



UNIVERSIDADE FEDERAL DO ESPÍRITO SANTO
CENTRO DE CIÊNCIAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM DOENÇAS INFECCIOSAS

PROCESSO SELETIVO – MESTRADO EM DOENÇAS INFECCIOSAS
EDITAL Nº 1/ 2018 – TURMA 2018/2

CHAVE DE CORREÇÃO

PROVA ESCRITA PARA AFERIR CAPACIDADE DE LEITURA E COMPREENSÃO
DE TRABALHO CIENTÍFICO ESCRITO EM INGLÊS, REALIZADA EM 03/05/2018

As respostas das questões devem ser dadas em PORTUGUÊS e estar estritamente baseadas nos textos.

Com base no texto “*Emerging Infectious Agents and Blood Safety in Latin America*”, disponível nas páginas 4 a 7, responda as questões de número **1 (um) a 5 (cinco)**.

EMERGING INFECTIOUS AGENTS AND BLOOD SAFETY IN LATIN AMERICA

Frontiers in Medicine, March 2018 | Volume 5 | Article 71, doi: 10.3389/fmed.2018.00071. eCollection 2018.

INTRODUCTION.

The first agent verified to be transmitted by blood transfusion was the malaria protozoa (1) followed by Syphilis, the latter leading to the introduction of predonation testing in the first decades of the previous century (2). During the next 70 years, the safety of blood transfusions was gradually increased, covering a growing range of agents, more importantly the hepatitis viruses and human immunodeficiency virus (HIV). In common, all these pathologies have a short symptomatic acute phase and a variable rate of progression to a chronic asymptomatic period that may last through life. Blood units collected from unaware infected donors are averted from being transfused by detecting specific antibodies against those agents. With the exception of the hepatitis B virus (HBV) surface antigen (HBsAg) detection, the hallmark of prevention by laboratorial analysis has been the development and implementation of immunoassays, including, in some countries, the anti-hepatitis B core antigen (anti-HBc), that detects occult B carriers lacking, by definition, detectable HBsAg. By the beginning of the millennia, the evolution of nucleic acid testing (NAT) allowed their incorporation to the blood screening routine, in order to interdict window-period donations, pursuing for an unattainable zero risk. A better selection of candidate



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CENTRO DE CIÊNCIAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM DOENÇAS INFECCIOSAS

donors with more stringent epidemiological and behavioral restrictions, summed to the arsenal of screening tests, have dropped the risk of transfusion transmission of infectious agents to a very low level, being nowadays a rare event (3).

Latin American (LATAM) countries are in general still struggling to motivate the population to donate blood voluntarily and regularly. Donations in the region are commonly insufficient for sustaining the transfusion demand, thereby resulting in a permanent blood shortage. In many countries, most of the donations come from replacement, often familiar donors (4) and emphasis is given to transform those into altruistic regular donors. Surprisingly, it has been observed that in some centers, repeat donors pose a risk that is similar or even higher than first-time donors concerning HIV transmission (5). This observation is justified by a fraction of repeat donors being indeed composed of HIV test seekers (6).

With some delay in comparison to developed countries, the four most important screening targets, HBV, HCV, HIV, and Syphilis, in addition to *Trypanosoma cruzi*, of local uttermost importance, were fully implemented in the 1990s (4).

Seroprevalence of these agents were and are still much higher when compared to those verified in blood donors from Europe, Japan, Canada, and the US (3, 4, 7). In this scenario, the explosive outbreaks of arboviruses with a high rate of asymptomatic subjects with a short-term viremia is new to the LATAM blood transfusion community; thus, there is a lot of uncertainty in how to deal with it. There are several proposed measures to mitigate this situation: averting blood collection in affected regions, applying pathogen reduction methods

for plasma and platelet concentrates, adopting NAT and quarantine while waiting for post-donation information of donor's health. Some countries may implement all them and others one or none. Certainly, this variability is not only due to scientific gaps in our knowledge but also to the resources available and political determination in each country or region. Table 1 summarizes selected features of the arboviruses representing today potential threats to the blood supply in LATAM.

