios para esclarecer este tema

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Consensus Statement on Childhood Tuberculosis

Working Group on Tuberculosis, Indian Academy of Pediatrics (IAP)

- This forms the basis of intermittent therapy.
- While RCTs in children using thrice weekly regime are awaited,
- RCTs from adults as well as observational studies including programmatic data in all age groups have shown that intermittent thrice a week therapy with higher dose is as effective as daily therapy with conventional dose and is an effective alternative
- However, intermittent therapy is not safe when self-administered, as there is no margin for any error in taking medications.
- The directly observed therapy under DOTS takes care of the adherence issues and therefore uses thrice a week intermittent therapy.

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Intermittent versus daily therapy for treating tuberculosis in children (Review)

Bose A, Kalita S, Rose W, Tharyan P

THE COCHRANE COLLABORATION®

Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* .2014, Issue 1

- TB drug regimens are standardised globally, and include a combination of drugs given daily for six months.

- More than **95%of children** are cured with this treatment. Giving anti-TB drugs **twice- or thrice-weekly** is more convenient to supervise than daily treatment but **may not be as effective** as daily treatment in curing children of TB.

- The **World Health Organization** currently recommends only **daily** treatments, but some national governments recommend twice- or thrice-weekly doses for children with TB.

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O B J E C T I V E S

To compare the efficacy and safety of intermittent, short-course anti-TB treatment regimens (twice- or thrice-weekly) with daily short-course anti-TB treatment regimens in treating childhood TB.

M E T H O D S

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and quasi-RCTs.

Types of participants

Inclusion criteria

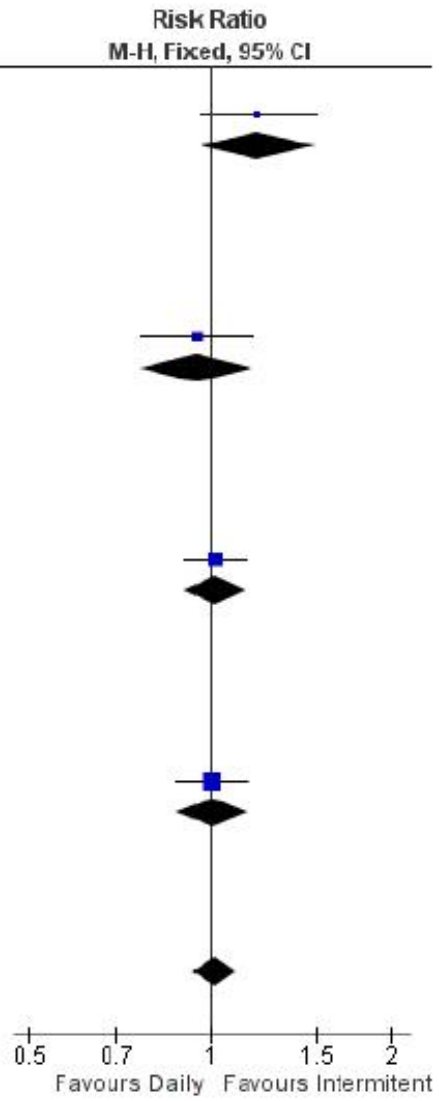
Children aged 15 years or younger, diagnosed as having TB in category 1, 2, or 3 according to the WHO diagnostic categories

Intermittent short-course anti-TB regimens compared to daily anti-TB regimens for treating TB in children with TB

Patient or population: Children with TB[1]
Intervention: Intermittent short-course twice-weekly anti-TB regimens (six to nine months)
Comparison: Daily anti-TB regimens (six to 12 months)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Daily anti-TB regimens	Intermittent short-course anti-TB regimens			
Cure Follow-up: 12 to 30 months	**836 per 1000**	**844 per 1000** (786 to 920)	**RR 1.01** (0.94 to 1.1)	465 (4 trials)	⊕⊕⊕⊕ **very low** [2,3,4,5]
Death from any cause	**8 per 1000**	**13 per 1000** (2 to 75)	**RR 1.52** (0.26 to 8.96)	213 (2 trials)[6]	⊕⊕⊕⊕ **very low**[3,7,8,9]
Relapse Follow-up: 12 to 30 months	**0 per 1000**	**0 per 1000** (0 to 0)	**RR 3.68** (0.15 to 89.33)	214 (1 trial)[10]	⊕⊕⊕⊕ **very low** [11,12,13]
Adherence to treatment	**840 per 1000**	**874 per 1000** (815 to 932)	**RR 1.04** (0.97, 1.11)	458 (4 trials)	⊕⊕⊕⊕ **very low**[3,4,14,15]
Treatment-limiting adverse events	**15 per 1000**	**6 per 1000** (1 to 39)	**RR 0.4** (0.06 to 2.6)	441 (4 trials)	⊕⊕⊕⊕ **very low**[2,3,4,16]

Figure 4. Forest plot: 1. Intermittent versus daily regimens, Outcome 1.1 Cure (as defined by clinical and radiological improvement): Intention to treat.



Study or Subgroup	Intermittent Events	Total	Daily Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Intermittent (daily 2 weeks, twice-weekly 8.5 months) versus daily treatment (12 months)						
Kansoy (Turkey) 1996 (1)	18	18	15	18	8.0%	1.19 [0.95, 1.50]
Subtotal (95% CI)		**18**		**18**	**8.0%**	**1.19 [0.95, 1.50]**
Total events	18		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.53 (P = 0.13)						
1.1.2 Intermittent (twice-weekly 6 months) versus daily treatment (daily 2 months, intermittent 4 months)						
Kumar (India) 1990 (2)	31	39	31	37	16.5%	0.95 [0.77, 1.17]
Subtotal (95% CI)		**39**		**37**	**16.5%**	**0.95 [0.77, 1.17]**
Total events	31		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
1.1.3 Intermittent (thrice-weekly 2 months, twice-weekly 4 months) versus daily treatment (9 months)						
Ramachandran (India) 1998 (3)	63	70	62	70	32.1%	1.02 [0.91, 1.14]
Subtotal (95% CI)		**70**		**70**	**32.1%**	**1.02 [0.91, 1.14]**
Total events	63		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.78)						
1.1.4 Intermittent (twice-weekly 6 months) versus daily treatment (6 months)						
Te Water Naude (South Africa) 2000 (4)	76	95	94	118	43.4%	1.00 [0.88, 1.15]
Subtotal (95% CI)		**95**		**118**	**43.4%**	**1.00 [0.88, 1.15]**
Total events	76		94			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
Total (95% CI)		**222**		**243**	**100.0%**	**1.01 [0.94, 1.10]**
Total events	188		202			
Heterogeneity: Chi^2 = 2.39, df = 3 (P = 0.50); I^2 = 0%						
Test for overall effect: Z = 0.34 (P = 0.73)						
Test for subgroup differences: Chi^2 = 2.35, df = 3 (P = 0.50), I^2 = 0%						

(1) Radiological resolution at 6 months

(2) Marked or moderate clinical or radiological improvement in the first 3 months.

