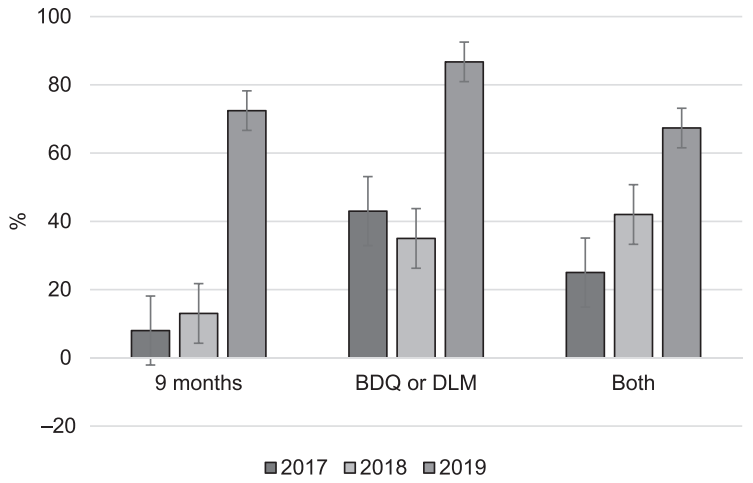

Figure Proportion of respondents indicating that shorter MDR-TB regimens and bedaquiline or delamanid (or both) were available in their country. BDQ = bedaquiline; DLM = delamanid; MDR-TB = multidrug-resistant tuberculosis.

of The Union has collaborated with RESIST-TB to survey Union members to assess the degree to which new multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant-TB (XDR-TB) treatment regimens are being used worldwide.

We recently reported progress between 2017 and 2018.[1] The survey has now been repeated for 2019 using the same methods of data collection as in 2017 and 2018. The questions asked were, "Have shorter MDR-TB regimens (9–11 months) been piloted in your country?" and "Is your country currently using bedaquiline- or delamanid-based treatment for XDR-TB or pre-XDR-TB?"

In 2019, there were 99 respondents, representing all six WHO regions. The results show continued increases in the roll-out of the 9-month regimen and in the use of bedaquiline (BDQ) and delamanid (DLM) (Figure).

These results indicate that the shortened regimen and the use of BDQ and/or DLM continue to be more readily available. We conclude that this likely represents substantial improvement in global access to effective treatment for patients with MDR- and XDR-TB.

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References

1 Held K, McAnaw S, Chiang C-Y, Trébucq A, Horsburgh C R. Progress in global rollout of new multidrug-resistant tuberculosis treatments. Int J Tuberc Lung Dis 2019; 23; 996–969.

Reference values of impulse oscillometry (IOS) for healthy Indian adults

Dear Editor,

Impulse oscillometry (IOS) is gaining ground within clinical lung function laboratories because it is effort-independent, allowing paediatric, elderly and differently abled patients to breathe at tidal volumes, without the need for effort-dependent respiratory manoeuvres.[1] IOS indices of resistance (R), reactance (X) and impedance (Z) provide a comprehensive assessment of the functional status of the airways, particularly the small airways, which is not achieved by conventional lung function testing.[1]

India comprises 18% of the global population of asthma and chronic obstructive pulmonary disease (COPD). With 93.2 million patients, India contributes to 32% of the global disability-adjusted life years (DALYs) in chronic respiratory diseases.[2] The aetiology and disease manifestation in patients with asthma and COPD in India may differ from those observed in other populations due to several non-classical exposures, including biomass fuel use, frequent childhood respiratory illnesses, poor nutrition and industrial/occupational exposures.[2] IOS could provide much-needed diagnostic support to Indian clinicians to help reduce the risk of misdiagnosis.

Current reference models for IOS in adults are limited, and there is large heterogeneity in model construction. Moreover, due to ethnic and physiological variations between Indians and other populations, these equations do not fit well. Therefore, we undertook to develop reference equations for the clinically important IOS indices in Indian adults.

Based on theoretical deductions of the standard deviation of airway resistance values at 5Hz (R_{5Hz}) of 0.07 $kPaL^{-1}Sec^{-1}$ in healthy Indians,[3] with a precision of 5%, an alpha risk of 0.05 and an anticipated non-cooperation rate of 15%, we estimated that we would need a total sample size of 202 (101 for each sex). We recruited non-smoking healthy volunteers aged 18–88 years with no clinical history of asthma, COPD, emphysema, allergic rhinitis, respiratory tuberculosis, respiratory infections within 4 weeks of testing, chest deformity (as observed on chest X-ray), cardiovascular disease; obesity (body mass index $>$ 30 kg/m^2), hospitalisation in the last 6 months, pregnancy or concomitant drug therapy affecting muscarinic and adrenergic receptors. We also excluded those non-smokers who reported exposure to biomass fuel or vapour, dust, gas and fume (VGDF) at work.

