Peer review

1.Table 1 case detection rate is 80%. However, when the number of undiagnosed cases of 417 976 is divided by 2.82 million (first row table 1), the case detection rate is calculated as (100-14.8) = 85.2%. Please explain.

2.In the 'onion model' of TB by the WHO, the fifth outermost layer is designaged as "access to healthcare facilities but don't go". Assuming that 10% of the undetected cases (see point 1) originate from this category, then no amount of increase of speed or accuracy of detection will decrease the mortality rate to the extent as that calculated in the manuscript, because this population subgroup will not present itself to the computer vision diagnostic in the first place. Please re-calculate the numbers (or provide an alternative calculation) in your manuscript while taking this factor into account. While you do mention this in your manuscript as a limitation, "…..we do not attempt to quantify the impact of the roll-out of a best-in-class computer vision system in reducing deaths that occur because of incident cases not entering treatment…" There should be recalculated numbers reported.

3.Different X-ray machines (manufactured by different vendors) will output different quality/resolution of images. Please present data or analysis to show that the computer vision AI will be able to process these different quality images from machines made with different vendors and diffferent specifications with the same sensitivity and specificity. In fact, https://www.qure.ai/product/qtrack presents different AUC for different vendors.

4.There is approximately 86% cell phone penetration in India. Explain why a simple TB skin jab by door-to-door visiting health care professional with instructions to the patient to upload an image of the injection site at 24 hours post injection will not be a better alternative to a portable X-ray machine with AI. This dispenses with the need for portable x-ray machines, AI, and replaces them with a visit by the local health care nurse or professional. Discuss in the manuscript.

5.you state "….Such avoidance of pulmonary TB deaths would have meant that in 2022, India's HIV-negative TB mortality rate per 100,000 would have been 14.2 (assuming a reduction in mortality in line with our point estimate) instead of WHO's point estimate of 23.4 and provide a significant boost to help WHO and the Government of India reach their respective mortality target rates for the mid-2020s….." Please explain where these numbers originate from and how they were calculated.

6.To continue from point 4, the CDC estimates that 80% of active TB cases arise from latent infection and treatment of latent infection is 90% effective at preventing progression to active infection. https://www.cdc.gov/tb/hcp/clinical-overview/latent-tuberculosis-infection.html, Hence, instead of being retro-active and treating active cases, it would be better public health policy to treat latent TB infections, which can be easily detected with the skin test (as can active infections). Please explain and describe in the manuscript, why this approach would not be more preferable than treating active TB patients.

7.Equation 8 adds the exsiting cases of TB with the mortality due to these existing cases. In doing so, it seems to me that you have artificially inflated the numbers that can be saved by the your computer vision diagnostic. Please explain.
8.Please provide approximate (first approximation is OK) costs to implement this policy and the cost per additional person saved ratio.

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1. **Table 1 case detection rate is 80%. However, when the number of undiagnosed cases of 417 976 is divided by 2.82 million (first row table 1), the case detection rate is calculated as (100-14.8) = 85.2%. Please explain.**

   A: The case detection rate of 80% and the 95%CI bounds in Table 1 were incorrectly calculated. When calculating them initially, we did not take into account 146 383 cases of "*thereof previously treated patients, excluding relapse cases (pulmonary or extrapulmonary, bacteriologically confirmed or clinically diagnosed)"*. This has now been corrected in Table 1. As this estimate is not used in subsequent computations, no other correction is necessary.

2. **In the 'onion model' of TB by the WHO, the fifth outermost layer is designaged as "access to healthcare facilities but don't go". Assuming that 10% of the undetected cases (see point 1) originate from this category, then no amount of increase of speed or accuracy of detection will decrease the mortality rate to the extent as that calculated in the manuscript, because this population subgroup will not present itself to the computer vision diagnostic in the first place. Please re-calculate the numbers (or provide an alternative calculation) in your manuscript while taking this factor into account. While you do mention this in your manuscript as a limitation, "…..we do not attempt to quantify the impact of the roll-out of a best-in-class computer vision system in reducing deaths that occur because of incident cases not entering treatment…" There should be recalculated numbers reported.**