(3) Radiological resolution at end of treatment and excluding those requiring additional treatment

(4) Clinical and radiological criteria- extrapolated from composite treatment response scores in those assessed for clinical response at 6 months

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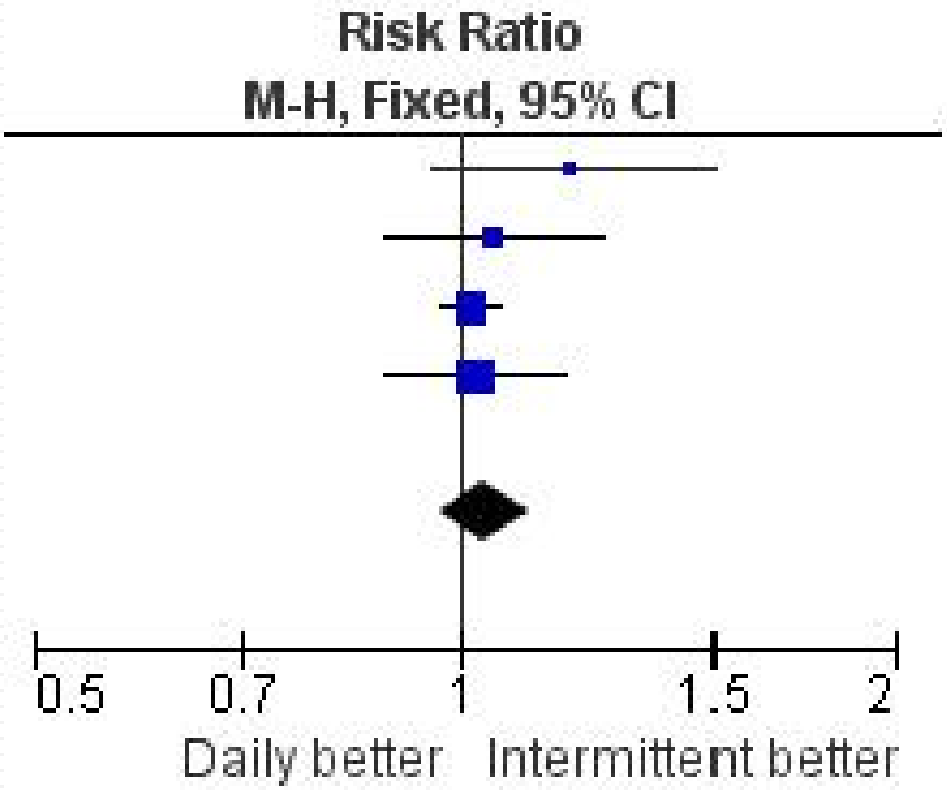
Forest plot: 1. Intermittent versus daily regimens, Outcome 1.5 Adherence to treatment.



Study or Subgroup	Intermittent Events	Total	Daily Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kansoy (Turkey) 1996 (1)	18	18	15	18	8.0%	1.19 [0.95, 1.50]
Kumar (India) 1990 (2)	33	37	33	39	16.6%	1.05 [0.89, 1.26]
Ramachandran (India) 1998 (3)	69	70	68	70	35.2%	1.01 [0.97, 1.07]
Te Water Naude (South Africa) 2000 (4)	70	89	90	117	40.2%	1.02 [0.88, 1.18]
Total (95% CI)		**214**		**244**	**100.0%**	**1.04 [0.97, 1.11]**

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Conclusiones

- There is **insufficient evidence** to support or refute the use of intermittent (twice-weekly or thrice-weekly) short-course treatment regimens over daily short-course treatment in children with TB.

- Intermittent and daily regimens may have **similar effects** in children with TB, but further research is required to confirm the observations in this review.

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Intermittent or Daily Short Course Chemotherapy for Tuberculosis in Children: *Meta-analysis of Randomized Controlled Trials*

P RAMESH MENON, R LODHA, S SIVANANDAN AND SK KABRA

Objective: To compare the effectiveness of **intermittent with daily chemotherapy** (both containing rifampicin) in childhood tuberculosis (age ≤16yrs) in achieving cure/ significant improvement.

Design: Systematic Review and Meta-analysis.

Methods: MEDLINE and the Cochrane Library were searched for randomized trials of antitubercular regimens containing rifampicin, in children 16 yrs or less with tuberculosis. Two reviewers independently assessed trial eligibility and quality. Data from full articles of selected studies were independently extracted by two authors and analyzed. The odds ratio was obtained for the pooled data in two groups (intermittent and daily therapy).

Outcome variables: Cure/significant improvement, relapse rate and adverse events.

INDIAN PEDIATRICS VOLUME 47__JANUARY 17, 2010

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Intermittent or Daily Short Course Chemotherapy for Tuberculosis in Children: *Meta-analysis of Randomized Controlled Trials*

P RAMESH MENON, R LODHA, S SIVANANDAN AND SK KABRA

Results: Four randomized controlled trials comparing twice weekly and daily therapy including 466 children (pulmonary 439; extrapulmonary 27) met the inclusion criteria. Baseline data were comparable.
Per protocol analysis showed that children receiving **intermittent** regimen were **less likely to be cured** than those receiving daily therapy **(OR 0.27; 95% CI: 0.14, 0.51)**.
The results of intention to treat analysis suggest similar trend towards lower cure rates with twice weekly regimen (OR 0.66; 95% CI: 0.23-1.84).

Conclusion: Twice weekly intermittent short course therapy is less likely to cure tuberculosis in children as compared to daily therapy.
There is a need for better quality randomized controlled trials for assessing efficacy of alternate schedule for intermittent therapy for childhood tuberculosis.

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Presentación combinadas

Tabletas completas vs fraccionadas

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Isoniazid, Pyrazinamide and Rifampicin Content Variation in Split Fixed-Dose Combination Tablets

- **Setting**: In most developing countries, **paediatric tuberculosis is treated with split tablets leading to potential inaccuracy in the dose delivery and drug exposure.** There is no data on the quality of first-line drugs content in split fixed-dose combination tablets.

- **Objective**: To determine Isoniazid, Pyrazinamide and Rifampicin content uniformity in split FDC tablets used in the treatment of childhood tuberculosis.

- **Design**: Drug contents of 15 whole tablets, 30 half tablets and 36 third tablets were analysed by high performance liquid chromatography. The content uniformity was assessed by comparing drug content measured in split portions with their expected amounts and the quality of split portions was assessed applying qualitative specifications for whole tablets.

- **Results**: All whole tablets measurements fell into the USP proxy for the three drugs. But a significant number of half and third portions was found outside the tolerated variation range and the split formulation failed the requirements for content uniformity. To correct for the inaccuracy of splitting the tablets into equal portions, a weight-adjustment strategy was used but this did not improve the findings.

