





# Global survey of transfusion medicine curricula in medical schools: Challenges and opportunities

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## Abstract

**Background:** Physician's knowledge in transfusion medicine (TM) is critical for patient safety. Therefore, ensuring that medical schools provide adequate education in TM is important. The aim of this study was to assess the status of TM education at a global level.

**Study Design and Methods:** A comprehensive anonymous survey to assess TM education in existing medical school curricula was developed. The survey was distributed to deans and educational leads of medical schools in a range of low-, medium-, high-, and very high-human development index (HDI) countries. It included 20 questions designed to assess specific domains including structure of TM curriculum and teaching faculty.

**Results:** The response rate was 53%. The majority of responding schools from very-high-HDI countries offered a 6-year curriculum after high school or a 4-year curriculum after college education, whereas most schools from medium-HDI countries offered a 5-year medical curriculum. A formal teaching program was available in only 42% of these schools in contrast to 94% of medical schools from very high-HDI. Overall, 25% of all medical schools did not offer structured TM teaching. When offered, most TM teaching was mandatory (95%) and integrated within the third and fourth year of medical school.

**Abbreviations:** GTF, Global Transfusion Forum; HDI, human development index; SRA, Super Resolution Analytics; TM, transfusion medicine; UNDP, United Nations Development Program.

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Formal assessment of TM knowledge was done in 72% of all responding medical schools. More than half of the deans considered the TM education in their medical schools as inadequate.

**Conclusion:** Despite its limitations, the current survey highlights significant gaps and opportunities of TM education at a global scale.

#### KEYWORDS

curriculum, education, medical school, medical student, transfusion medicine

## 1 | INTRODUCTION

Blood transfusion is the most frequently performed procedure in hospitalized patients, yet globally, the teaching of transfusion medicine (TM) as a discipline receives little attention in medical school curricula. As a result, physicians' knowledge of TM remains inadequate and with a negative impact on clinical practice and proper selection of blood components.<sup>1</sup> Deficiencies and gaps in TM knowledge are known to result in wide variation in transfusion practice and potentially inappropriate transfusions, which can affect patient safety.<sup>2-4</sup> Concerns are ongoing regarding the infectious and noninfectious potential consequences from blood transfusion and their cost implications.<sup>5-9</sup> In addition, blood is a scarce and increasingly costly resource, and transfusion of blood components continues to increase in cost and hence it should be used appropriately based on evidence-based decisions.<sup>5,10</sup> Adequate training in basic transfusion practice is an essential requirement to prevent unnecessary transfusions, complications, and patient harm as well as wastage of a precious resource.

It is important to improve TM education at an early stage of a physician's career, preferably before they begin their clinical practice and start prescribing blood transfusions. It has previously been shown that the most common setting to receive formal TM education is in medical school.<sup>11</sup> It is therefore essential to develop adequate curricula for medical students and ensure that all practicing physicians, irrespective of their specialty, have sufficient TM knowledge. Although a comprehensive medical school TM curriculum has been previously proposed,<sup>12</sup> currently there is no consensus or standardization in regard to duration, teaching content, delivery, and knowledge assessment. Considerable heterogeneity in TM curricula exists between countries and even within the same country.<sup>13,14</sup> Many medical schools and learners worldwide may benefit from the development of an online standardized basic curriculum with defined goals and objectives.

Members of the Education Subcommittee of the AABB Global Transfusion Forum (GTF) designed and

distributed a survey to assess the current status of TM curricula in different medical schools and evaluate gaps and opportunities in TM education in countries with diverse United Nations Development Program (UNDP) human development index (HDI).<sup>15</sup>

## 2 | MATERIALS AND METHODS

### 2.1 | Generation of the knowledge assessment questions

A comprehensive self-administered survey was developed based on a previously published international forum to assess TM education in medical schools.<sup>14</sup> The survey consisted of 20 questions covering demographics, educational format, involvement of faculty, evaluations, and knowledge assessments. In addition, opinions on TM educational adequacy and needs were assessed. The draft survey was developed by two GTF TM specialists and was reviewed/revised with input from members of the GTF Education Subcommittee. Survey questions were provided in English language. The survey and output were generated by computer software (Qualtrics, Provo, UT; <https://www.qualtrics.com>) and beta-tested by GTF nonparticipant members before distribution.