EMERGING VIRUSES

Dengue. Viruses transmitted by arthropods (arboviruses) have always been of concern to human health but never much in the radar of blood banks. Dengue was the first arbovirus to cause epidemics in a global scale in the twenty-first century, globally affecting millions, from the Far East to the Americas. In LATAM, Brazil has been the country with the largest number of cases, experiencing yearly outbreaks from moderate to high intensity. Moreover, all four serotypes are now endemic, but there is still a large number of subjects naïve to at least one of the four serotypes, meaning that outbreaks will continue to occur.

The main impact of dengue outbreaks to the blood system is the fall in the number of candidate donors, thus shortening the supply of blood products, aggravated by the universal practice of transfusing dengue patients with low platelet counts (8).

As most dengue infections are asymptomatic, it is likely that such infected subjects are able to donate and thus eventually transmit the dengue virus to recipients. This possibility was demonstrated by several studies detecting viremic donors in Brazil (9–11), Honduras (9), Mexico (12), and Puerto Rico (13) among others.



UNIVERSIDADE FEDERAL DO ESPÍRITO SANTO
CENTRO DE CIÊNCIAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM DOENÇAS INFECCIOSAS

However, there is an obvious discrepancy in between the dengue incidence and rates of viremia verified among blood donors during outbreaks and the paucity of reports of dengue cases by the transfusional route (TT-DENV). The most comprehensive study on TT-DENV showed that recipients have an approximately 36% risk to get the virus from a viremic donor but was unable to depict dengue-specific symptoms on those infected (11). Several reasons have been presented to explain this (un)finding, discussed in detail elsewhere (14), but may be summarized as follows: it seems that dengue viruses are well adapted to the mosquito to human cycle, and, passage through the invertebrate host and inoculation by its bite are required to cause disease on us. So, although TT-DENV is a recognized risk in many endemic countries in LATAM, preventive measures were never taken, since it did not convince clinicians and authorities of its morbidity for recipients. However, it is necessary to emphasize that, in rare instances, severe dengue-associated symptoms were observed on recipients of viremic donations (13, 15), thereby leading to the implementation of laboratorial screening in Puerto Rico, first by using NS1 antigen testing further replaced by NAT (16) but in nowhere else in LATAM.

West Nile Virus (WNV).

Zika. The trajectory of Zika virus (ZKV) from an obscure agent to a global health emergence has been comprehensively described (20). The well-studied outbreak in French Polynesia revealed the important association of ZKV to Guillain-Barré syndrome (21), while Brazil was the country to raise and prove the hypothesis of a shocking causal association of this Flavivirus to microcephaly and other fetal neural abnormalities (22). Concerns about blood safety were raised by Musso and co-workers in French Polynesia where NAT, pathogen inactivation and quarantine were deployed to protect the blood supply (23). So far, there are only two published clusters of TT-ZKV, both from Brazil (24, 25). Similar to TT-DENV, on those reports it was shown that ZKV was indeed transmitted to transfusion recipients but they did not develop any symptom associated with Zika disease. In French Polynesia, look-back of 12 recipients transfused with red blood cells from ZKV-RNA+ donors has not also identified any post-transfusion symptoms (23). Even though solid evidence for a severe clinical outcome of TT-ZKV is still missing, the precautionary principle led Fundação Pró-Sangue/Hemocentro de São Paulo, Brazil, to develop a validated in-house NAT (26) and adopt it, from February 2016 on, to provide Zika-RNA-free blood units to approximately 20 pregnant women per month. In Martinique, Guadeloupe, and the French Guyana, pregnant women received blood collected in mainland France (Xavier de Lamballerie, personal communication) while donations were screened by individual NAT in Marseille, France (27).