PLOS ONE July 2014 | Volume 9 | Issue 7 | e102047

	Drug	Mean variation %	%CV	Variation range (%)	Number outside USP proxy
Whole (n = 10)	INH	101	5.19	97.6–105	0
	PZA	95.4	2.43	93.8–97.1	0
	RIF	93.4	3.94	90.7–96.0	0
Halves (n = 30)	INH	105	9.10	88.1—123	5 (16.7%)
	PZA	98.6	7.72	88.3–118	1 (3.33%)
	RIF	87.1	10.7	73.4–109	14 (46.7%)
Third (n = 36)	INH	107	17.1	67.8–137	18 (50.0%)
	PZA	101	15.0	72.6–138	12 (33.3%)
	RIF	88.0	16.7	54.3–112	13 (36.1%)

USP proxy defined as 85–115% of the expected content.

doi:10.1371/journal.pone.0102047.t003

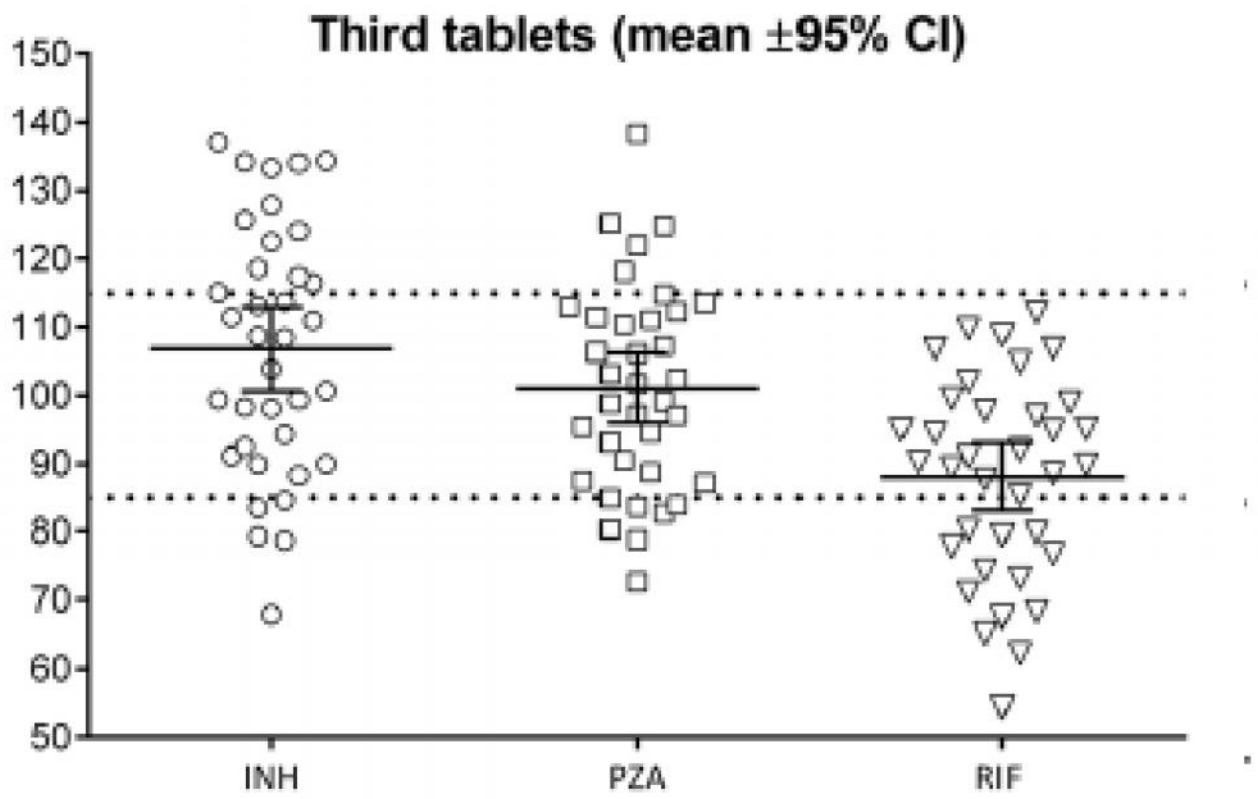
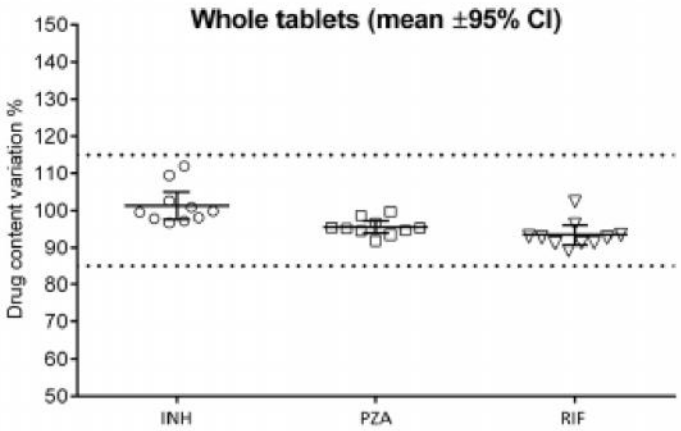
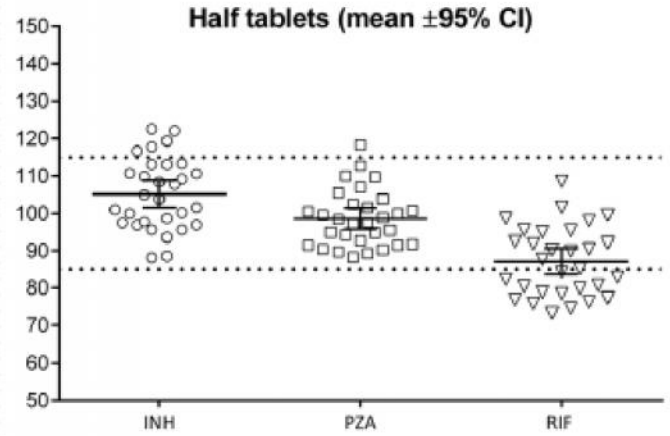
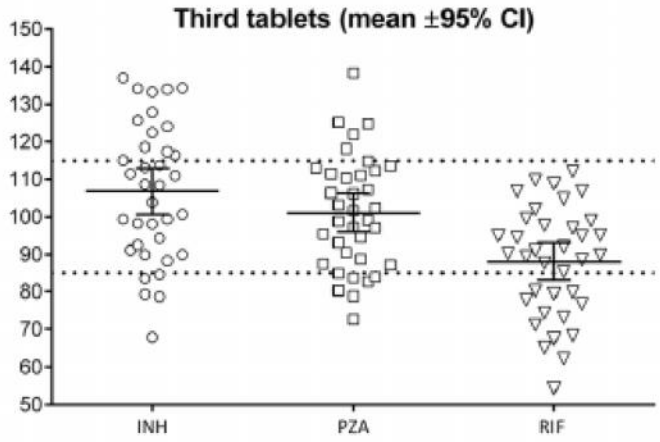


Figure 1. Labelled content variation in whole, half and third tablets. Results are presented as individual values and with mean and the 95% confidence interval of the mean for each drug and dataset. The dashed lines represent the 85–115% USP proxy.
doi:10.1371/journal.pone.0102047.g001







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doi:10.1371/journal.pone.0102047.g001

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Conclusiones

- En **tabletas fraccionadas** el contenido de los 3 farmacos es ***no uniforme*** y excede las recomendaciones.

