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Improving Prehospital Stroke Services in Rural and Underserved Settings With Mobile Stroke Units

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In acute stroke management, time is brain, as narrow therapeutic windows for both intravenous thrombolysis and mechanical thrombectomy depend on expedient and specialized treatment. In rural settings, patients are often far from specialized treatment centers. Concurrently, financial constraints, cutting of services and understaffing of specialists for many rural hospitals have resulted in many patients being underserved. Mobile Stroke Units (MSU) provide a valuable prehospital resource to rural and remote settings where patients may not have easy access to in-hospital stroke care. In addition to standard ambulance equipment, the MSU is equipped with the necessary tools for diagnosis and treatment of acute stroke or similar emergencies at the emergency site. The MSU strategy has proven to be effective at facilitating time-saving stroke triage decisions. The additional on-board imaging helps to determine whether a patient should be taken to a primary stroke center (PSC) for standard treatment or to a comprehensive stroke center (CSC) for advanced stroke treatment (such as intra-arterial therapy) instead. Diagnosis at the emergency site may prevent additional in-hospital delays in workup, handover and secondary (inter-hospital) transport. MSUs may be adapted to local needs—especially in rural and remote settings—with adjustments in staffing, ambulance configuration, and transport models. Further, with advanced imaging and further diagnostic capabilities, MSUs provide a valuable platform for telemedicine (teleradiology and telestroke) in these underserved areas. As MSU programmes continue to be implemented across the world, optimal and adaptable configurations could be explored.

Keywords: mobile stroke unit, rural health, prehospital, telemedicine, telestroke

INTRODUCTION

Stroke is one of the most frequent causes of disability and death worldwide (1, 2). Acute ischaemic stroke has enormous societal and financial costs due to rehabilitation, long-term care, and lost productivity (3). Due to rapid advances over the last decades, there are now safe and effective treatments for stroke (4, 5). However, leading therapeutic modalities, intravenous thrombolysis, and mechanical thrombectomy are extremely time-dependent (6–9). International guidelines now

support the use of thrombolysis up to 4.5 h after symptom onset as well as mechanical thrombectomy as a viable option within 6–24 h of last known normal for select patients with a mismatch between clinical deficit and infarct (4, 5). However, urgency remains as in case of mechanical thrombectomy, as for each 30 min delay before reperfusion, the relative likelihood of a good clinical outcome decreases by approximately 15% (10, 11).

With this in mind, concerted efforts have been made to improve in-hospital management of stroke by minimizing delays and optimizing protocols and personnel. However, despite substantial efforts to streamline care, a limited number of patients receive thrombolysis and fewer than 1–2% receive mechanical thrombectomy (12, 13). According to a recent survey of European stroke experts, 7.3% of ischaemic stroke patients in Europe received thrombolysis with 13 countries reporting rates higher than 10% with the highest rates in the Netherlands (20.6%), Denmark (19.9%) and Austria (18.4%), and lowest of <1% (14). Thrombolysis rates vary both between and within nations, with rates as high as 28.5% in the German state of Baden-Württemberg compared to the national-level rate of 17.5% in Germany (14, 15). Furthermore, thrombolysis rates have continued to increase over time—for example, increasing from 4.0% (2003–2005) to 7.0% (2010–2011) in the United States—and continue to increase after publication of large trials (such as ECASS III) which have expanded 3- to 4.5-h since onset window (13, 16). These low rates of treatment are largely due to the fact that patients do not reach the hospital in time for assessment and treatment within the narrow therapeutic windows. In fact, only 15–60% of acute stroke patients arrive at the hospital within 3 h after onset of symptoms (17, 18).

The Mobile Stroke Unit (MSU)—first proposed and studied in Homburg, Germany—is an innovation in the prehospital phase which aims to address this urgency by bringing the hospital to the patient (Figure 1) (19, 20). This is achieved by equipping an ambulance with the necessary tools for diagnosis and treatment of acute stroke or similar, time-sensitive emergencies. Thus, in addition to standard ambulance equipment, the MSU is equipped with a small-bore portable CT scanner, a point-of-care laboratory, and stroke medication. Via incorporated telemedicine, CT images, and real-time videos can be bidirectionally transmitted between the hospital and ambulance for expert consultation. These images can be integrated with hospital medical records. With the point-of-care laboratory, hematological parameters (thrombocytes, erythrocytes, leukocytes, hemoglobin), coagulation parameters [international normalized ratio (INR), activated partial thromboplastin time (aPTT)], clinical chemistry parameters (gamma-glutamyltransferase, pancreatic amylase, creatinine, glucose), and others can be analyzed within minutes in the MSU (19–36).