   Noted. At the end of the results section, we now use the transformational properties of expected values to calculate the sensitivity of our results to the percentage of undiagnosed cases that will not seek treatment despite having access to computer vision diagnostic services. We were unable to find any studies about what percentage of active TB patients currently have access to diagnostic services and choose not to use them (which would be a good proxy for the analogous percentage upon a full-scale roll-out of computer vision diagnostic services) so we use three scenarios at 10%, 20% and 30%, respectively. We summarize the results in a new table (Table 7). In addition to resubmitting a new clean manuscript, the attached pdf document has Track Changes turned on to follow our changes to the manuscript easily.

3. **Different X-ray machines (manufactured by different vendors) will output different quality/resolution of images. Please present data or analysis to show that the computer vision AI will be able to process these different quality images from machines made with different vendors and diffferent specifications with the same sensitivity and specificity. In fact, https://www.qure.ai/product/qtrack presents different AUC for different vendors.**

   Actually, the AUC curves you are referring to on https://www.qure.ai/product/qtrack compare qure.ai's qXR system to systems of other vendors of AI-based computer vision systems and not the result of the qXR system when analyzing images taken with the machines of different x-ray vendors.

   A study we cited and discussed in the literature review by Codlin, A.J., Dao, T.P., Vo, L.N.Q. *et al*. state that the quality of the X-ray equipment affected the systems' performance (they assessed 12 systems, including qXR) without giving further data. We highlight their finding in the manuscript. Another study cited and discussed in more detail in our manuscript (by Nxumalo ZZ, Irusen EM, Allwood BW, Tadepalli M, Bassi J and Koegelenberg CFN) concluded that the system achieved a sensitivity of 90% using the existing imaging

infrastructure found in local hospitals in South Africa and their sensitivity ratio is what we used in our modelling.

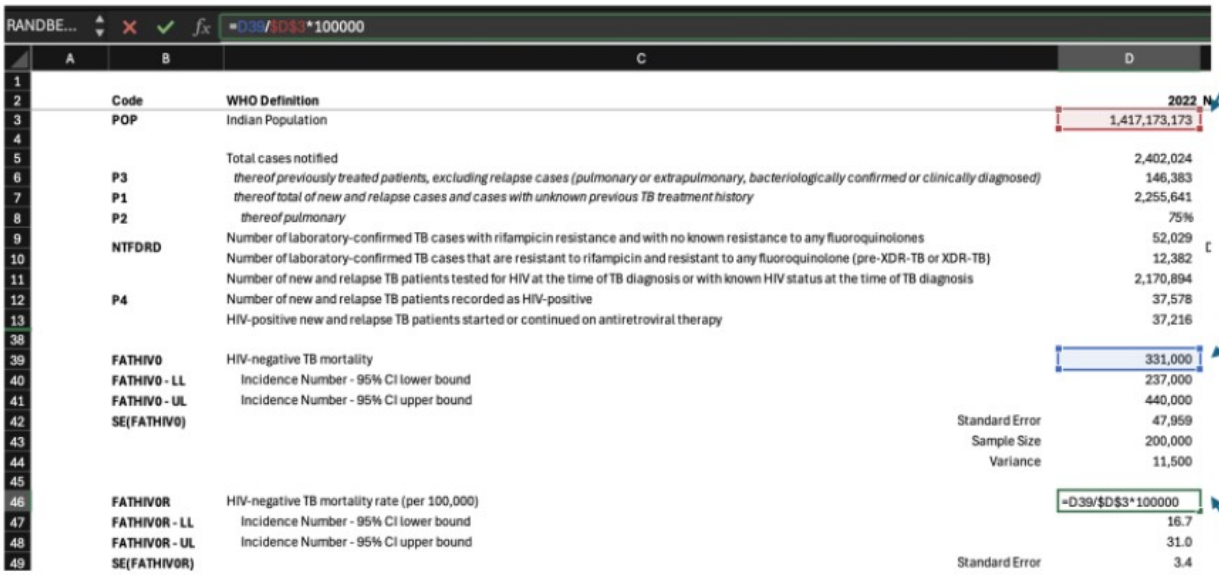
Also, the same page on qure.ai's website states that qXR "*supports all major CR, DR and ultraportable X-rays*", and their reported AUC sensitivity of 90.81% is above the 90% parameter we use in our modelling, which we take from the South African study above. Furthermore, since a full-scale rollout of a computer vision system would necessitate investment in new imaging equipment, including ultraportable X-rays, to broaden diagnostic coverage, it is reasonable to assume that they would be compatible with the chosen computer vision system.