The study and survey were approved by the internal review board from the University of California at San Francisco (UCSF) Medical Center and distributed late May to mid August 2019. Participation was anonymous and voluntary. Invitations for participation were sent to deans and education leaders/officers in TM in medical schools across four continents (Africa, North America, Asia, and Europe) and from each of the four UNDP HDI groups worldwide. UNDP HDI classification was selected because it is a statistical tool to measure a country's overall achievement in its social and economic dimensions based on the health of people, their level of education attainment, and their standard of living. Names and emails of medical schools' deans and education leaders in TM were obtained from a general medical school database (<https://wfme.org/>) as well as from

GTF members' networks. The deans of the medical schools were also invited to share the survey with educational leaders/officers in TM in their institutions. The complete text of the survey is available in Appendix A.

## 2.2 | Survey validation and descriptive statistics

The purpose of a *content validity* study is to assess whether the items adequately represent a performance domain of specific interest.<sup>16</sup> In this study, we assessed the content validity of the AABB GTF 2019—global undergraduate TM curricula survey. A panel of two independent experts from Super Resolution Analytics (SRA), with a broad expertise in qualitative and quantitative survey analysis, evaluated the content validity of the survey and judged whether the survey's items adequately sampled the domain of interest: evaluation of the TM curricula potential in improving teaching practices and student performance worldwide. This performance domain was defined based on two objectives that were well established *a priori* by members of the AABB GTF Education Subcommittee: (a) to define the TM education and (b) to identify gaps in TM education.

Four practical decisions directed the *content validity* of the survey:

1. Should objectives be weighted to reflect their importance? (That is, the researchers assume that all objectives stated for a given domain are equal or suggest weighting objectives in terms of their importance before matching items to objectives.)
2. How should the item-matching task be formulated? (That is, matching each individual item to the list of objectives.)
3. What aspect of the item should be examined? (That is, a clear description of the item and domain characteristics will be provided to consider matching items to a performance domain.)
4. How should results be summarized? (That is, percentage of items matched to objectives.)

## 2.3 | Results for content validity

The SRA researchers decided that all objectives for the evaluation of the survey potential in improving teaching practices and student performance were equal in value; therefore, weighting or rank ordering objectives in terms of their importance was not necessary. In the second step, they matched each individual item to the list of objectives provided by the researchers who created the survey. They wrote each item on a separate card, compared each item to

the list of objectives, and recorded the outcome of the matching decision on a standard form. The matching decision as a dichotomy was based on whether the item matched or did not match the list of objectives. In the third step, the creators of the survey supplied clear descriptions of the items and domain characteristics to consider in matching items to the performance domain. These domains were as follows: medical school organization, structure of TM education, information about TM faculty, TM curriculum, and beliefs about TM education. After a careful inspection of results, the researchers from SRA found that the items of the survey matched objectives of this project in percentage of 90%. They identified two items in the survey with problematic content in the demographic domain and decided to discard one of them. In addition, they changed the multichoice answers for one of the items from the structure of TM education domain and checked their decision with one of the creators of the survey. The descriptions of the survey items and domain characteristics were refined to match the descriptions and survey objectives. Most variables were presented as means or medians if continuous or proportions if categorical. Descriptive statistics and graphs were performed using computer software (Microsoft Excel, Microsoft 365 Version 16.39.(2020), Microsoft Corp.; retrieved from <https://office.microsoft.com/excel>).

