## Use, effectiveness and safety of isoniazid in the treatment of latent tuberculosis infection, what do we know?

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## Abstract

Background The treatment strategy for latent tuberculosis (TB) infection (LTBI) aims to promote a reduction in the number of cases that develop into TB and, consequently, a reduction in the transmission of pathogenic bacteria. Objectives The objective was to know the safety, effectiveness and adherence of the use of INH in two pharmaceutical presentations (300mg or 100mg tablet) reported in scientific studies. Methods A review protocol was registered a priori with PROSPERO (number CRD42020176694). The electronic databases Cochrane; PubMed; Embase; LILACS, Scopus, and Web of Science were searched for studies on use of INH for LTBI. The results and methods were presented in line with the PRISMA guidelines, and the methodological quality of the included reviews was assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Results Most of the studies used isoniazid (H) as a treatment for LTBI, with a duration of 9 months. There was significant variation in the of use of isoniazid, ranging from 0.3% to 98.6% of the participants. A similar variation was found in the 52 studies that similarly presented the rate of adherence to treatment with H, which ranged from 18% to 100% among study participants completing INH treatment for LTBI. In studies, the adverse events reported most frequent events reported were included hepatotoxicity, gastric intolerance, and neuropathy, the rates of occurrence of these with isoniazid, rang from < 1% to 48%. In the studies that evaluated effectiveness of isoniazid for latent tuberculosis infection, a variation from 0 to 19.7% of people who did not have active TB after the follow-up period was observed, with the highest rate among HIV-positive individuals. Conclusion Our findings indicate that isoniazid is being widely used in the world as a prophylactic treatment for tuberculosis, rates of adherence to isoniazid were above 50%. It is important to emphasize the importance of keeping the follow-up of the person who uses isoniazid due to the risk of developing unwanted events resulting from the drug. Even with treatment challenges, we identified low rates of people who used isoniazid and developed active tuberculosis during the period they were followed. We believe that isoniazid continues to contribute to tuberculosis control in the world and better care actions are needed.

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Figura 1. Study Selection Flow

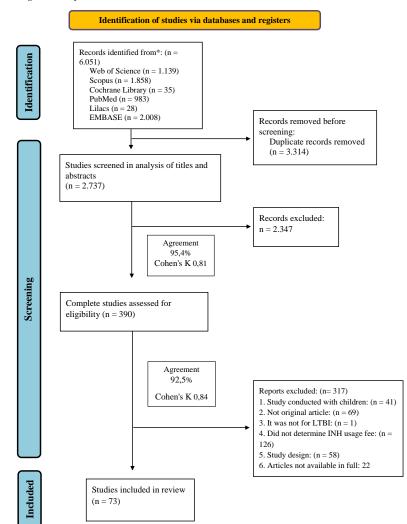
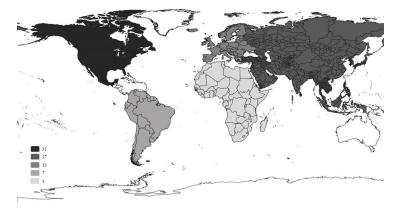


Figure 2. Number of studies included, by continent.



## Figure 3. Treatment adherence in continents

Adherent Sample Adherence (%)