The study was approved by the Clinical Research Ethics Committee of the Allergy & Asthma Research Centre, Kolkata, India, and all the participants provided signed informed consent.

Spirometry and IOS were performed in all participants using a Jaeger MasterScreen™ PFT system (Jaeger Co, Wurzburg, Germany) equipped for both tests. Spirometry was performed according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[4] Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1) and the FEV_1/FVC ratio were measured using established Indian reference equations,[5] in line with ATS/ERS criteria for acceptability and repeatability.[6]

IOS was undertaken according to the ATS/ERS statement.[6] Airway impedance (Z) between 5Hz and 20 Hz frequencies was measured, and at least three successive efforts were recorded and quality inspected by at least two clinicians with substantial subject expertise. We reported respiratory impedance at 5Hz (Zrs), resistance (Rrs) at 5Hz and 20Hz (R_5, R_{20}), reactance (Xrs) at 5Hz, resonant frequency (F_{res}), integrated area of low-frequency reactance (AX) and the absolute difference of R_5 and R_{20} ($R_{5–20}$).

We tested the linear relationships between each of the IOS indices and age, height and weight using generalised additive models (GAM), respectively, taking natural or natural-logarithmic transformations of both the IOS and principal factors, age, height and weight. Based on GAM results, we created different sets of linear regression models for each of the IOS indices taking their natural-logarithmic transformation. We also created additional models using quantile regression with quadratic terms of age, height and weight; however, due to the best-fit criterion, only the linear models were retained. Heteroskedasticity and goodness-of-fit of the models were tested using k-fold cross-validation ($k = 5$), root mean square error (RMSE) of the residuals and Akaike's Information Criteria (AIC). Collinearity between the explanatory variables was measured using variance inflation factor (VIF). All analyses were performed in STATA v15.1 (StataCorp, College Station, TX, USA).

After excluding nine males and two females (for non-reproducible spirometry, suspected air leaks during oscillometry and non-tidal breathing patterns at rest), we incorporated data on 92 males (mean age 45 ± 18 years) and 99 females (mean age 41 ± 17 years). All participants were non-obese (mean body mass index 23.5 ± 4.5 kg/m^2), and had normal spirometry (mean FEV_1% predicted = 93.4 ± 19.1 and mean FEV_1/FVC = 80.3 ± 9.5). For IOS, females had consistently higher overall impedance (Z_5) than males (median 0.46 kPa/L/sec, IQR 0.35–0.57 vs. median 0.63 kPa/L/sec, IQR 0.55–0.80). Resistance (R_5, R_{20} and $R_{5–20}$) and reactance (X_5) values were consistently higher among females than their male counterparts (data not shown).

Sex-specific reference models of the commonly used IOS indices are presented (see Table). We found weight had the most significant influence on the models, whereas height had the lowest, in both sexes. All IOS indices achieved high goodness-of-fit values as measured using adjusted R^2 and RMSE, except AX for males. No collinearity between the explanatory variables was observed (VIF $<$ 2) in any of the models.

We observed that all oscillometry resistance values were higher among females, which is consistent with other studies.[7,8] However, unlike other studies, we found higher overall reactance (more negative X_5) among females.[7,8] One plausible explanation for this finding could be because Indian females, unlike Europeans females, have higher BMI than their male counterparts,[9] and because higher BMI reduces airway elastance,[10] Indian females are likely to have higher (more negative) reactance values than males.