## 3 | RESULTS

The survey was sent to 60 medical schools in 31 countries across four continents (Africa, North America, Asia, and Europe), 15 medical schools per HDI category of countries. Over a period of 3 months, 32 medical schools from 17 countries responded, with an overall response rate of 53% (32/60) and country response rate of 55% (17/31) representing three of the four UNDP HDI categories of development: medium, high, and very high. Classification of responses per UNDP HDI and education models followed are provided in Table 1. Medical schools from countries with very high HDI represent the majority of responders (56%, 18/32) followed by medical schools from medium HDI (38%, 12/32). Only two medical schools from high-HDI countries responded (6%). No responses were received from low-HDI countries.

### 3.1 | Medical education models

Of the responding medical schools, 12 of the 32 (38%) offered a 6-year medical curriculum after high school (European model). A 4-year medical curriculum after college secondary education (U.S. model) and other models were each offered in approximately one-third of the

**TABLE 1** Response rate and educational models of medical schools (n = 32) on TM curricula survey according to UNDP HDI classification of country

UNDP HDI classification and (range)	n (%)	Educational models, n (%)		
		European model	U.S. model	Others
Medium HDI (0.560-0.689) <sup>a</sup> <i>Cameroon, Ghana, India, Iraq, Kyrgyzstan, Morocco, Pakistan</i>	12 (38%)	4 (33)	0	7 (58)
High HDI (0.710) <i>Uzbekistan</i>	2 (6%)	1 (50)	1 (50)	0
Very high HDI (0.806-0.922) <i>Bahrain, Canada, Qatar, Serbia &amp; Montenegro, Oman, Saudi Arabia, Turkey, UK, US</i>	18 (56%)	7 (39)	9 (50)	2 (11)

Abbreviations: N, number of responding medical schools.

<sup>a</sup>One medical school did not indicate the educational model used.

medical schools (10/32, 31%; and 9/32, 28% respectively; Table 1). One medical school did not indicate the educational model used. As for medical schools that offered other educational models; two medical schools in the very high-HDI countries offered more than one type of program: a 5-year program after high school diploma (in 90% of cases) or a 4-year program after college degree (United Kingdom) and 4- or 3-year programs after an undergraduate degree (Canada). The majority of medical schools from medium-HDI countries (64%, 7/11) offered mostly a 5-year medical curriculum. Within the same category, one medical school in Ghana offered both the European and the U.S. model of medical education, while one medical school in Cameroon offered a 7-year medical curriculum.

## 3.2 | Education in TM

### 3.2.1 | Availability

Formal teaching in the discipline of TM based on an existing curriculum was offered in the majority (69%, 22/32) of medical schools, whereas 28% (9/32) did not have a formal program; in one medical school the status of TM education was not known. Almost all responding medical schools from very high-HDI countries (with exception of Turkey) had formal TM teaching (94%, 17/18) in contrast to less than half of responding medical schools in medium HDI countries (42%, 5/12).

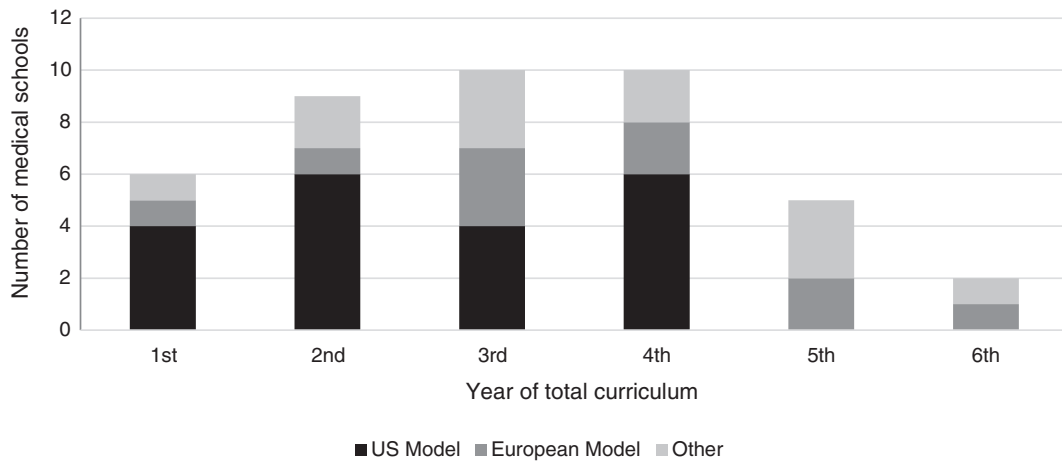
### 3.2.2 | Characteristics of TM education