- **Presentaciones pediatricas** para el tratamiento de tuberculosis

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Tratamiento de tuberculosis

Resistencia al medicamento

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Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis.

- Systematic review and meta-analysis reviewed treatment outcomes for children with MDR-TB.
- Eight studies, which reported outcomes on **315** patients, contributed to the database.
- Average duration of treatment ranged from 6 months to 34 ms.
- The pooled estimate for t**reatment success (defined as a composite of cure and completion) was 81.7%** with death in 5.9%, and default in 6.2% of patients.
- Adverse reactions occurred in **39.1%** of the children, the most common of which were nausea and vomiting followed by hearing loss, psychiatric effects and hypothyroidism.

Resultados positivos en niños tratados por TB-MDR

Ettehad D, Schaaf HS, Seddon JA, Cooke GS, Ford N. Lancet Infect Dis 2012;12:449-56.

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Genexpert util en el diagnostico de la TB infantil

-Mayor sensibilidad que el esputo **(también en VIH+ y BK-)**, cercano al cultivo

* Evita perder enfermos
* Uso en muestras extrapulmonares

-Permite además

* Diferenciar entre M.TB y otras
* Resistencia a RIF

- Rápido (2 horas)
- (Mas caro del BK)

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Line Probe Assay (LPA/Genotype/HAIN) para Drogas anti-TB de Segunda Línea

Table 1. Advantages and disadvantages of conventional culture and drug susceptibility testing compared with line probe assay (GenoType MTBDR*plus* version 2) and Xpert MTB/RIF

	Conventional culture and DST (automated liquid culture method)	LPA (GenoType MTBDR*plus*)	Xpert MTB/RIF (Xpert)
Laboratory infrastructure	High-level infrastructure and staff	High level infrastructure and staff	Basic infrastructure and staff
Risk of contamination	Moderate to low	Moderate to low	Low
Cost per sample [10]	MGIT culture only – similar to Xpert; when combined with additional phenotypic DST: MGIT > twice Xpert cost	More than Xpert	Used as comparison[a]
Time to DST result	2–6 weeks (depending on organism load)	Directly on specimen within hours; with cultured isolates dependent on culture time	Within 2 h
DST results	First and second-line DST on isolates	Provides both INH and RIF DST results as well as mutation conferring INH resistance[b] If mycobacteria isolated, further DST can be done. LPA for second-line DST available but not as reliable as INH/RIF DST	Only provides DST result for RIF. No further DST possible on same specimen
Sensitivity [11]	Gold standard for culture	100% in smear-positive specimens; 58–60% in smear-negative, culture-positive specimens	100% in smear-positive specimens; 58–60% in smear-negative, culture-positive specimens
Type of specimen	Any specimen obtained	Any specimen obtained	Mainly sputum; recently used with several other specimens, e.g. gastric aspirates, fine needle aspiration, other body fluids and even stool (with special preparation) [12–15]

OPEN ACCESS Freely available online

PLOS ONE

Enhancing TB Case Detection: Experience in Offering Upfront Xpert MTB/RIF Testing to Pediatric Presumptive TB and DR TB Cases for Early Rapid Diagnosis of Drug Sensitive and Drug Resistant TB

August 2014 | Volume 9 | Issue 8 | e105346

Neeraj Raizada[1*], Kuldeep Singh Sachdeva[2], Sreenivas Achuthan Nair[3], Shubhangi Kulsange[1], Radhey

- 4,600 pediatric presumptive pulmonary TB → 590 PTB diagnosed.
- Overall 10.4% (CI 9.5–11.2) of presumptive PTB cases had positive results by Xpert MTB/RIF, compared with 4.8% (CI 4.2–5.4) who had smear-positive results.
- Upfront Xpert MTB/RIF testing of presumptive PTB and presumptive DR-TB cases resulted in diagnosis of 79 and 12 rifampicin resistance cases, respectively.
- PPV for rifampicin resistance detection was high (98%, CI 90.1–99.9), with no statistically significant variation with respect to past history of treatment.
- Conclusion: …two-fold increase in bacteriologically-confirmed PTB, and increased detection of rifampicin-resistant TB cases under routine operational conditions across India.

