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Conducting clinical trials only in India's large cities is unlikely to sample the country's ethnicity sufficiently well

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Around the world, there have been calls to include participants of diverse ethnicities in every clinical trial. In India, some years ago, a Parliamentary Committee was informed that trials are run in cosmopolitan cities of the country, and that this ensured suitable ethnic representation. The Indian Council of Medical Research, New Delhi, has defined six zones of the country from where sampling needs to be done to ensure good ethnic

coverage. We found that no city has adequate representation from all the zones. However, possibly, a suitable sampling strategy in some cities could replace running trials from a few zones.

Keywords: Clinical trials, cosmopolitan cities, diversity, ethnicity, sampling strategy.

PATIENTS of any age, gender, ethnicity, etc. may require a particular drug. However, clinical trials that are conducted to confirm whether a candidate drug is efficacious and not toxic usually do not adequately include representatives of the various sub-populations that will need it¹⁻³. As such, much clinical research is sub-optimal and can result in unexpected adverse or serious adverse events when a drug is rolled out to the general population⁴.

Increasing the diversity of trial participants is a non-trivial task. Nevertheless, as a result of a range of efforts⁵⁻⁸, the diversity in trials in the USA, for instance, has increased in the last couple of decades⁹.

In India, too, the need to include various ethnic groups in trials has received attention. In 2012, the 59th Parliamentary Report, by the Parliamentary Standing Committee on Health and Family Welfare, Government of India¹⁰, commented that 'In response to a question as to how various ethnic groups are being enrolled in Phase III clinical trials, the Committee was informed that "most trials were taking place in cosmopolitan towns. It is understood that cosmopolitan cities have a heterogeneous population comprising various ethnic groups. Otherwise, there is no proactive, specific procedure to test new drugs on different ethnic groups"¹⁰. However, the Standing Committee considered it inadequate that a drug was only trialled in Mumbai, for instance. Furthermore, in response to the Standing Committee highlighting various inadequacies with the drug testing and approval processes, the Ranjit Roy Chaudhury Committee was established in order to, inter alia, provide guidance on clinical trials. In 2013, this Committee, too recommended that diverse ethnicities be included in trials run in India¹¹.

Let us return to the issue of diversity in metropolitan India. Assuming for the moment, that sufficient ethnic diversity does exist in some of India's largest cosmopolitan cities, this raises the question, 'How should one define a city as cosmopolitan?'. We examine this below.

In terms of defining the variety of ethnicities in India at the broadest level, the Indian Council of Medical Research (ICMR), New Delhi, has divided the country into six zones, viz. East, West, North, South, Central and North East¹². Although there has been migration within the country, each zone is characterized by a dominant ethnicity¹³. Therefore, we define each zone as being characterized by ethnicity different from that in another zone. We list the constituent states and Union Territories (UTs) of each zone, largely based on Government categorizations (Table 1).

Separately, we use the Census 2011 data at the town level, which records the total number of speakers of each of the

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Table 1. Six zones of India, and constituent states and Union Territories (UTs)*

Zone	State/UT	Zone	State/UT
Northern ^a	Haryana	Southern ^a	Andhra Pradesh
	Punjab		Karnataka
	Himachal Pradesh		Kerala
	Rajasthan		Tamil Nadu
	Jammu & Kashmir		Telangana
	NCT Delhi		Puducherry
	Chandigarh		Gujarat
Eastern ^a	Ladakh ^b	Western ^a	Maharashtra
	Bihar		Goa
	Jharkhand		Dadra & Nagar Haveli; Daman & Diu
	Odisha		Arunachal Pradesh
Central ^a	West Bengal	North East ^c	Assam
	Uttarakhand		Manipur
	Uttar Pradesh		Meghalaya
	Chhattisgarh		Mizoram
	Madhya Pradesh		Nagaland
			Tripura
			Sikkim

^ahttp://interstatecouncil.nic.in/iscs/wp-content/uploads/2016/08/states_reorganisation_act.pdf

^bOur own classification.