Transfusion medicine education was mandatory in almost all medical schools that offered it (95%, 21/22) and optional in only one school. The TM education was integrated

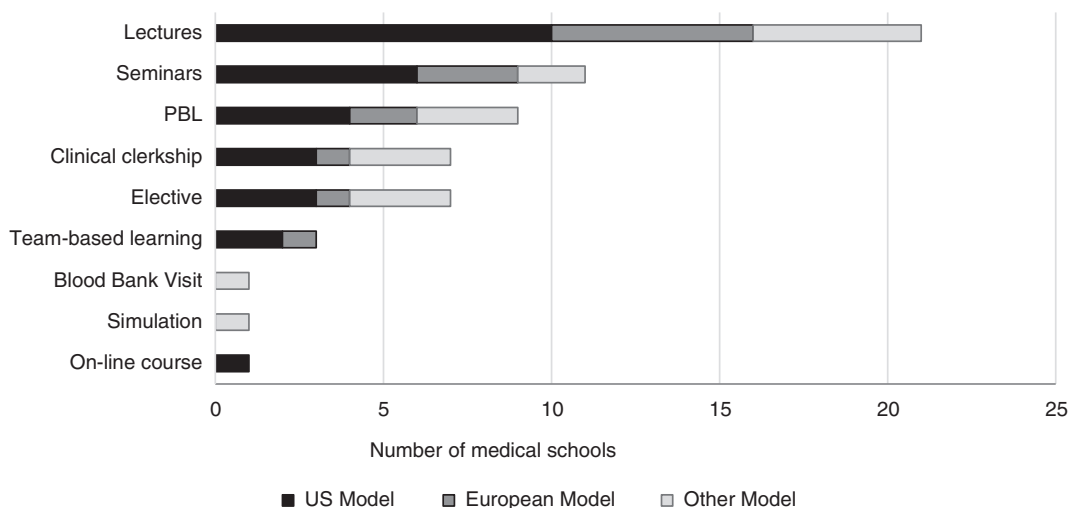
within the third and fourth year of medical training in more than half of all medical schools with mandatory curriculum, across all education models, while six medical schools (27%, 6/22) also offered TM teaching in the first year. Distribution of TM education across training years in various systems is illustrated in Figure 1. The number of years in which TM education was available was different between medical schools. Of the 12 medical schools using the European model, only five out of seven schools that offered TM education responded with the number of years the TM education was integrated. One school offered it only in 1 year and two schools in 2 years, while three schools offered it in three or more years; however, none had an integrated medical school curriculum available in all years of training. In contrast, most schools using the U.S. model (60%, 6/10) taught TM within 2 or 3 years out of the 4-year medical school curriculum, and approximately one-third taught TM only in 1 year. Only one medical school within the U.S. model taught TM in all years of medical education.