-These results suggest that routine Xpert MTB/RIF testing is a promising

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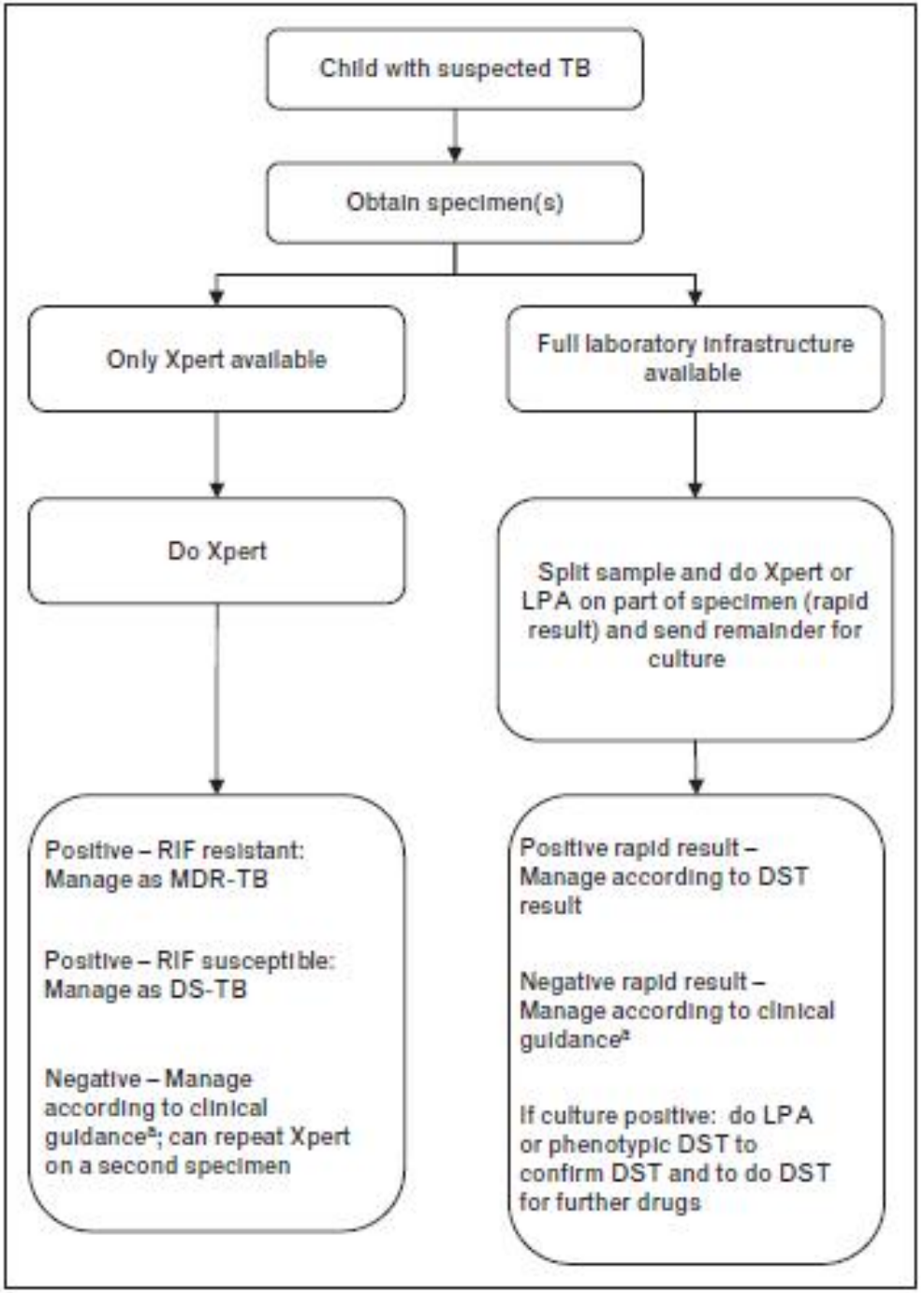
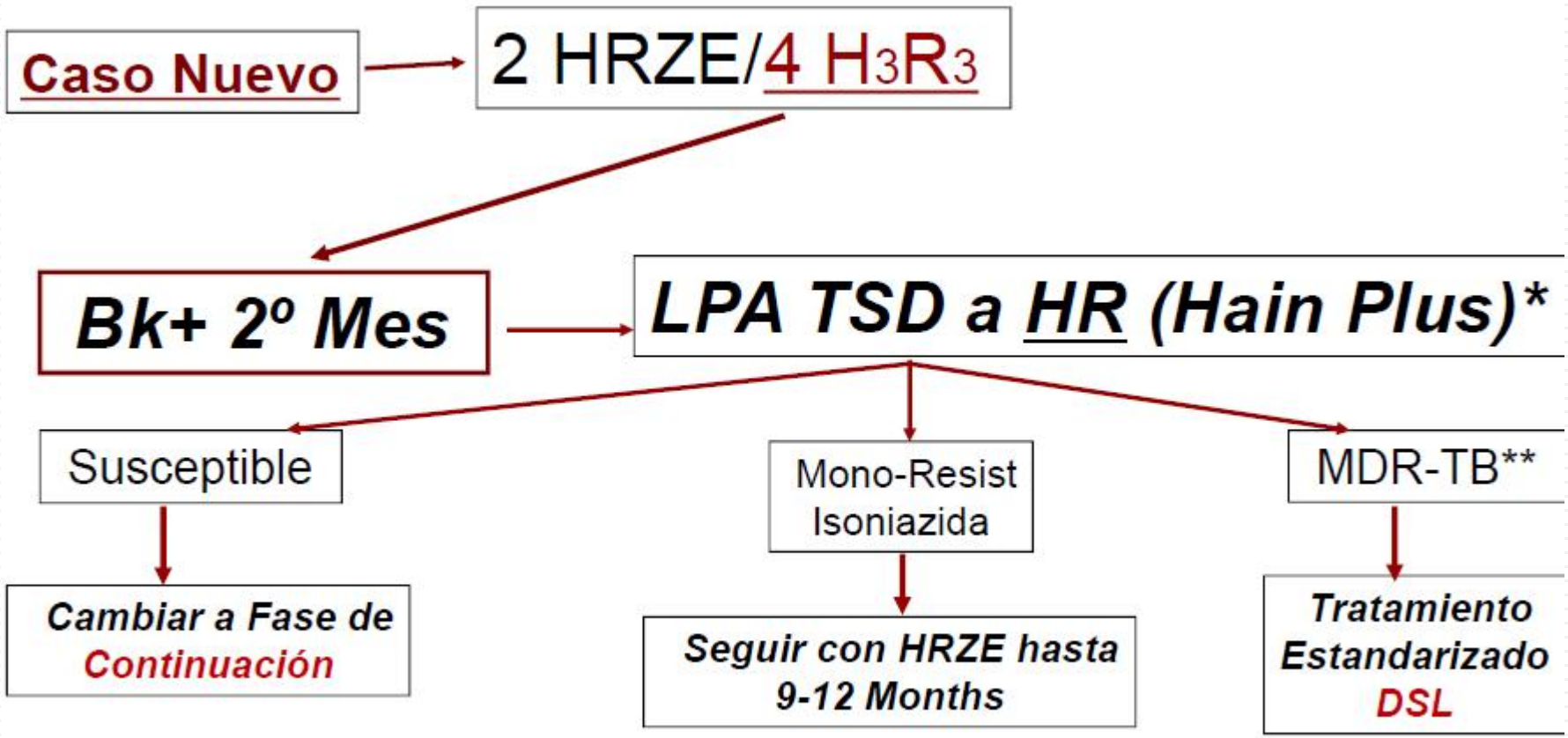
Managing multidrug-resistant tuberculosis in children: review of recent developments