North America				
Shukla et al. (2002)	318	388	81.96 [77.76; 85.66]	-+-
Swift et al. (2020)	118	173	68.21 [60.71; 75.07]	<b>—</b>
Araújo et al. (2020)	249	300	83.00 [78.26; 87.07]	
Ronald et al. (2020)	3573	9684	36.90 [35.93; 37.87]	
Wheeler & Mohle-Boetani (2019)	39	92	42.39 [32.15; 53.14]	
Plourde et al. (2019)	3001	4985	60.20 [58.83; 61.56]	
Macaraig et al. (2018)	27	55	49.09 [35.35; 62.93]	
Eastment et al. (2017)	115 137	222 202	51.80 [45.02; 58.54]	
Perez et al. (2017) Simkins et al. (2017)	92	110	67.82 [60.90; 74.21] 83.64 [75.38; 90.00]	
McClintock et al. (2017)	115	224	51.34 [44.59; 58.05]	<b>—</b>
Juarez-Reyes et al. (2015)	28	154	18.18 [12.43; 25.19]	<b></b>
Fiske et al. (2014)	456	807	56.51 [53.00; 59.96]	
Rivest et al. (2013)	2532	2895	87.46 [86.20; 88.65]	•
Smith et al. (2011)	5242	8689	60.33 [59.29; 61.36]	+
Jafrietal. (2011)	7	15	46.67 [21.27; 73.41]	
Liet al. (2010)	6173	14030	44.00 [43.17; 44.82]	
Xu, Schwartzman. (2010)	74	124	59.68 [50.49; 68.39]	<b>_</b> _
Young et al. (2009)	416	639	65.10 [61.26; 68.80]	-+-
Larizabal et al. (2006)	113	213	53.05 [46.11; 59.90]	
Page et al. (2006)	493	770	64.03 [60.52; 67.42]	-
Cook et al. (2006)	98	149	65.77 [57.56; 73.34]	-+
Scholten et. al. (2003)	259	607	42.67 [38.70; 46.71]	-
McNeill et al. (2003)	67	114	58.77 [49.17; 67.91]	
South America				_
Picone et al. (2020)	196	210	93.33 [89.07; 96.31]	_ 4
Santos et al. (2017)	26	39	66.67 [49.78; 80.91]	
Lemos et al. (2013) Stugshi et al. (2012)	59 18	65 27	90.77 [80.98; 96.54] 66.67 [46.04; 83.48]	
Stucchi et al. (2012)	10	21	00.07 [40.04, 03.40]	
Africa				_
LaCourse et al. (2017)	249	351	70.94 [65.88; 75.64]	
Johnson et. al. (2014)	30	39	76.92 [60.67; 88.87]	
Europe				
Villa et al. (2020)	12227	15716	77.80 [77.14; 78.45]	*
Sentís et al. (2019)	13417	13881	96.66 [96.34; 96.95]	٥
Sentis et al. (2019)	11893	13348	89.10 [88.56; 89.62]	•
Abreu et al. (2017)	14	15	93.33 [68.05; 99.83]	
Pina et al. (2013)	648	863	75.09 [72.06; 77.94]	<u>+</u>
Codecasa et al. (2013)	8764	11832	74.07 [73.27; 74.86]	
López et al. (2011)	271 316	400 426	67.75 [62.93; 72.31]	
Fresard et al. (2011) Diaz et. al. (2010)	70	426	74.18 [69.75; 78.27] 66.67 [56.80; 75.57]	
Anibarro et al. (2010)	442	546	80.95 [77.40; 84.16]	-
/(iibairo crai: (2010)	442	040	00.00 [11.40, 04.10]	
Asia				
Noh et al. (2019)	9	12	75.00 [42.81; 94.51]	
Kyaw et al. (2019)	855	1278	66.90 [64.25; 69.48]	
Park et al. (2019)	34	43	79.07 [63.96; 89.96]	<b>-</b> _
Lee et al. (2018)	14	14	100.00 [76.84; 100.00]	
Huang et al. (2018)	50	50	100.00 [92.89; 100.00]	—
Lee et al. (2017)	186	219	84.93 [79.49; 89.39]	
Khawcharoenporn et al. (2017) Park et al. (2016)	15 9	16 22	93.75 [69.77; 99.84] 40.91 [20.71; 63.65]	<del></del>
Park et al. (2016) Huang et al. (2016)	9 515	22 590	40.91 [20.71; 63.65] 87.29 [84.33; 89.87]	
Park et al. (2015)	45	590 61	73.77 [60.93; 84.20]	
Cansu et al. (2014)	46	61	75.41 [62.71; 85.54]	
Chee et al. (2004)	721	876	82.31 [79.61; 84.78]	-
			0	20 40 60 80 100
			U	Treatment Adherence (%)

Figure 4. Quality assessment of cross-sectional studies