### 3.2.3 | Education modality

Lectures and seminars were the most widely used education modalities regardless of the medical school model applied (Figure 2). Lectures represent educational activity in which a single speaker formally presents and delivers the content to a large group of students, whereas in a seminar, the group is smaller and the focus is a discussion amongst the learners so the learners themselves contribute most of the content. Problem-based learning was the third educational modality preferred and was slightly more prevalent in the U.S. model. Collectively, 70 % offered clinical clerkship and/or electives in TM. A clinical clerkship is a required rotation in which a medical student applies clinical knowledge and skills to a particular patient population, whereas



**FIGURE 1** Distribution of TM education across training years in various systems in medical schools with mandatory formal TM education (n = 22). X-axis gives year of total curriculum; Y-axis gives number of medical schools



**FIGURE 2** Educational modalities used for teaching TM in various medical schools with existing formal TM education (n = 22). X-axis gives number of medical schools. PBL, problem-based learning

an elective is an optional more in-depth experience selected by a medical student with an interest in a specific area of medicine. Other educational modalities included team-based learning and clinical case discussion. Blood bank visits, online courses, and simulations were rarely available.

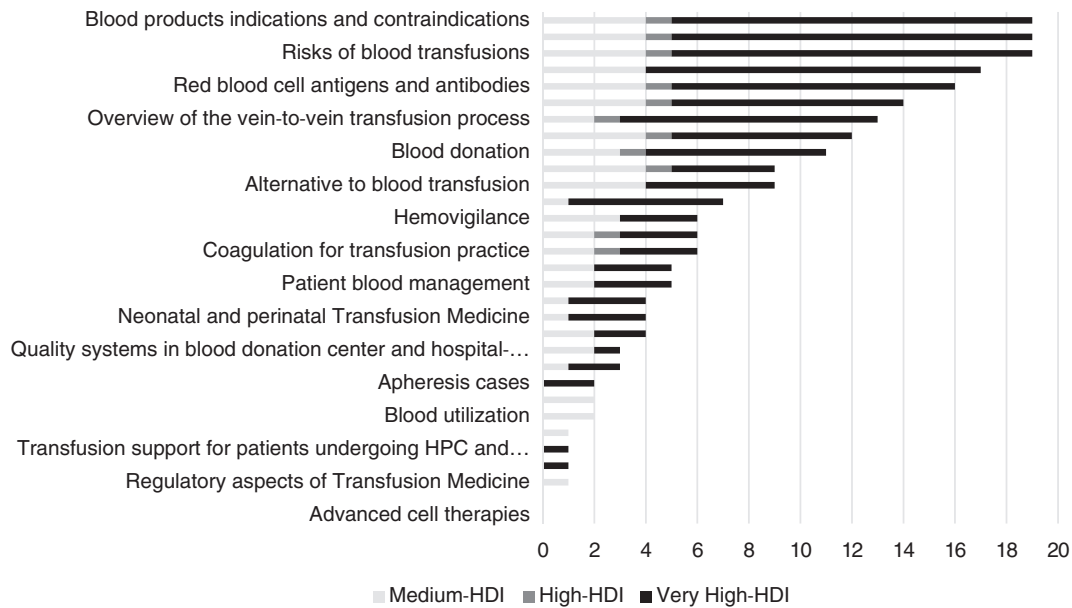
### 3.2.4 | Curricular structure

Transfusion medicine curriculum is standardized in 82% (18/22) of responding medical schools with TM education. However, curricula were variable in their composition. The mean number of TM topics taught is  $12 \pm 5$  representing less than half ( $39\% \pm 16\%$ ) of the total of 30 topics investigated. All of these medical schools taught the basics of blood testing, blood product indications and contraindications, and risks of blood transfusions. More than half of medical

schools taught other topics such as transfusion reactions, vein-to-vein transfusion, red blood cell antigens and antibodies, blood donation, basic blood physiology, special products, and alternatives to blood transfusions (Figure 3). Only one curriculum included education on transfusion practice in oncology and transplantation; hematopoietic progenitor cell (HPC) collection, processing, and transplantation; transfusion support for patients undergoing HPC and organ transplant; and logistics of blood supply. No medical school reported formal teaching in advanced cell therapies.