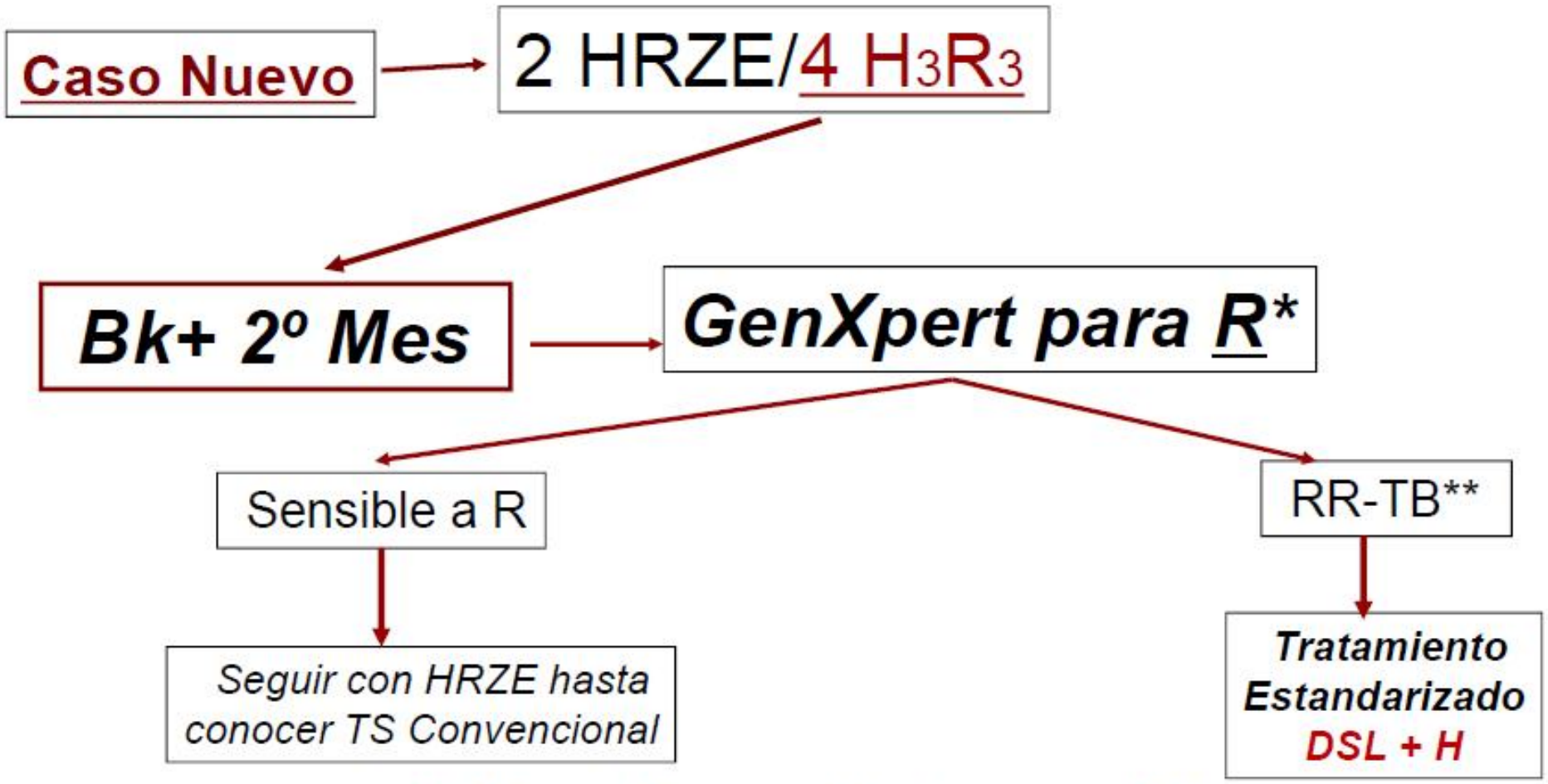
H. Simon Schaaf[a], Anthony J. Garcia-Prats[a], Anneke C. Hesseling[a], and James A. Seddon[a,b]



Managing multidrug-resistant tuberculosis in children Volume 27 Number 3 June 2014



* Realizar simultáneamente T.S. Convencional a H+R
** Realizar TS a Fq+Invect..



* Realizar simultáneamente T.S. Convencional a H+R
** Realizar TS a Fq+Inyect..

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TABLE IV MANAGING PATIENTS WITH INTERRUPTIONS IN TREATMENT

Duration of therapy	Duration of interruption	Decision
Upto 4 weeks	<2 weeks	Resume original regime
	> 2 weeks	Reassess and start treatment again
4-8 weeks	<2 weeks	Resume original regime
	2-8 weeks	Extend intensive phase by 1 month more
	>8 weeks	Category II if diagnosis is still TB
> 8 weeks	<2 weeks	Resume original regime
	>2 weeks	Review activity • continue same treatment if no active disease • Category II therapy for active diseases

INDIAN PEDIATRICS VOLUME 47__JANUARY 17, 2010

Cuadro 9.7 Esquemas recomendados en niños con VIH/SIDA y posible resistencia a fármacos

Resistencia a:	Esquemas		Observaciones
	Fase inicial	Fase de sostén	Se debe iniciar tratamiento antituberculosis lo antes posible y los TARAA de dos a cuatro semanas después.
Ninguna	H,R,Z,E o S (2 meses) o H,Rb,Z,E o S (2 meses)	H,R (4 meses) H,R (7 meses)* o H + Rb (4 meses)	La rifampicina puede ser utilizada cuando el esquema ARV incluya efavirenz y 2 ITRAN, ritonavir y uno o más
Isoniazida	R,Z,E,S (3 meses)** o Rb,Z,E,S (3 meses)**	R,Z,E (9 meses)** o Rb,Z,E (9 meses)**	ITRNN o se use la combinación 2 IP (ritonavir y saquinavir). La dosis de rifabutina se disminuye en pacientes que toman ritonavir (con o sin saquinavir) o se incrementa la dosis cuando reciben efavirenz.
Rifampicina	H,Z,S,E (3 meses)**	H,Z,E (9 meses)**	Pueden utilizarse todos los fármacos ARV.
Isoniazida y rifampicina	Se maneja igual que en los pacientes sin VIH.		

Isoniazida: actúa en poblaciones bacilares con crecimiento rápido.

Rifampicina: actúa en poblaciones bacilares con crecimiento intermitente.

Pirazinamida: actúa en poblaciones bacilares con crecimiento lento y medio ácido.

Etambutol: actúa en todas las poblaciones.