4. **There is approximately 86% cell phone penetration in India. Explain why a simple TB skin jab by door-to-door visiting health care professional with instructions to the patient to upload an image of the injection site at 24 hours post injection will not be a better alternative to a portable X-ray machine with AI. This dispenses with the need for portable x-ray machines, AI, and replaces them with a visit by the local health care nurse or professional. Discuss in the manuscript.**

   Noted. This ties in with point 6 in that the two-stage TB skin test you are referring to tests whether you have Mycobacterium tuberculosis in your body, in latent or active form. Therefore, the limitations we discuss as part of our response to point 6 also apply to this point. The skin test you are referring to is one of the two families of tests that are used for diagnosing TB via the skin or blood work. Furthermore, since the TB skin test does not differentiate between latent and active TB (source: CDC) and since the treatment of latent TB is different from that of active TB (source: CDC), a positive result of a TB skin test would necessitate a further check for active TB via X-ray and sputum testing.

5. **you state "….Such avoidance of pulmonary TB deaths would have meant that in 2022, India's HIV-negative TB mortality rate per 100,000 would have been 14.2 (assuming a reduction in mortality in line with our point estimate) instead of WHO's point estimate of 23.4 and provide a significant boost to help WHO and the Government of India reach their respective mortality target rates for the mid-2020s….." Please explain where these numbers originate from and how they were calculated.**

   Please see the following screenshot of the calculation model that shows the calculation of both numbers.



RANDBE... =D39/$D$3*100000

	A	B	C		D
1					
2		Code	WHO Definition		2022_N
3		POP	Indian Population		1,417,173,173
4					
5			Total cases notified		2,402,024
6		P3	*thereof previously treated patients, excluding relapse cases (pulmonary or extrapulmonary, bacteriologically confirmed or clinically diagnosed)*		146,383
7		P1	*thereof total of new and relapse cases and cases with unknown previous TB treatment history*		2,255,641
8		P2	*thereof pulmonary*		75%
9		NTFDRD	Number of laboratory-confirmed TB cases with rifampicin resistance and with no known resistance to any fluoroquinolones		52,029
10			Number of laboratory-confirmed TB cases that are resistant to rifampicin and resistant to any fluoroquinolone (pre-XDR-TB or XDR-TB)		12,382
11			Number of new and relapse TB patients tested for HIV at the time of TB diagnosis or with known HIV status at the time of TB diagnosis		2,170,894
12		P4	Number of new and relapse TB patients recorded as HIV-positive		37,578
13			HIV-positive new and relapse TB patients started or continued on antiretroviral therapy		37,216
38					
39		FATHIV0	HIV-negative TB mortality		331,000
40		FATHIV0 - LL	Incidence Number - 95% CI lower bound		237,000
41		FATHIV0 - UL	Incidence Number - 95% CI upper bound		440,000
42		SE(FATHIV0)		Standard Error	47,959
43				Sample Size	200,000
44				Variance	11,500
45					
46		FATHIV0R	HIV-negative TB mortality rate (per 100,000)		=D39/$D$3*100000
47		FATHIV0R - LL	Incidence Number - 95% CI lower bound		16.7
48		FATHIV0R - UL	Incidence Number - 95% CI upper bound		31.0
49		SE(FATHIV0R)		Standard Error	3.4