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Chikungunya. Chikungunya (CHKV), in common with Zika and Dengue, is also transmitted by mosquitos from the *Aedes* genus, causing similar symptoms, making difficult to perform a diagnosis relying solely on clinical manifestations. Noticeably, arthralgia is much more pronounced and may last for months in some patients. Its



UNIVERSIDADE FEDERAL DO ESPÍRITO SANTO
CENTRO DE CIÊNCIAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM DOENÇAS INFECCIOSAS

transmission by blood transfusion remains theoretical since no single case of TT-CHKV has ever been published. CHKV was introduced to LATAM in 2013, hitting first the Saint Martin Island in the Caribbean, brought probably from the South Pacific. The implicated CHKV Asian strain rapidly spread over the Caribbean and to South, Central, and North America (34). In the French West Indies, concerns about blood safety led to early implementation of a lab-developed NAT, in addition to pathogen reduction and quarantine (35). They were able to detect four viremic donors, two of them developed fever after donation and the other two remained asymptomatic. A large outbreak occurred a few months later in Puerto Rico with up to 2.1% of donors testing CHKV-RNA+ (36). In contrast to the fast adoption of NAT for WNV, upon solid evidence of the clinical impact of TT-WNV, and for Zika, even lacking such parallel data, NAT for CHKV was never implemented in Puerto Rico. From the Caribbean, the Asian strain spread first to the Northern countries of South America; Colombia, Venezuela, Suriname, Guyana, and the French overseas territory of French Guyana (37). The Brazilian Amazon state of Amapá, contiguous to the French Guyana, was the first to report autochthonous cases in September 2014. Curiously, at about the same time, an infected individual brought the East–South–Central Africa (ECSA) strain to the Northeastern state of Bahia, resulting in hundreds of cases and the establishment of this lineage as endemic in the region (38). In the following years, growing number of presumed CHKV cases were verified in Brazil, 38,499 in 2015, 271,824 in 2016, and approximately 200,000 in 2017, with dozens of deaths (39, 40). It is suspected that another arbovirus, Mayaro (MAYV), belonging to the same Alphavirus genus from the *Togaviridae* family, may be hidden among cases attributed to CHKV (41) and DENV (42). There is a fear in LATAM in general, that huge outbreaks of CHKV will take place in the next years, since the majority of the population is still naïve to this virus. Strategies to mitigate the risk of TT-CHKV are not being actively discussed, since the risk of getting infected by mosquitoes is much higher and the associated clinical picture absolutely clear. In LATAM countries, with several social and health demands, it is debatable whether the resources to prevent a few TT-CHKV should not be invested in vector control, in order to benefit a larger number of inhabitants, including blood recipients that are off course also susceptible to mosquitoes' bites in daily life outside blood transfusion settings. However, availability of, in development, arboviral multiplex NATs allowing for simultaneous detection of Dengue, Chikungunya, and Zika and/ or pathogen reduction technologies acting on whole blood (43) or components, necessarily including red cells (44) may perhaps result in cost-effective measures to be implemented in endemic areas, home to the majority of the LATAM population.

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UNIVERSIDADE FEDERAL DO ESPÍRITO SANTO
CENTRO DE CIÊNCIAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM DOENÇAS INFECCIOSAS

Responda as questões considerando o artigo científico acima referenciado:

QUESTÃO 1

A transmissão de agentes patogênicos por via sanguínea tem constituído uma das grandes preocupações para assegurar a segurança nas transfusões sanguíneas, e quer as doações, quer a segurança das mesmas, têm aumentado a nível global de forma consistente nos últimos 70 anos. Contudo, nos países da América Latina (AL) permanecem ainda algumas limitações nesta temática. Quais são elas? Quais são os principais agentes infecciosos que são alvo de rastreio no sangue doado nos países da AL?

Os países latino-americanos ainda estão lutando para motivar a população a doar sangue voluntariamente e regularmente. As doações na região são geralmente insuficientes para sustentar a demanda de transfusão, resultando, assim, em uma falta permanente de sangue. Em muitos países, a maioria das doações vem frequentemente de doadores familiares, e é dada ênfase para transformá-los em altruístas regulares. Surpreendentemente, observou-se que, em alguns centros, os doadores de repetição apresentam um risco semelhante ou até maior que aqueles que doam pela primeira vez em relação à transmissão do HIV. Essa observação é justificada por uma fração de doadores repetidos composta por pessoas que buscam o teste de HIV.

Nos países da América Latina, os quatro principais agentes infecciosos rastreados na doação de sangue são HBV, HCV, HIV e Sífilis, além do Trypanosoma cruzi, de acordo com a importância local.