### 3.2.5 | Teaching faculty

A variable number of faculty (ranging from one to more than six) was reported to be involved in TM education. Most medical schools with formal TM education had two



**FIGURE 3** Topics (Y-axis) covered within existing TM curricula in various medical schools with existing formal TM education and a standardized curriculum (n = 19; four medical schools from medium-HDI countries, one from high-HDI, and 14 from very high-HDI countries). X-axis gives number of medical schools

teaching faculty (36%, 8/22) while 27% (6/22) had more than six teaching faculty. Within this category, four medical schools belonged to very high-HDI countries and two were part of the medium-HDI category. Most of the TM teaching faculty (78%) were specialists in the TM field, while 56% were adult hematologists. Hematopathologists and clinical pathologists contributed to the teaching in approximately one-third of the responding medical schools. Three medical schools in very high-HDI countries reported that surgeons, infectious disease physicians, and intensivists were teaching the TM curriculum.

Only 32% (7/22) of the responding medical schools with formal TM education had full-time faculty dedicated solely to teaching TM, whereas the majority of medical schools (68%, 15/22) had faculty members with joint duties in clinical service, research, administration, and other teaching responsibilities. Board certification was required in nine of 22 (41%) medical schools with teaching faculty of their standardized curriculum. Board certification was not required in four of 22 (18%) and was optional in the remaining medical schools. Most responding medical schools indicated that TM in their countries is a separate medical subspecialty (73%, 22/30), while only in 10% (3/30) is a specialty on its own.

### 3.2.6 | Knowledge assessment

The majority of the responding medical schools with a standardized TM curriculum (72%, 13/18) had formal knowledge assessment or examination (all schools with

European model schools, 55% of all U.S. model schools, and 75% of schools not belonging to these models). All used multiple-choice questions for knowledge assessment regardless of the education model. Essays, case-based discussions, formative assessment, and portfolio-type cases were used more in European model medical schools, while only one school utilizing the U.S. model reported the use of such methods of assessment.

### 3.2.7 | Adequacy of TM education and opportunities for intervention

More than half of the deans and education leaders/officers in TM of medical schools with standardized curricula (55%, 12/22) confirmed that TM education is not adequate and unanimously felt that it should be expanded. Half of the deans and education leaders/officers in TM considered 2 weeks as the minimum required contact time in TM, while five (23%) considered that 1 month would be required. Ten (45%) of the respondents reported a variable range of time devoted to TM from 2 hours to an entire semester. Of the responding medical schools, 77% (23/30) were extremely or moderately likely to integrate a professional online TM course within their medical school curriculum, if available.

## 4 | DISCUSSION

This study confirms that medical students in very high-HDI and medium-HDI receive a variable degree of TM

education, regardless of the medical education model applied. Even in medical schools with standardized curriculum, the extent of teaching during the years of medical education and the topics covered are variable. The majority of the medical schools have integrated TM education in the third and fourth years of medical education, with lectures being the most common method of delivery. It is reassuring to see that the main TM topics taught in all medical schools with a standardized curriculum were basics of blood testing, blood product indications and contraindications, and risks of blood transfusions. It is important to address these fundamental aspects of TM knowledge and the practical applications to ensure safe transfusion practice.

Previous literature has indicated that the methods of teaching are variable, ranging from lectures (which are the main form of content delivery mostly within the curriculum of pathology or hematology) to problem-based learning.<sup>14,17</sup> A comprehensive medical school education in TM is important to prepare future residents considering that they will be predictably involved in clinical transfusion decisions and practice. The frequent involvement of junior physicians in clinical transfusion decisions and considering that experience in a specific field by itself does not appear to correlate with improved TM knowledge highlight the importance of improving transfusion education delivery.<sup>11,18,19</sup> Didactic sessions and innovative methods, such as simulation with debriefing can be utilized for medical students near graduation.<sup>20</sup> Previous studies have also indicated that most medical schools in the United States cover only ABO and Rh blood group systems and adverse effects of blood transfusion.<sup>17</sup> To standardize TM education in the United States, grants were provided for the development of TM curricula for undergraduate medical education, which were published in 1983 and 1989.<sup>12,21</sup> Similarly, a proposed TM curriculum from Canada was published as part of a larger curriculum in laboratory medicine.<sup>22</sup> A curriculum content based on complexity and incremental level of training and ascending order of complexity has been proposed more recently.<sup>23</sup> Application of similar models to TM education seems feasible since, in addition to a basic level of knowledge, many specialties require more in-depth command of specific topics along with the acquisition of specific skill sets. Hence the basic knowledge of indications, recognition, and management of adverse events, although critical, represents only the very basics of TM education.