With MSUs, earlier thrombolytic therapy—within the first, or golden, hour—after acute ischaemic stroke has been shown to be beneficial for patients with improved functional outcomes—for both patients who were independent and those who needed assistance in activities of daily living before their stroke (28, 37–40). When compared to hospital-based thrombolysis in the first hour after acute stroke, MSUs have been shown to have comparable functional outcomes and mortality at 3 months (41).

MSUs have been shown to facilitate shorter alarm-to-treatment times without increasing adverse events (such as secondary intracerebral hemorrhage) (19, 28).

MSUs have been shown to play an integral role in evolving stroke services. They have been demonstrated to be effective in improving key prehospital temporal metrics (such as alarm-to-therapy and alarm-to-imaging times) in many centers worldwide (19, 25, 28, 29, 34, 42, 43). However, there remain relevant stroke treatment gaps for rural patients. MSU models and services can be adapted to improve stroke services for these patients. In addition to acute stroke triage, here, MSUs can provide telemedicine services to patients who are underserved. As stroke services continue to evolve, it is important to consider both the core and additional services which can be provided by MSUs.

INCORPORATING MSUs INTO STROKE SERVICE PLANNING

Primary Stroke Centers and Comprehensive Stroke Centers

The organization of acute stroke care has evolved significantly during the past few decades (Figure 2) (44). Primary Stroke Centers (PSCs) have been implemented to improve stroke care. PSCs include acute stroke teams, stroke units, written care protocols, and an integrated emergency response system (45). Comprehensive Stroke Centers (CSCs) integrate specialized services for the management of most severe cerebrovascular disease. These are typically staffed with experts in neurointervention and vascular neurology, have advanced round-the-clock, neuroimaging capabilities including MRI and cerebral angiography, specialize in surgical and endovascular techniques (including clipping and coiling of intracranial aneurysms, carotid endarterectomy, and intra-arterial thrombolytic therapy), and have specific infrastructure such as an intensive care unit (46).

As of 2017, comprehensive stroke centers accounted for roughly one-third of all stroke centers in the United States (327 of 1,148) and in France (37 of 132) (47–49). Considering large, densely populated European countries, the number of endovascular therapy capable centers range from 135 in Germany (1.7 per million inhabitants) to 28 in the United Kingdom (0.1 per million inhabitants) (14). In Finland, an example of a sparsely populated country, 5 of all 333 hospitals met criteria for classification as comprehensive stroke centers (50). In 2011, 66% of Americans were within a 60 min ground transfer to a primary stroke center (51). However, only 56% of Americans had 60 min ground transfer proximity to a CSC (52). As a result, in some settings it is difficult to transport patients directly to CSC, especially with standard ambulance services. Population distribution and density are important to consider when planning stroke services.

Onsite Triage to Avoid Secondary Transfer and In-Hospital Delays

Accurate triage and selection of the appropriate target hospital avoids the transfer of patients with large-vessel occlusion to hospitals without endovascular treatment services. It is estimated



FIGURE 1 | Mobile Stroke Unit (MSU). The Mobile Stroke Unit is an ambulance which contains a multimodal CT scanner, a point-of-care laboratory, as well as a telemedicine system, which allows transfer of CT images and videos of patient examination for input from hospital specialists. Pictured is the MSU in Homburg, Germany.