Despite the increasing use of IOS in clinical practice, population-specific reference equations are lacking, with the exceptions of reference models for Caucasian,[7,8] Australian[11] and Japanese populations.[12] Our prediction equations differ significantly from both Caucasian, Australian and Japanese models (data not shown), but are representative of the Indian population. The utility of IOS is fast gaining acceptability for accurate clinical diagnosis, and its use has increased significantly among Indian clinicians in recent years because of the availability of low-cost and portable IOS instruments. Developing reference equations for the Indian population is therefore important. For the first time, we present predictive models for the clinically relevant IOS

Table Sex-specific prediction models for IOS indices*

Parameters	Models	Adjusted R^2	RMSE	Mean VIF
Males				
lnR_5	−0.30 + 0.003(*Age*) + 0.01(*Weight*) − 0.83(*Height*)	0.04	0.40	1.48
lnR_{20}	−0.14 − 0.001(*Age*) + 0.01(*Weight*) − 0.99(*Height*)	0.10	0.26	1.48
$lnR_{5–20}$	−4.05 + 0.02(*Age*) + 0.004(*Weight*) + 0.68(*Height*)	0.02	1.13	1.47
lnZ_5	0.79 + 0.008(*Age*) + 0.008(*Weight*) − 1.42(*Height*)	0.09	0.43	1.25
X_5	−0.23 − 0.002(*Age*) − 0.002(*Weight*) + 0.15(*Height*)	0.01	0.23	1.48
lnAX	−0.20 + 1.24(*lnAge*) + 0.01(*Weight*) − 2.98(*Height*)	0.20	1.02	1.25
lnFres	2.44 + 0.39(*lnAge*) + 0.001(*Weight*) − 0.55(*Height*)	0.15	0.34	1.25
Females				
lnR_5	0.003 + 0.004(*Age*) + 0.007(*Weight*) − 0.66(*Height*)	0.08	0.33	1.07
lnR_{20}	0.164 + 0.0003(*Age*) + 0.007(*Weight*) − 0.92(*Height*)	0.12	0.22	1.07
$lnR_{5–20}$	−3.35 + 0.007(*Age*) + 0.01(*Weight*) + 0.68(*Height*)	0.02	0.86	1.06
lnZ_5	−0.68 + 0.27(*lnAge*) + 0.003(*Weight*) − 0.53(*Height*)	0.08	0.32	1.06
X_5	−0.60 − 0.004(*Age*) − 0.001(*Weight*) + 0.37(*Height*)	0.16	0.16	1.07
lnAX	−2.33 + 0.76(*lnAge*) + 0.004(*Weight*) − 0.004(*Height*)	0.08	0.80	1.06
lnFres	1.19 + 0.27(*lnAge*) + 0.0002(*Weight*) + 0.68(*Height*)	0.07	0.31	1.06

* Models were built using linear regression analysis taking age (in years), weight (in kg) and height (in meters) as main explanatory variables.
IOS = impulse oscillometry; RMSE = root mean square error; VIF = variance inflation factor; ln: natural logarithm.

indices in an adult Indian population aged 18–88 years; this will allow clinicians to use IOS more frequently and help estimate the degree of airway obstruction with greater precision.

One of the major strengths of our equations is that our model-building approach consisted of a series of methods that were tested for 1) nature of relationship (linear vs. non-linear) between IOS indices and explanatory variables, 2) heteroskedasticity, 3) goodness-of-fit, and 4) cross-validation. Moreover, we tested collinearity between the explanatory variables (using VIF), which may often lead to an inaccurate estimation of the effects.[13] However, one of the limitations of the study is that we did not have a cohort for external validation. Large epidemiological studies are therefore a necessary next step in confirming the robustness of our models.

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References

1 McNulty W, Usmani O S. Techniques of assessing small airways dysfunction. Eur Clin Respir J 2014; 1. doi: 10.3402/ecrj.v1.25898.

2 India State-Level Disease Burden Initiative CRD Collaborators. The burden of chronic respiratory diseases and their heterogeneity across the states of India: the Global Burden of Disease Study 1990–2016. Lancet Glob Health 2018; 6 (12): e1363–e1374.
3 Rafie S, Moitra S, Brashier B. Association between the serum metabolic profile and lung function in chronic obstructive pulmonary disease. Turk Thorac J 2018; 19: 13–18.
4 Miller M R, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005; 26 (2): 319–338.
5 Dasgupta A, Ghoshal A G, Mukhopadhyay A, et al. Reference equation for spirometry interpretation for Eastern India. Lung India 2015; 32: 34–39.
6 King G G, Bates J, Berger K I, et al. Technical Standards for Respiratory Oscillometry. Eur Respir J 2019; pii: 1900753.
7 Pasker H G, Schepers R, Clement J, et al. Total respiratory impedance measured by means of the forced oscillation technique in subjects with and without respiratory complaints. Eur Respir J 1996; 9: 131–139.
8 Vogel J, Smidt U. Impulse oscillometry. Analysis of lung mechanics in general practice and clinic, epidemiological and experimental research. Frankfurt, Germany: PMI-Verlagsgruppe, 1994.
9 Rush E C, Freitas I, Plank L D. Body size, body composition and fat distribution: comparative analysis of European, Maori, Pacific Island and Asian Indian adults. Br J Nutr 2009; 102 (4): 632–641.
10 van de Kant K D, Paredi P, Meah S, et al. The effect of body weight on distal airway function and airway inflammation. Obes Res Clin Pract 2016; 10 (5): 564–573.
11 Newbury W, Crockett A, Newbury J. A pilot study to evaluate Australian predictive equations for the impulse oscillometry system. Respirology 2008; 13: 1070–1075.
12 Shiota S, Katoh M, Fujii M, et al. Predictive equations and the reliability of the impulse oscillatory system in Japanese adult subjects. Respirology 2005; 10: 310–315.
13 Narchi H, AlBlooshi A. Prediction equations of forced oscillation technique: the insidious role of collinearity. Respir Res 2018; 19: 48.