^c<https://mdoner.gov.in/about-north-east>

*The islands of (i) Andaman and Nicobar and (ii) Lakshadweep are left out of this classification.

121 languages, of which 22 are scheduled and 99 are non-scheduled (https://censusindia.gov.in/2011Census/Language_MTs.html). Our sample consists of 10 major cities from different regions. We used STATA 16 to compute the percentage of speakers for each language in the 10 cities (<https://www.stata.com/>).

By way of illustration, let us consider Bengaluru. If a trial were to recruit participants from this city, the ethnicities of the South would certainly be included in the trial. However, in order to define Bengaluru as cosmopolitan, where sampling in the city could substitute for that in at least one other zone, we can consider the problem as follows: Is a significant percentage of the population of Bengaluru, a native speaker of a language that is dominant in another zone? One could (arbitrarily) define a significant extent as a minimum of 1% of the population of that city.

Figure 1 provides graphs for 10 major cities by way of examples of the distribution of languages which are the mother tongue of a significant part of the population of each city.

In the case of 5 of the 10 cities, the mother tongue of at least 1% of the population indicates that this sub-population originated in another zone. These are (i) Delhi (North) – Bengali, spoken in the Eastern zone; (ii) Mumbai (West) – Tamil and Telugu, spoken in the Southern zone; (iii) Bengaluru (South) – Marathi, spoken in the Western zone; (iv) Guwahati (North East) – Bengali, spoken in the Eastern zone and (v) Hyderabad (South) – Marathi, spoken in the Western zone. Hindi and Urdu are spoken by a significant percentage of the population in several zones, but we cannot state unequivocally which zones the speakers of these languages represent. If one wants to consider the Hindi- or Urdu-speakers as representing particular zones in a trial, one

would separately have to ascertain the state of origin of the individual.

In another study (manuscript submitted), we have found that phase 2 or phase 3, interventional, drug or biologic trials run in India and registered with the Clinical Trials Registry-India, have inadequately recruited trial participants from the six zones. It is logistically more challenging to run trials in far-flung areas of a large country than to sample the various ethnicities that reside in a few cosmopolitan cities. However, our analysis reveals that it is unlikely that any Indian city is sufficiently cosmopolitan so that there is significant representation from all six zones of the country. At best, a suitable sampling strategy in some of our cities, based on the mother tongue (and state of origin for Hindi- or Urdu-speakers), could replace sampling from some zones.

It has been reported that of the drugs approved in the US over the period 2008–13, one in five had a differential outcome, or potential for differential outcome due to differences in exposure, for patients of different ethnicities^{14,15}. The underlying reason for the ethnicity-based differential outcomes could be genetic, lifestyle or nutritional reasons¹⁶. Aside from differences in outcomes, the side effect profile may also differ¹⁷. Given the increasing recognition of the impact of ethnicity on the safety and efficacy of a given drug, regulators in the West now welcome data from trials run in other parts of the world, that would be relevant to their immigrant populations¹⁸.

The differential outcomes for patients of different ethnicities in the recent COVID-19 pandemic¹⁹ have been a strong reminder that if determined efforts are not made to include diverse ethnicities in each trial, this could lead to ethical transgressions in the form of the partially wasted efforts of