UNIVERSIDADE FEDERAL DO ESPÍRITO SANTO
CENTRO DE CIÊNCIAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM DOENÇAS INFECCIOSAS

QUESTÃO 2

A nova classe de agentes arbovirais, transmitidos por artrópodes, tem sido responsável por surtos de patologias. Por que razão constituem uma grande preocupação no controle da qualidade do sangue no momento das doações e que medidas devem ser implementadas para garantir esse controle?

A grande preocupação está relacionada as altas taxas de indivíduos assintomáticos com viremia de curto prazo em regiões onde há surtos explosivos de arbovírus. Como esse fato é novo nas comunidades de transfusão de sangue na América Latina, há muita incerteza em como lidar com isso.

Existem várias medidas propostas para amenizar esta situação, como evitar a coleta de sangue nas regiões afetadas, aplicando métodos de redução de patógenos para concentrados de plasma e plaquetas, adotando testes de ácidos nucléicos e quarentena enquanto aguarda informações pós-doação da saúde do doador. Alguns países podem implementar todos eles e outros, um ou nenhum. Certamente, essa variabilidade não se deve apenas a lacunas científicas em nosso conhecimento, mas também aos recursos disponíveis e determinação política em cada país ou região.

QUESTÃO 3

A infecção pelo vírus da Dengue tem uma característica que facilita/possibilita a sua disseminação no momento da doação sanguínea. Qual é ela? Justifique a sua resposta com os estudos apresentados no texto que fundamentam essa possibilidade.

Como a maioria das infecções por dengue é assintomática, é provável que esses indivíduos infectados sejam capazes de doar sangue e, assim, eventualmente, transmitir o vírus da dengue para os receptores. Essa possibilidade foi demonstrada em vários estudos que detectaram doadores virêmicos no Brasil, Honduras, México, Porto Rico, entre outros. No entanto,



UNIVERSIDADE FEDERAL DO ESPÍRITO SANTO
CENTRO DE CIÊNCIAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM DOENÇAS INFECCIOSAS

existe uma discrepância óbvia entre a incidência de dengue e as taxas de viremia verificadas entre doadores de sangue durante os surtos e a escassez de relatos de casos de dengue por via transfusional. O estudo mais abrangente envolvendo casos de dengue por via transfusional mostrou que os receptores têm um risco de aproximadamente 36% de obter o vírus de um doador virêmico, mas foram incapazes de descrever os sintomas específicos da dengue naqueles infectados.

QUESTÃO 4

A preocupação relativa à presença de vírus Zika em sangue de transfusões foi evidenciada por um grupo de investigadores. Diga que medidas foram adotadas nesses procedimentos, referindo que colaboradores foram esses. Que protocolo de ação foi definido numa Instituição Brasileira de referência para assegurar sangue doado livre de Vírus Zika?

Preocupações sobre a segurança de sangue de transfusão foram levantadas por Musso e colaboradores na Polinésia Francesa, onde testes de ácidos nucleicos, inativação de patógenos e quarentena foram implantados para proteger o suprimento de sangue. Até o momento, existem apenas dois relatos publicados de casos de Zika por via transfusional, ambos do Brasil. Semelhante aos casos de dengue por via transfusional, nesses relatos foi demonstrado que, de fato, o Zika vírus foi transmitido aos receptores da transfusão, mas eles não desenvolveram nenhum sintoma associado à doença Zika. Na Polinésia Francesa, estudo retrospectivo de 12 receptores transfundidos com hemácias de doadores positivos para RNA de Zika, também não identificou nenhum sintoma pós-transfusional. Apesar de ainda não existirem evidências sólidas para desfecho clínico grave de casos de Zika por via transfusional, o princípio da precaução levou a Fundação Pró-Sangue / Hemocentro de São Paulo a desenvolver um teste de ácido nucleico para detecção de RNA de Zika. O teste foi validado internamente e adotado a partir



UNIVERSIDADE FEDERAL DO ESPÍRITO SANTO
CENTRO DE CIÊNCIAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM DOENÇAS INFECCIOSAS

de fevereiro de 2016, a fim de fornecer unidades de sangue livres de RNA de Zika para, aproximadamente, 20 mulheres grávidas por mês.