The survey shows that the majority of the faculty delivering the TM education are either TM specialists or adult hematologists, the majority of whom are also involved in other duties. This stands in contrast to previous work from the United States where TM physicians and pathologists were found to be the main teaching faculty.<sup>17</sup> This finding

is not surprising given the wide variety of specialties that are involved in TM practices worldwide. In many countries TM is not a recognized medical specialty or subspecialty with a separate qualification, while in other countries there are different university diplomas available for blood transfusionists.<sup>14</sup> Many countries have TM as a subspecialty of internal medicine, hematology, pediatrics, or pathology/laboratory medicine. TM is also taught in combination with immunology in other countries, like Sweden.<sup>14</sup> Also in the United States, the TM subspecialty training is available to physicians from various specialties leading to a diversity of practice, knowledge, and skill sets. The assessment aims at providing an accurate, timely, and reliable evaluation.<sup>24,25</sup> While multiple-choice questions can be given to a large group of participants over a short period of time and assess many different components of knowledge, they may not truly reflect the knowledge of the respondents when compared to open-ended questions.<sup>26,27</sup>

All surveyed deans and education leaders in TM agree that there is room for expansion of TM education, but the duration of this expansion is variably appreciated from 5 hours to 6 months. The majority considers 2 weeks the minimum curriculum contact time. In general, the amount of teaching for a specific topic widely varies between medical schools, with no data existing regarding comparative curricular adequacy.<sup>16,28,29</sup> There is evidence of limited teaching of TM in medical school curricula.<sup>17,30</sup> Minimal lecturing time needed in undergraduate and postgraduate levels is difficult to determine.<sup>14</sup> The need for additional TM training of medical students and residents was acknowledged in a previous international forum.<sup>14</sup> Overall, there is a recognized demand to improve both background knowledge and practical application to ensure safe bedside practice of TM. Additional teaching could be adapted and implemented at different times during medical school with a focus on theoretical background during earlier years, while highlighting the practical aspects at later years and at the start of internship or residency. Gaps in TM education are illustrated by the restricted quality of current clinical practice and because a substantial number of under- and postgraduate curricula are limited by time, focus, and comprehensiveness.<sup>31-34</sup>

Medical education in TM could be further enhanced during the first year of residency in the blood-prescribing medical specialties, to reinforce important concepts and promote compliance with safe and efficacious transfusion practices, for example, liberal vs restricted thresholds.<sup>35</sup> Clear outcomes need to be established and should be aligned with assessments. In doing so, clear differences in curriculum content should be established between what is required of a general physician providing blood on an *ad hoc* basis, compared to what would be required of a clinical specialist.<sup>36</sup> The essential role of patient

Human development groups	Education I ratio		
	Primary school-age population (%)	Secondary school-age population (%)	Tertiary school-age population (%)
Low-HDI	98	43	8
Medium-HDI	110	73	24
High-HDI	103	96	50
Very high-HDI	102	106	72