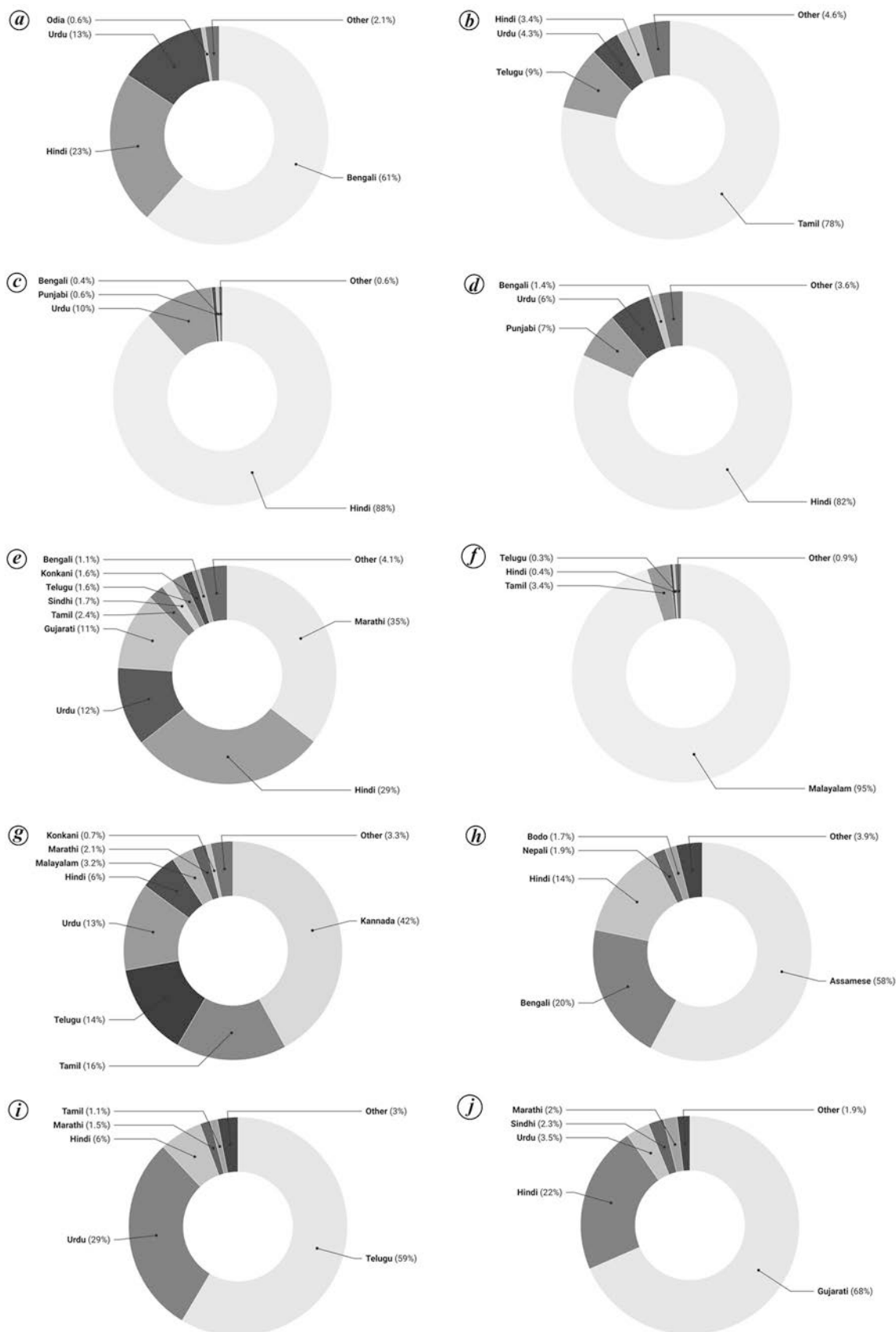


Figure 1. Fraction of the population speaking a particular mother tongue in 10 major cities of India: *a*, Kolkata; *b*, Chennai; *c*, Lucknow; *d*, Delhi; *e*, Mumbai; *f*, Thiruvananthapuram; *g*, Bengaluru; *h*, Guwahati; *i*, Hyderabad; *j*, Ahmedabad.

trial volunteers^{20,21} and medical discrimination in the form of somewhat ineffective or more toxic drugs. All trialists need to strive to run trials that are as representative of diverse ethnicities as possible.

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