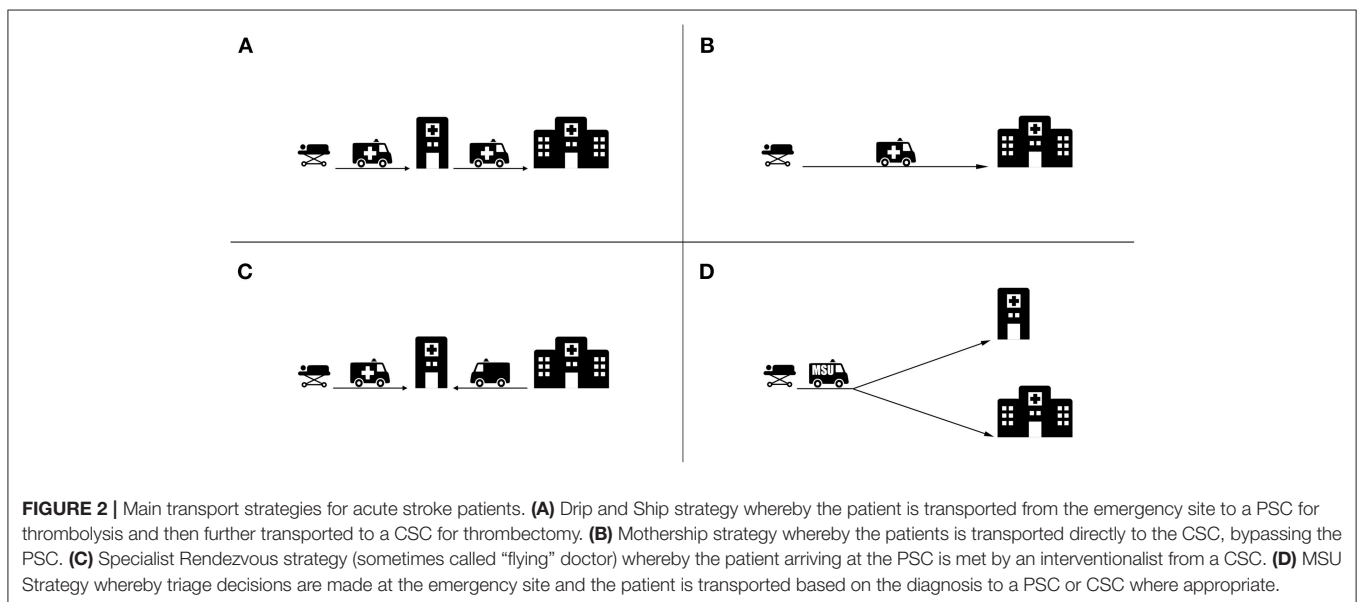


FIGURE 2 | Main transport strategies for acute stroke patients. **(A)** Drip and Ship strategy whereby the patient is transported from the emergency site to a PSC for thrombolysis and then further transported to a CSC for thrombectomy. **(B)** Mothership strategy whereby the patients is transported directly to the CSC, bypassing the PSC. **(C)** Specialist Rendezvous strategy (sometimes called “flying” doctor) whereby the patient arriving at the PSC is met by an interventionalist from a CSC. **(D)** MSU Strategy whereby triage decisions are made at the emergency site and the patient is transported based on the diagnosis to a PSC or CSC where appropriate.

that every minute of delay in transfer reduces the probability that patients will receive intra-arterial treatment by 2.5% (53). Further, by identifying thrombectomy-eligible patients, appropriate triage prevents the overloading of comprehensive stroke centers.

The MSU strategy has been shown to be effective for the triage of stroke patients (54). CT-angiography has been used in MSUs to assess for LVO at the emergency site (19). Even use of non-contrast CT has been associated with reduction of delay before intra-arterial treatment (30). For patients with haemorrhagic stroke, MSU-based triage allows for transport to hospitals with neurosurgery services, bypassing hospitals without

such capabilities (26). In the urban setting of Berlin, patients with hemorrhage transported to hospitals without neurosurgery services decreased from 43% in the conventional treatment group to 11% in the MSU group (43, 55). MSUs are also valuable for investigating other time-sensitive cerebral conditions such as traumatic brain injury or status epilepticus (56).

STROKE TREATMENT GAPS FOR RURAL PATIENTS

For rural patients, distance and travel time to the nearest stroke center is a crucial issue for time-sensitive stroke treatment (57,

58). Times from symptom onset to rural hospital admission range from 5 to 30 h have been reported (59, 60). These transport delays contribute to the low rate of thrombolysis of 1–6% for patients in rural areas worldwide (61, 62). Further, rural-urban disparities in thrombolysis administration have increased in recent decades (63). This trend is seen not only in low and middle-income countries but also in high-income countries (59, 64, 65). In Australia, only 3% of rural patients were able to access stroke units in a timely manner compared to 77% of urban patients (66). In Canada, patients living in rural areas are less likely to receive stroke unit care, brain imaging within 24 h, carotid imaging, and neurologist consultations. Furthermore, rural patients were less likely to be transferred to inpatient rehabilitation facilities and less likely to receive physiotherapist, occupational therapist, and speech and language therapist review (67). In the United States, the Get With the Guidelines—Stroke Registry has identified the arrival to a rural hospital as one of the factors associated failure of thrombolytic therapy (68).

The treatment gap between urban and rural areas is even more pronounced with endovascular treatment options for acute stroke (69). For the provision of intra-arterial therapy, the center requires highly specialized staff (such as vascular neurologists, neurointensivists, neuroradiologists, and anaesthesiologists), capable facilities and technical resources. This complex infrastructure is only available in limited CSCs which are located almost exclusively in urban centers (70). Consequently, patients living in rural and remote areas have limited access to timely IAT services (71).