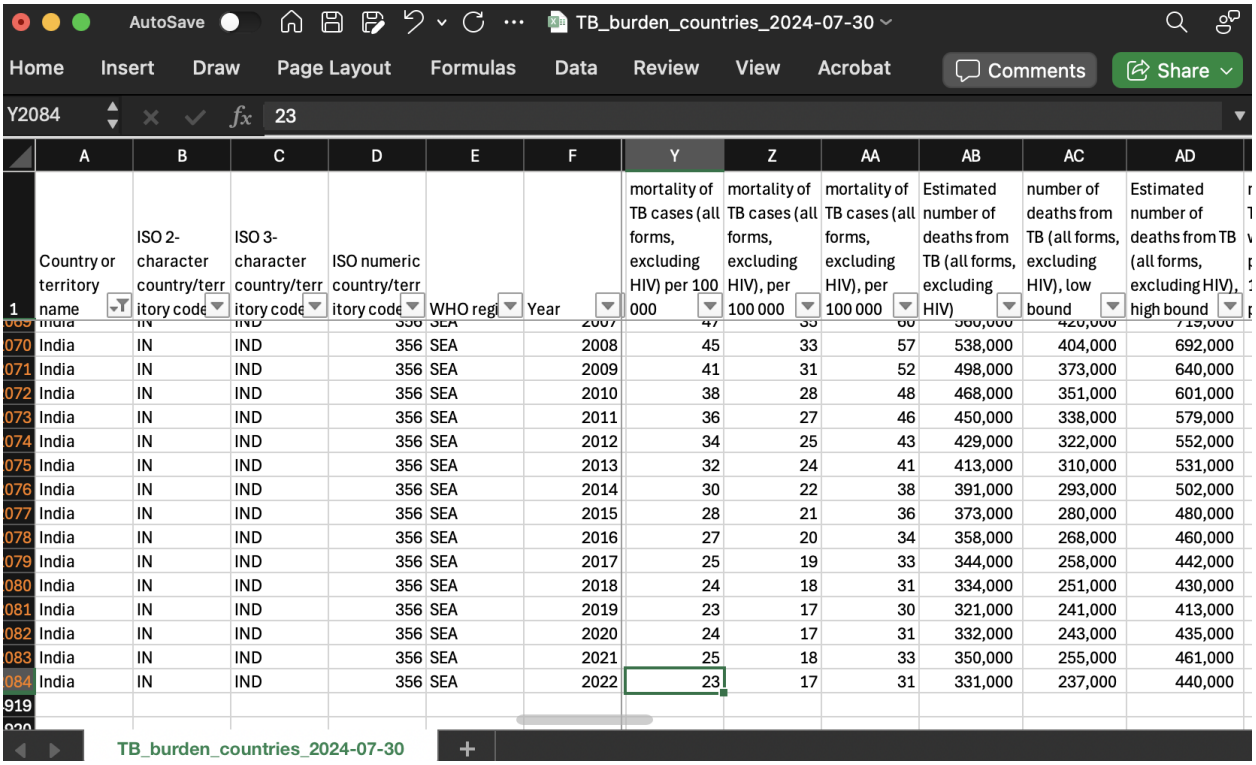
POP = 2022 population of India (source: WHO)

FATHIV0 = HIV-negative TB mortality in 2022 (source: WHO)

=D39/$D$3*100000

FATHIV0R = FATHIV0 / POP x 100 000
= 23.4

Please note that our calculation of 23.2 is in line with WHO's published data for India as included in their TB_Burden_Countries_2024_07_30 database (please see a screenshot below), which rounds all numbers to the closest whole number.