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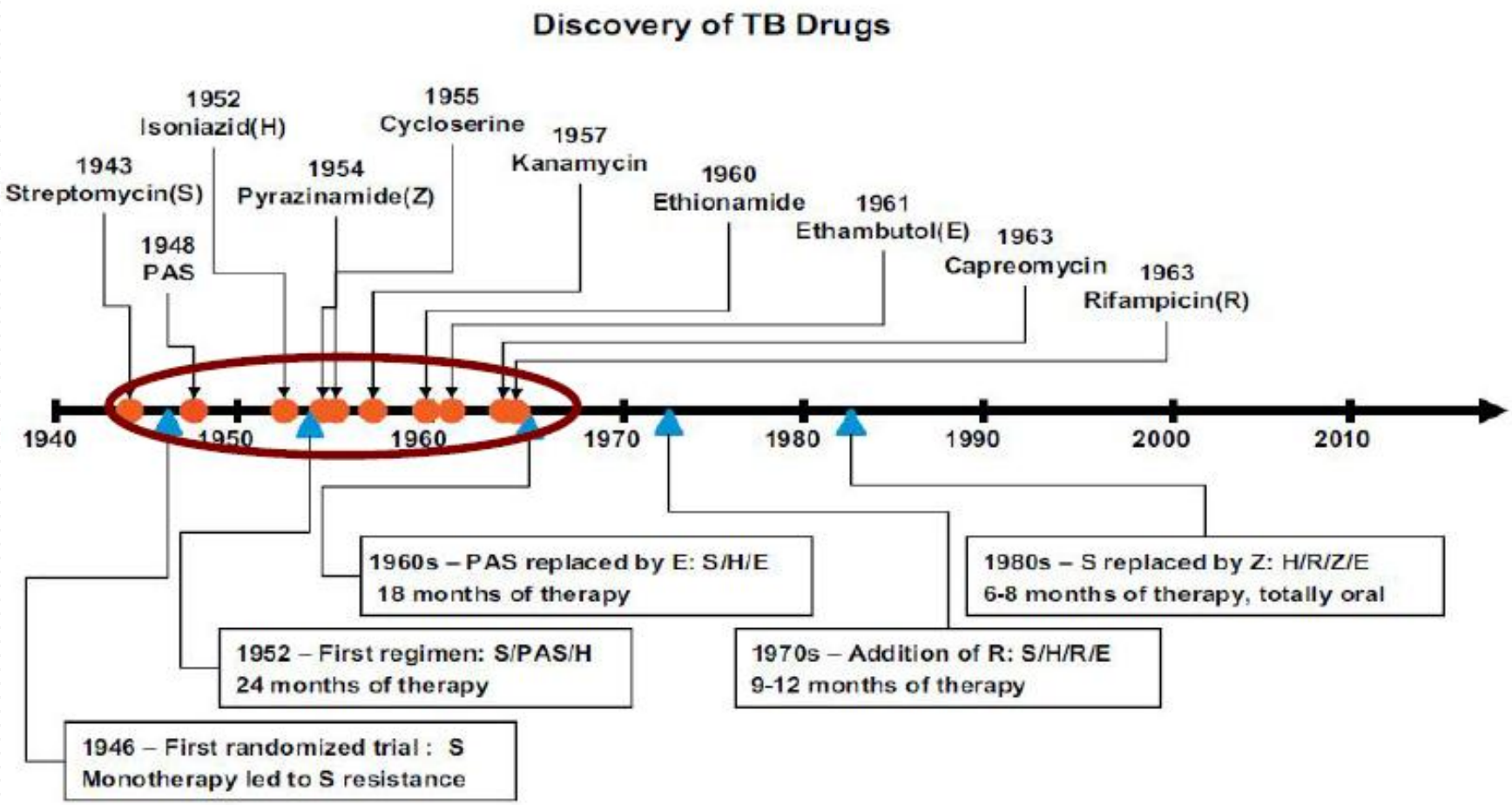
Tratamiento de tuberculosis

¿Nuevos medicamentos?



Ma Z, Lienhard C. Clin Chest Med 30 (2009) 755–768

Table 2. Re-purposed and new antituberculosis drugs under investigation for the management of drug-resistant tuberculosis in children [69]

Drug class	Drug target	Compound	Stage of adult investigations	Stage of paediatric investigations and use
Fluoroquinolones	DNA gyrase	Gatifloxacin	Phase III	Not used
		Moxifloxacin	Phase III	Used in MDR tuberculosis. Not licensed
Riminophenazine dye [70]	Intracellular redox cycling and membrane destabilization	Clofazimine	Phase II & III	Used in XDR tuberculosis (off-label)
Diarylquinoline	ATP synthase	Bedaquiline (TMC-207)	Phase III. Provisional FDA registration for MDR tuberculosis	Dose-finding and safety studies planned in MDR tuberculosis (HIV-positive and negative)
Nitroimidazoles	Bioreduction	Delamanid (OPC-67683)	Phase III. Provisional EMA registration for MDR tuberculosis	Dose-finding and safety studies ongoing in children with MDR tuberculosis (HIV-negative)
		PA-824 (Pa)	Phase IIa	None
Ethylenediamine	Cell wall synthesis	SQ-109	Phase IIa	None
Oxazolidinones	Ribosome	Linezolid	Phase IIb. Off-label use in MDR/XDR-tuberculosis patients	Used in MDR/XDR-tuberculosis (off-label)
		Sutezolid (PNU-100480)	Phase IIb	None
		AZD5847	Phase IIb	None

EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; MDR, multidrug-resistant; XDR, extensively drug-resistant.

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Fluoroquinolones for the treatment of tuberculosis in children

S. Thee [a, b, *], A.J. Garcia-Prats [a], P.R. Donald [a], A.C. Hesseling [a], H.S. Schaaf [a]

- The **fluoroquinolones** are key components of current multidrug-resistant tuberculosis (MDR-TB) treatment regimens and are being evaluated in shortened treatment regimens as well as in the prevention of drug-resistant TB.

- The objective of this review was to identify existing evidence for the use of the fluoroquinolones: ofloxacin, levofloxacin and moxifloxacin in the **treatment of TB in children**.

S. Thee et al. / Tuberculosis 95 (2015) 229e245

- **Fluoroquinolone** use has been restricted in children due to concerns about **drug-induced arthropathy**. The available data does not demonstrate any serious arthropathy or other severe toxicity in children.

- Although there is **limited paediatric safety data** for the prolonged treatment of MDR-TB, extended administration of fluoroquinolones in adults with MDR-TB does not show serious adverse effects and there is **no evidence** suggesting less tolerability of fluoroquinolones in children.

- Additional study of moxifloxacin and levofloxacin for TB treatment and prevention in **children** is an **urgent priority**.

S. Thee et al. / Tuberculosis 95 (2015) 229e245

INT J TUBERC LUNG DIS 16(12):1588–1593

http://dx.doi.org/10.5588/ijtld.12.0322
E-published ahead of print 2 October 2012

Linezolid-containing regimens for the treatment of drug-resistant tuberculosis in South African children

The dose of linezolid used was 20 mg/kg daily for children aged <10 years. For two children, this dose was split and administered twice daily. In one child, a daily dose was given, as only tablets were locally available. Children aged ≥10 years received 300 mg daily, except for patient 6 who was aged 10 and

Contents lists available at ScienceDirect

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REVIEW

Linezolid for the treatment of drug-resistant tuberculosis in children: A review and recommendations

Table 5
Recommendations for the use of linezolid in children with drug-resistant tuberculosis.