Several strategies have been implemented in an effort to increasing thrombolysis rates. Health system factors generally associated with higher thrombolysis rates are urban location, centralized or hub and spoke models, treatment by a neurologist/stroke nurse, in a neurology department/stroke unit or teaching hospital, being admitted by ambulance or mobile team and stroke-specific protocols (72). Thrombolysis rates may be dependent on the hospital's level of stroke service (with stroke centers having the highest rates and hospitals without stroke units having the lowest rates) and patient factors such as age and preexisting disabilities (15). Accordingly, organizational streamlining by bypassing hospitals without stroke units may be sensible. However, in sparsely populated areas with long distances to the nearest stroke unit, it may be reasonable to initiate thrombolysis at a local hospital (supported by telemedicine, if available) before transferring the patient to center with a higher level of stroke care (73).

ADAPTING MSU APPROACHES TO RURAL HEALTHCARE

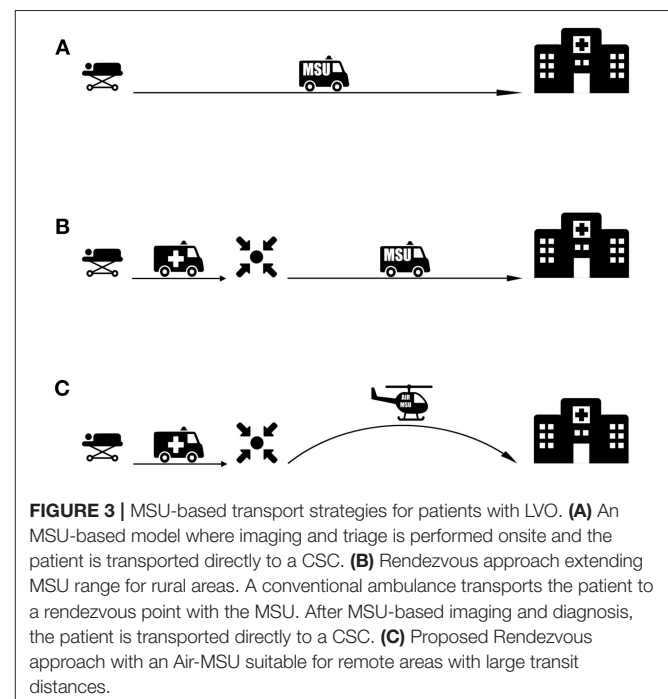
MSUs provide a valuable resource to rural and remote settings where patient may not have easy access to in-hospital stroke care (74). The MSU model can be adapted to local settings based on local needs. Accessing telemedicine technologies through cellular communication provides instant information enabling healthcare providers to reach out beyond the doors of the hospital.

As MSUs typically look to integrate with local emergency response services, there are several models of MSU staff composition. On board personnel can include vascular neurologists, paramedics, nurses or radiographers (25). Staff composition can be adapted to address the need of rural settings. In Norway, MSU staffing and responsibilities have been developed to work together with the existing EMS framework for rural and remote health (32, 75–77). In these smaller urban areas, the MSU is staffed with an anaesthesiologist, a paramedic and a nurse paramedic. Anaesthesiologists have been trained to identify and treat stroke (76). The anaesthesiologist may also provide resuscitation and perform invasive emergency procedures to any unstable or critically ill patient (77). Evolving telestroke technology requires staff to have ongoing, intermittent or mock training (78).

Subsequent iterations of the MSU have adapted to their respective settings. Larger vehicles have the advantage of carrying larger scanners and more specialized personnel, robustness in rural off-road conditions, and allowing relatives to accompany patients to provide history and procedural consent (79). Smaller vehicles may have greater access to narrow roads and lower cost. With this in mind, vehicle models should be selected according to the specific needs of the region and healthcare setting (25).

In Australia, a potential solution to serving remote patients with an Air Mobile Stroke Unit (Air-MSU) is being explored (80). With this approach, the MSU concept is being extended to another transport vehicle by equipping a helicopter or airplane with the CT scanner, POCT, and telemedicine connectivity.

A rendezvous model has been studied to enable the MSU cover large rural areas (**Figure 3**). With this approach, a conventional EMS ambulance is dispatched to the patient location and then travels toward the hospital. The EMS ambulance is met at



predetermined rendezvous locations—approximately half the distance—by the MSU. Predetermined rendezvous points are selected based on factors including catchment area, ease of road access, road connectivity and wireless signal strength (35). In a large rural area in Northern Alberta, Canada, this rendezvous approach has increased the catchment area to a 250 km radius surrounding the Comprehensive Stroke Center (35). This approach can be adapted to urban areas close to the periphery of the MSUs direct response area, effectively increasing the catchment areas of these units.