	A	B	C	D	E	F	Y	Z	AA	AB	AC	AD
1	Country or territory name	ISO 2-character country/territory code	ISO 3-character country/territory code	ISO numeric country/territory code	WHO region	Year	mortality of TB cases (all forms, excluding HIV) per 100 000	mortality of TB cases (all forms, excluding HIV), per 100 000	mortality of TB cases (all forms, excluding HIV), per 100 000	Estimated number of deaths from TB (all forms, excluding HIV)	number of deaths from TB (all forms, excluding HIV), low bound	Estimated number of deaths from TB (all forms, excluding HIV), high bound
069	India	IN	IND	356	SEA	2007	47	33	60	560,000	420,000	719,000
070	India	IN	IND	356	SEA	2008	45	33	57	538,000	404,000	692,000
071	India	IN	IND	356	SEA	2009	41	31	52	498,000	373,000	640,000
072	India	IN	IND	356	SEA	2010	38	28	48	468,000	351,000	601,000
073	India	IN	IND	356	SEA	2011	36	27	46	450,000	338,000	579,000
074	India	IN	IND	356	SEA	2012	34	25	43	429,000	322,000	552,000
075	India	IN	IND	356	SEA	2013	32	24	41	413,000	310,000	531,000
076	India	IN	IND	356	SEA	2014	30	22	38	391,000	293,000	502,000
077	India	IN	IND	356	SEA	2015	28	21	36	373,000	280,000	480,000
078	India	IN	IND	356	SEA	2016	27	20	34	358,000	268,000	460,000
079	India	IN	IND	356	SEA	2017	25	19	33	344,000	258,000	442,000
080	India	IN	IND	356	SEA	2018	24	18	31	334,000	251,000	430,000
081	India	IN	IND	356	SEA	2019	23	17	30	321,000	241,000	413,000
082	India	IN	IND	356	SEA	2020	24	17	31	332,000	243,000	435,000
083	India	IN	IND	356	SEA	2021	25	18	33	350,000	255,000	461,000
084	India	IN	IND	356	SEA	2022	23	17	31	331,000	237,000	440,000
919												
920												

TB_burden_countries_2024-07-30

			Based on simulation with 100,000 iterations			
		E(X)	Mean(X)	SD(X)	LL(X)	UL(X)
LS100HIV1	Lives Saved at 100% roll-out HIV+	5,417	5,413	1,850	1,791	9,042
LS100RD	Lives Saved at 100% roll-out drug-resistant TB	2,263	2,284	1,230	-	4,674
LS100HIV0NRD	Lives Saved at 100% HIV- and non-drug-resistant TB	127,305	127,701	69,201	-	262,940
LS100	Lives Saved at 100% roll-out	134,985	135,398	69,237	-	270,689

	Sensitivity to Percentage of Patients Who Choose not to Seek Treatment	E(X) at 0%	E(X) at 10%	E(X) at 20%	E(X) at 30%
	Lives Saved at 100% roll-out HIV+	5,417	4,875	4,333	3,792
	Lives Saved at 100% roll-out drug-resistant TB	2,263	2,037	1,810	1,584
	Lives Saved at 100% HIV- and non-drug-resistant TB	127,305	114,575	101,844	89,114
	Lives Saved at 100% roll-out	134,985	121,487	107,988	94,490

Effect on Mortality Rate	**Actual**	**with Comp Vision**
HIV-negative TB mortality rate (per 100,000)	23.4	*100000
Incidence Number - 95% CI lower bound	16.7	
Incidence Number - 95% CI upper bound	31.0	