QUESTÃO 5

O vírus Chikungunya possui algumas características semelhantes e outras distintas do vírus da Dengue e do Vírus da Zika. Descreva-as, de acordo com os elementos apresentado no texto.

O Chikungunya, em comum com o Zika e a Dengue, também é transmitido por mosquitos do gênero Aedes, causando sintomas semelhantes, dificultando a realização de um diagnóstico baseado somente nas manifestações clínicas. Notavelmente, a artralgia é muito mais pronunciada e pode durar meses em alguns pacientes. Sua transmissão por transfusão sanguínea permanece teórica, já que nenhum caso foi publicado até o momento.



UNIVERSIDADE FEDERAL DO ESPÍRITO SANTO
CENTRO DE CIÊNCIAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM DOENÇAS INFECCIOSAS

Com base no artigo “*Factors associated with tuberculosis treatment delay in patients co-infected with HIV in a high prevalence area in Brazil*” cujos textos extraídos encontram-se abaixo, responda as questões de número **6 (seis) a 10 (dez)**.

FACTORS ASSOCIATED WITH TUBERCULOSIS TREATMENT DELAY IN PATIENTS CO-INFECTED WITH HIV IN A HIGH PREVALENCE AREA IN BRAZIL.

PLoS One. 2018 Apr 6;13(4):e0195409, doi: 10.1371/journal.pone.0195409. eCollection 2018.

[...]

Introduction

Despite significant advances in the treatment of HIV and tuberculosis (TB) worldwide, both HIV and TB remain major public health issues, and are of particular concern when presenting together as co-infections. Globally, about 11% of TB cases occur in people living with HIV (PLHIV) and it is the leading cause of death in this population. [1–3] Co-infection with HIV/TB is also the leading cause of hospitalization of adults and children living with HIV.[4]

As the most populated country of Latin America, Brazil accounts for more than 40% of all new HIV infections in the region, with an estimated prevalence of 0.4–0.6%. In 2015 there were estimated to be 830,000 PLHIV in Brazil, 44,000 new HIV infections, and 15,000 AIDS-related deaths. [4,5] The incidence rate of HIV was 19.1/100,000 population in Brazil in 2015, though nearly twice as high in the state of Rio de Janeiro. [5]

[...]

Studies from multiple countries have identified various factors associated with delay in TB diagnosis and treatment, with significant variation. Factors differ according to social and cultural issues, local TB and HIV prevalence, and characteristics of public health systems. The majority of these studies focused on TB mono-infection with few focused exclusively on those co-infected with HIV. [15–18] In Brazil, there have been studies examining factors associated with TB treatment delay [15–19] but only Coimbra et al [15] focused on PLHIV. The study evaluated total treatment delay in patients with only pulmonary TB who were attending HIV care services at the time that they developed TB symptoms. The presence of systemic symptoms, asthenia, chest pain, use of illicit drugs and a smear negative sputum were all associated with greater total delay in their study. [15] To the best of our knowledge, no study to date has included TB-HIV co-infected patients with recent diagnosis of HIV, nor separately examined patient and health care system delay in Brazil.

[...]



UNIVERSIDADE FEDERAL DO ESPÍRITO SANTO
CENTRO DE CIÊNCIAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM DOENÇAS INFECCIOSAS

Results

A total number of 201 patients diagnosed with TB-HIV were included in the analysis. The mean age was 39 years, ranging from 19 to 67 years. Most participants resided in Rio de Janeiro (66.17%) and most were male (70%). About 43% were diagnosed with HIV during the TB investigation and 57% knew of their diagnosis of HIV before the TB episode. In the previously diagnosed HIV patients, the mean time from HIV diagnosis to first visit to the clinic was 93 months. In this group, 73% of individuals were using antiretroviral therapy (ART), but only 27% of those were virologically suppressed (viral Load < 40 copies/mL).

[...]