Green Light Committee and drug-resistant-tuberculosis: how to address the new challenges?

Dear Editor,

We read with great interest Yassin et al.'s recent contribution in the *Journal*,[1] clearly summarising the origins and evolution of the Green Light Committee (GLC). Since its creation in 2000, the GLC has addressed the major barriers faced by countries in tackling drug-resistant tuberculosis (DR-TB). Collaboration with the Global Fund in 2007 further expanded the roles and responsibilities of the GLC.[2] While presenting the history of this successful relationship, the paper leaves open several questions about its present, and especially, its future strategies and plans.

The DR-TB landscape is constantly changing: with recent changes in classification of anti-TB drugs; the adoption of bedaquiline; frequent updates to WHO DR-TB treatment guidelines; the appearance of new drugs (e.g., pretomanid) and new regimens (shorter all-oral, and bedaquiline, pretomanid and linezolid); and new diagnostic technologies.[3–6] But what are the plans and priorities of the GLC in supporting countries in this rapidly evolving scenario? Given the limited available information on new drugs and regimens, what is the GLC's role in expanding fluoroquinolone resistance testing capability, active TB drug-safety monitoring and management (aDSM) in countries, and dissemination of locally collected information?[7,8]

It would also be useful to know the GLC's perspectives and future strategies in relation to strengthening local capacity for challenging cases (e.g., national and international Consilia), expanding access to the newest and more expensive drugs and all-oral regimens, application of whole-genome sequencing for TB diagnosis, susceptibility testing and surveillance.[9,10]

In summary, while thanking the authors for their excellent report,[1] we would invite them to address these questions and share their vision and perspectives with the readers of the *Journal*.

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References

1 Yassin M A, et al. Performance-based technical support for drug-resistant TB responses: lessons from the Green Light Committee. Int J Tuberc Lung Dis 2020; 24(1): 22–27.
2 World Health Organization. Green light committee (GLC) application instructions. WHO/HTM/TB/2010.1. Geneva, Switzerland: WHO, 2010.
3 Borisov S E, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. Eur Respir J 2017; 49(5): 1700387.
4 Tiberi S, et al. Tuberculosis: progress and advances in development of new drugs, treatment regimens, and host-directed therapies. Lancet Infect Dis 2018; 18(7): e183–e198.
5 Caminero J A, et al. The future of drug-resistant tuberculosis treatment: learning from the past and the 2019 World Health Organization consolidated guidelines. Eur Respir J 2019; 54(4): 1901272.
6 Pontali E, Raviglione M C, Migliori G B; and the writing group members of the Global TB Network Clinical Trials Committee. Regimens to treat multidrug-resistant tuberculosis: past, present and future perspectives. Eur Respir Rev 2019; 28(152): 190035.
7 Pontali E, et al. Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence. Eur Respir J 2017; 50(5): 1701462.
8 Borisov S, et al. Surveillance of adverse events in the treatment of drug-resistant tuberculosis: first global report. Eur Respir J 2019; 54(6): 1901522.
9 Tiberi S, et al. Challenging MDR-TB clinical problems: the case for a new Global TB Consilium supporting the compassionate use of new anti-TB drugs. Int J Infect Dis 2019; 80 (Suppl): S68–S72.
10 Meehan C J, et al. Whole genome sequencing of *Mycobacterium tuberculosis*: current standards and open issues. Nat Rev Microbiol 2019; 17(9): 533–545.