LS100RD = Lives saves at 100% roll-out – drug-resistant TB

LS100HIV0NRD = Lives saves at 100% roll-out – HIV and non-drug-resistant TB

='Estimated and Parameters'!D39-E65-E66)/'Estimated and Parameters'!$D$3*100000

= (FATHIV0 – LS100RD – LS100HIV0NRD) / POP x 100 000
= 14.2

Please see previous page

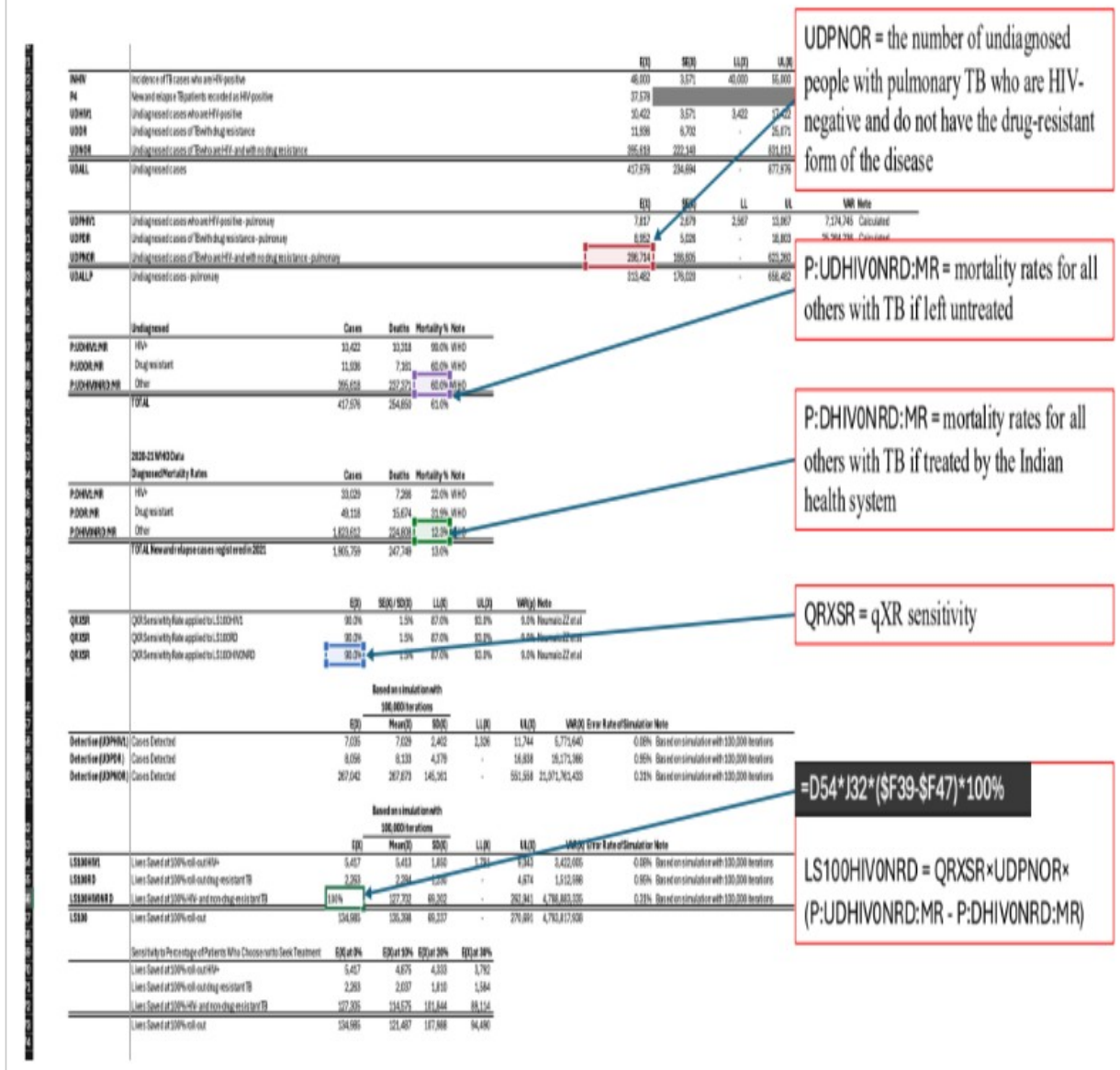
Please see previous page

6. **To continue from point 4, the CDC estimates that 80% of active TB cases arise from latent infection and treatment of latent infection is 90% effective at preventing progression to active infection. https://www.cdc.gov/tb/hcp/clinical-overview/latent-tuberculosis-infection.html, Hence, instead of being retro-active and treating active cases, it would be better public health policy to treat latent TB infections, which can be easily detected with the skin test (as can active infections). Please explain and describe in the manuscript, why this approach would not be more preferable than treating active TB patients.**

   Noted. We added a section on this potential approach, which also addresses point 4.

7. **Equation 8 adds the exsiting cases of TB with the mortality due to these existing cases. In doing so, it seems to me that you have artificially inflated the numbers that can be saved by the your computer vision diagnostic. Please explain.**

   Please see the following screenshot of the calculation model of Equation 8 with a breakdown of one of the components (*LS100HIV0NRD*). The other 2 components (*LS100HIV1* and *LS100RD*) follow a similar computation. There was also a typo on page 24, in the explanation of components of Equation 8, and perhaps this has led to the confusion. This component (*LS100HIV0NRD*) of Equation 8 calculates the expected number of lives saved (at the full-scale deployment of the qXR system) by taking the number expected number of '*Undiagnosed cases of TB who are HIV- and with no drug resistance – pulmonary*', the applicable QXR Sensivitity Rate and excess mortality of being untreated in the form of the difference between the mortality rate of such cases if left undiagnosed & untreated vs treated in the Indian health care system. Hence, because we take the difference in the mortality rates between treated and untreated cases, we are calculating the number of excess deaths and, therefore, the lives that can be saved via being diagnosed and entering treatment.