Discussion

In this study, we found that illiteracy was associated with both longer patient delay and longer health care delay. In terms of patient delay, illiteracy may lead to inadequate knowledge of TB and therefore a low perception of risk and negative attitudes toward seeking care even in the presence of symptoms. [25] While we did not specifically examine these potential explanations, the association between illiteracy and patient delay is consistent with prior studies. [25] To the extent of our knowledge, this is the first time illiteracy is found to also be associated with longer health care delay. We believe this may be due to lower adherence to visits and laboratory tests requested by physicians during their initial diagnostic visit, possibly because of poor understanding of the medical investigation process and inaccurate perception of TB risk.

Surprisingly, low income was not associated with patient or health care delay. The fact that PLHIV in Rio de Janeiro have the right to free public transportation [26] could have reduced the impact of low income as a limitation to seeking care in response to TB symptoms and remaining linked to care during TB investigation.

Interestingly, being married and prior TB infection were inversely related to patient delay. Marital status may be a proxy for social support, which may lead to seeking care earlier. [25] Having had a previous episode of TB may lead to less delay because of greater knowledge and awareness of TB symptoms from the previous episode. Furthermore, it is possible that those who had a previous episode of TB were able to navigate the public health system more easily or get quicker access in the current episode.

[...]

The identification of vulnerable populations across the country is important for the achievement of better outcomes and for reduction of TB-HIV co-infection. In this study, illiteracy was an important individual factor and the design of TB awareness interventions targeting this is a challenge that needs to be addressed. Furthermore, sustainable actions to reduce inequalities and improve education at the population level must be undertaken.



UNIVERSIDADE FEDERAL DO ESPÍRITO SANTO
CENTRO DE CIÊNCIAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM DOENÇAS INFECCIOSAS

Responda as questões considerando o texto extraído do artigo científico acima:

QUESTÃO 6

Qual é número de pessoas vivendo com HIV (PLHIV), a prevalência, o número de novas infecções e a incidência no Brasil, em 2015?

830.000 PLHIV, 0,4–0,6% de prevalência, 44.000 novas infecções e uma incidência de 19,1/100.000.

QUESTÃO 7

Quais os fatores que o estudo de Coimbra et al identifica como tendo influência, causando atraso, no tratamento da tuberculose?

Os fatores identificados pelo estudo de Coimbra et al foram: presença de sintomas sistêmicos, astenia, dor no peito, uso de drogas ilícitas e esfregaço de escarro com resultado negativo.

QUESTÃO 8

Quantos pacientes foram incluídos no estudo? Qual a sua idade média? Qual a porcentagem de pessoas do sexo masculino? Quantos estavam virologicamente suprimidos?

Número total de pacientes: 201

Idade média: 39 anos

Porcentagem de pessoas do sexo masculino: 70%

Porcentagem de suprimidos virologicamente: 27%



UNIVERSIDADE FEDERAL DO ESPÍRITO SANTO
CENTRO DE CIÊNCIAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM DOENÇAS INFECCIOSAS

QUESTÃO 9

Na discussão, os autores elaboram sobre o porquê do achado de analfabetismo estar associado a atraso pelo paciente em procurar cuidados de saúde e a atraso em receber cuidados de saúde. Explique o seu racional.

Os autores afirmam que o analfabetismo pode levar a uma baixa percepção de risco e a atitudes negativas em relação à procura de cuidados, mesmo na presença de sintomas. Pelo seu estudo, acreditam que a aderência às visitas e a realização dos testes laboratoriais possa ter sido negativamente influenciada, devido a uma pobre compreensão do processo médico a uma percepção incorreta do risco de TB.

QUESTÃO 10

Reescreva a conclusão do artigo (o último parágrafo em inglês apresentado nesta prova) em português, com as suas próprias palavras.

A identificação de populações vulneráveis, no país, é importante para melhorar os resultados em saúde e para diminuir a coinfeção TB-HIV. Neste estudo, o analfabetismo foi identificado como factor importante e, nesse sentido, é necessário existirem intervenções que diminuam o seu impacto. Para além disso, são necessárias acções sustentáveis que diminuam desigualdades e melhorem a educação da população.