Indications	
XDR-TB	Should be used routinely in all cases
Pre-XDR-TB, failed treatment with second-line drugs	Should be used routinely in all cases
Pre-XDR-TB, meningitis	Consider, depending on severity of illness, extent of disease, other available drugs, response to treatment
Pre-XDR-TB, standard cases	Consider, depending on severity of illness, extent of disease, other available drugs, response to treatment
MDR-TB, failed treatment with second-line drugs	Should be used routinely in all cases
MDR-TB, meningitis	Consider, depending on severity of illness, extent of disease and other available drugs
MDR-TB, standard cases	Not routinely recommended
Dosing	
<12 years of age	10 mg/kg twice daily
≥12 years of age	10 mg/kg once daily up to 300 mg
Monitoring	
Full blood picture – monthly	Dose reduction for cytopaenias
Active clinical monitoring for peripheral neuropathy	Dose reduction for peripheral neuropathy; discontinuation if no improvement
Monitoring visual acuity where able; challenge with such monitoring in young children should not limit linezolid use when otherwise indicated	Discontinuation if any signs of optic neuropathy
Monitoring for lactic acidosis, rhabdomyolysis, other rare adverse effects only if clinically indicated	Dose reduction or discontinuation depending on severity

Tuberculosis 2014; 94: 93

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Conclusiones

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Conclusiones

- Evitar uso de presentaciones de adultos
- Evitar fraccionar presentaciones
- Necesarias presentaciones pediatricas
- Necesarios nuevos metodos diagnosticos genotype/Xpert
- Necesarios mas estudios de dosis intermitentes vs diaria en niños

INGRESAR A POBLACION PEDIATRICA AL PROGRAMA DE CONTROL DE NIÑO SANO

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Dosis 30 kg Fase intensiva

Medicmentos	P	Dosis	L	M	M	J	V	S	D
Isoniacida (H) Bactericida	Comprimido 100 mg	15 hasta 300 mg	300	300	300	300	300	300	300
Rifampicina (R) Bactericida Esterilizante	Cápsulas 300 mg Jarabe 100 mg/5 ml	15 hasta 600 mg	450	450	450	450	450	450	450
Pirazinamida (Z) Bactericida Esterilizante	Comprimido 500 mg	25-40 hasta 2 g	750	750	750	750	750	750	750
Etambutol (E) Bacteriostático	Comprimido 400 mg	15-30 hasta 1.2 g	450	450	450	450	450	450	450

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Dosis 30 kg Fase sosten

Medicmentos	P	Dosis	L	M	M	J	V
Isoniacida (H) Bactericida	Comprimido 100 mg	20mg/kg hasta 600 mg	600		600		600
Rifampicina (R) Bactericida Esterilizante	Cápsulas 300 mg Jarabe 100 mg/5 ml	20mg/kg hasta 600 a 900 mg	600		600		600

INTERMITENTE

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Dosis 30 kg Fase sosten

Medicmentos	P	Dosis	L	M	M	J	V	S	D
Isoniacida (H) Bactericida	Comprimido 100 mg	15 hasta 300 mg	300	300	300	300	300	300	300
Rifampicina (R) Bactericida Esterilizante	Cápsulas 300 mg Jarabe 100 mg/5 ml	15 hasta 600 mg	450	450	450	450	450	450	450
Pirazinamida (Z) Bactericida Esterilizante	Comprimido 500 mg	25-40 hasta 2 g							
Etambutol (E) Bacteriostático	Comprimido 400 mg	15-30 hasta 1.2 g							

DIARIO

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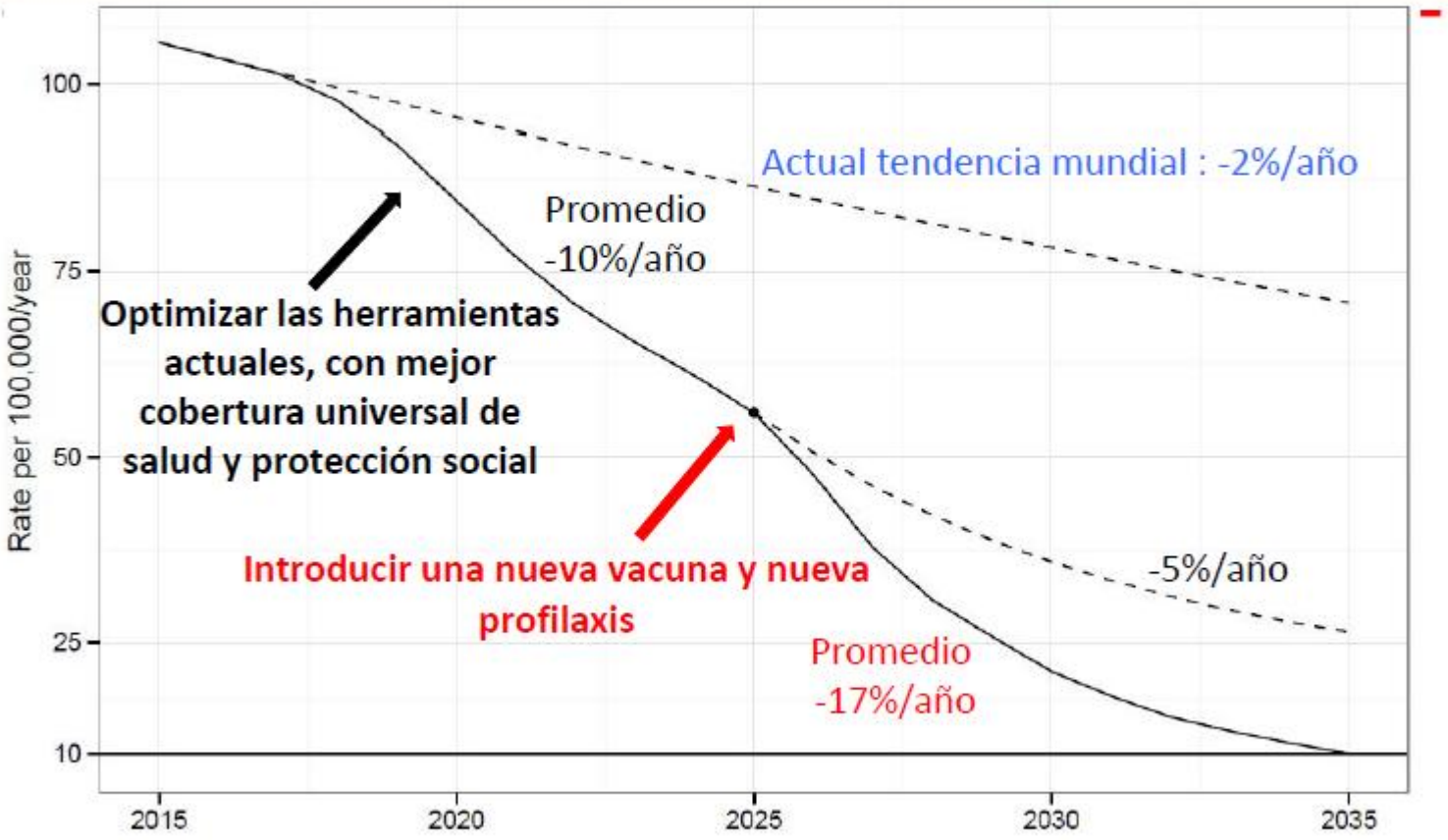
Proyección de disminución acelerada de la incidencia de TB hacia las metas

WHO THE STOP TB DEPARTMENT



Post-2015 vision for new TB strategy and targets

GLOBAL TB PROGRAMME

Organización Mundial de la Salud

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