UDPNOR = the number of undiagnosed people with pulmonary TB who are HIV-negative and do not have the drug-resistant form of the disease
P:UDHIV0NRD:MR = mortality rates for all others with TB if left untreated
P:DHIV0NRD:MR = mortality rates for all others with TB if treated by the Indian health system
QRXSR = qXR sensitivity
=D54*J32*($F39-$F47)*100%
LS100HIV0NRD = QRXSR×UDPNOR×
(P:UDHIV0NRD:MR - P:DHIV0NRD:MR)

8. **Please provide approximate (first approximation is OK) costs to implement this policy and the cost per additional person saved ratio.**

   Qura.ai's website has some headline figures for cost savings per confirmatory test and per notified test but no cost information. We contacted qura.ai to assist us with the cost of implementing the policy and will include it in our manuscript when we hear back from them. While we source cost data, we are resubmitting our manuscript with the changes and corrections per your other points.

Thank you for addresssing my comments. However, I find that points 4 and 6 have only been addressed from the viewpoint of latent versus active infections; whereas the comments argue for testing of latent infections with a view to prevent active infections (given the CDC statistics) as well as the ease of identifying and treating such latent infections given the significant cell phone penetration and the ease of uploading the images from the skin test. Please include a discussion of points 4 and 6 in these contexts in the manuscripts.
The comments are not meant to diminish your contribution, but, rather to also make the reader aware of other potential approaches that may be less costly but equally as effective. I reproduce the points below.

Point 4: There is approximately 86% cell phone penetration in India. Explain why a simple TB skin jab by door-to-door visiting health care professional with instructions to the patient to upload an image of the injection site at 24 hours post injection will not be a better alternative to a portable X-ray machine with AI. This dispenses with the need for portable x-ray machines, AI, and replaces them with a visit by the local health care nurse or professional. Discuss in the manuscript.

Point 6:To continue from point 4, the CDC estimates that 80% of active TB cases arise from latent infection and treatment of latent infection is 90% effective at preventing progression to active infection. https://www.cdc.gov/tb/hcp/clinical-overview/latent-tuberculosis-infection.html, Hence, instead of being retro-active and treating active cases, it would be better public health policy to treat latent TB infections, which can be easily detected with the skin test (as can active infections). Please explain and describe
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Open response questions
Comments to author Thank you for addresssing my comments. However, I find that points 4 and 6 have only been addressed from the viewpoint of latent versus active infections; whereas the comments argue for testing of latent infections with a view to prevent active infections (given the CDC statistics) as well as the ease of identifying and treating such latent infections given the significant cell phone penetration and the ease of uploading the images from the skin test. Please include a discussion of points 4 and 6 in these contexts in the manuscripts. The comments are not meant to diminish your contribution, but, rather to also make the reader aware of other potential approaches that may be less costly but equally as eHective. I reproduce the points below. Point 4: There is approximately 86% cell phone penetration in India. Explain why a simple TB skin jab by door-to-door visiting health care professional with instructions to the patient to upload an image of the injection site at 24 hours post injection will not be a better alternative to a portable X-ray machine with AI. This dispenses with the need for portable x-ray machines, AI, and replaces them with a visit by the local health care nurse or professional. Discuss in the manuscript. Point 6:To continue from point 4, the CDC estimates that 80%

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Response Thank you for your response. It is well noted. We expanded the section entitled "Identification and treatment of latent TB to prevent incidents of active TB" to include a discussion in the context of your points under 4 & 6. The attached track changes version of the manuscript shows the additions and revisions (there are also a few minor corrections elsewhere) to our manuscript. Thank you again.

Accepted.