**TABLE 2** Differences between HDI categories of countries with respect to the education element (primary, secondary, tertiary) indicators of the index

blood management, as an integral aspect of TM practice and good patient-oriented clinical care, should be emphasized.<sup>36–39</sup> It should also be recognized that the medical workforce, worldwide, has become much more mobile, with an exodus of medical doctors moving in particular from lower- to higher-income countries.<sup>40–42</sup> In addition, it has been estimated that the number of retirees of the entire health care force will outstrip the number of entrants by a large margin, which means that patient care will be left to a progressively less experienced and junior group of graduates.<sup>43</sup> The abundant alternative teaching methods, including a combination of face-to-face interactions and social media, online teaching videos, and platforms as well as massive open online courses, may potentially have a great impact, particularly in poorly resourced settings where sufficiently experienced faculty may not be present to meet the needs to teach and train medical students in TM.<sup>44</sup> As the current impact of the coronavirus disease 19 (COVID-19) shows, there is a clear shift from the traditional in-person education toward digitization and remote learning. However, this potential impact may be challenging to achieve in settings where resources are prohibitive.<sup>45</sup> Paradoxically, the post-COVID-19 era may provide an opportunity to change and narrow the existing knowledge gap in the deprived low- and medium-HDI countries.<sup>46</sup>

Our study has several strengths. To the best of our knowledge, it represents the first attempt to survey medical school TM curricula across low-, medium-, high-, and very high-HDI countries. Such studies to illustrate educational gaps are needed. Specialists with different forms of expertise in TM and medical education agreed upon the most important domains to be investigated and formulated the questions. They cover the medical school educational model, TM curriculum, teaching faculty, methods of knowledge assessment, and further education in TM. Despite these specific strengths, the study also has some limitations. First, the statistical power of the inferential procedures to analyze data from the validation study is limited in small studies.<sup>16</sup> Larger samples would be needed to reflect a high level of accuracy of the

validity estimates of population data. In this study, only two medical schools from high-HDI countries and none from low-HDI countries responded and were assessed. In addition, the survey does not provide qualitative information on TM education, but the data published in the UNDP 2018 update of HDI and indicators<sup>15</sup> points in a direction when considering human capacity and competency differences between the HDI categories of countries (Table 2). The lower the HDI the greater the decrement in secondary and particularly tertiary (higher education, medical school, university) education enrollment; thus, tertiary education in the very high-HDI countries shows 72% enrollment,<sup>15</sup> where enrolment in the medium and low HDI parts of the world is only 24% and 8%, respectively. Also, most medical schools and universities (tertiary education) in developing countries are relatively young and date back to the last part of the colonial era, the second half of the 19th, and the first half of the 20th century.<sup>46</sup> Education needs an environment and climate to become effective and contribute to improvement. This environment can only be created and developed when there is a structure and a competent management cadre. That depends on the existence of a well-educated cadre of “intelligentia.” The data collected and published by UNDP in their 2018 statistical update illustrate the weakness and gaps in, for example, the (tertiary) education element of the HDI besides the other key elements of economics.<sup>15</sup> The results of the survey illustrate that most of the observed weaknesses and gaps in the tertiary TM education were reported by the less advanced countries and their medical schools involved. Education in these countries has been focused almost exclusively on vocational education of laboratory skills (testing and processing) with limited theoretical attention (knowledge) and rudimentary attention to topics such as governance, human capacity investment, and appropriate clinical use of blood.<sup>17,47,48</sup>

In conclusion, despite its inherent limitations, this study highlights critical aspects of TM education. There is a significant need to expand and make TM education more accessible not only because of its importance in



clinical medicine but also due to current many-level disparities. TM curriculum needs further restructuring to include basic principles and knowledge applicable to clinical practice but also minimum components of important topics in TM, such as patient blood management and hemovigilance, as well as feasible and effective delivery methods, observing the need for tailoring details to the diversities of health care settings and stages of development of countries. Because a prevalent shift toward digitalizing the curricular methods in the future is anticipated in the post-COVID-19 era,<sup>45</sup> more research is needed to come to a balanced framework. We strongly advocate for an online, standardized TM curriculum covering vein-to-vein the basics of blood donation and supply, blood products safety and efficacy, transfusion practice, and tailor-made advanced TM areas likely to irreversibly change the medical practice. In this respect COVID-19 might turn out to be a blessing in disguise.


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## CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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