For rural and remote patients, there are also opportunities for incorporation of the MSU concept with the air ambulance service. In these situations, the air ambulance can act as the first responding vehicle to meet and transport the patient. Here, the patient can be transported to a predetermined rendezvous point or to a PSC where the patient can be met by the MSU. For a proposed Air-MSU, the CT-equipped airplane may land at the emergency site, and undertake onsite specialized stroke care and imaging (80). Alternatively, conventional EMS (ground or air) can meet the patient at the emergency site and transport the patient to a rendezvous point or PSC where the patient is met by the Air-MSU.

COST EFFECTIVENESS

While the MSU strategy remains an innovative approach to prehospital acute stroke management, more data is required to best understand the costs of the MSU, its staffing, and operation. Two independent preliminary analyses of cost-effectiveness have reported encouraging results. Based on the Homburg trial, analysis demonstrated an improvement in cost-benefit with reduction of personnel and an optimal cost-benefit with an operating radius between 43.01 and 64.88 km (81). In an analysis of Berlin-based MSUs, a higher rate of thrombolysis and earlier treatment for MSU patients resulted in reduced disability and its associated costs (82). While both of these studies suggest cost benefits, prospective cost efficiency data comparing MSUs to standard management is expected and awaited from the BEST-MSU trial (83).

MSU cost-effectiveness may be improved by substituting onboard physicians for telemedicine-linked remote experts (84). Considering the onboard CT scanners, there is the possibility for increased demand and improved technology to help reduce this high startup cost as economies of scale take their effect (85). Future services may be expanded to include other cerebral emergencies and treatment modalities.

Considering rural and underserved areas, the cost impact of frequency of deployment, operational area, personnel costs and support or replacement of other services may differ from urban settings and trial scenarios. MSU programmes may involve single or multiple units to cover large geographic areas and may require additional co-ordination with local EMS if, for example, a rendezvous approach is taken. Payment and reimbursement models particular to a health care system would impact cost burden to emergency and hospital services (86). In some rural settings, ambulance agencies may not be directly

affiliated with the relevant hospital impacting costs for the health services involved (74).

Future prospective research is required in defining costs for establishing and maintaining MSUs and costs for both acute and long-term care of patients managed both on MSUs and by standard emergency services. It is important that this financial cost is weighed with the perspective of important stakeholders in acute stroke care and consideration of total hospital and long-term care costs to the health care system for each stroke patient. As MSU configuration and operation is influenced strongly by setting, further health economic analyses in a variety of settings are required.

TELEMEDICINE FOR MSUs

Telecommunication approaches between MSUs and the stroke center via systems can provide real-time remote specialist advice by teleradiology (transmission of high-quality images) and telestroke assessment (real-time bidirectional videoconferencing and high-speed videos transmission) (25). As such, MSUs can provide advanced imaging and expert consultation at either the emergency site or at smaller healthcare centers which otherwise would not have this capability.

Teleradiology enables the transmission of images and information to physicians and specialists for use in remote diagnoses and medical consultation. Through MSU-based teleradiology high-resolution medical images (such as CT scans) can be obtained onsite, transmitted while stationary or en route, and interpreted by experts at a major university medical center.

Telestroke planning can be organized into a distributed network or hub-and-spoke model. In a distributed network model, the telestroke specialist is affiliated with a third party employer which provides contracted services with the originating hospital site (87). In a hub-and-spoke model, specialty care is provided to patients at community settings (spokes) by specialists affiliated with larger, more comprehensive tertiary care centers (hubs). Spokes are primary and secondary care centers which can be linked to distant sites—even more than 300 km away—where the telestroke provider is located. At hubs, vascular neurologists and other acute stroke specialists compose a call panel delivering telestroke services (78). Hubs further act as recipients for patients which require transfer to a higher level of care. Hub-and-spoke models have been shown to be cost-effective and to increase the catchment population (88, 89).

Reliability of MSU-Based Telemedicine

Technical innovation in the transmission of data between the hospital and MSU plays an important role. Early studies encountered difficulties in telecommunication in part due to suboptimal 3G public network availability (90–94). Fortunately, with improved technology and 4G mobile systems telecommunication is becoming more reliable (25). Telemedicine encounters between the MSU and hospital have been shown to be successfully completed for 99% of patients with 4G connectivity (95). Low-cost, tablet-based platform via commercial cellular networks (4G/LTE) were used to reliably perform prehospital neurologic assessments (NIHSS) of actors in

both rural (central Virginia) and urban settings (San Francisco Bay Area) via videoconferencing (96). With innovation it is important to ensure that bidirectional telecommunication is encrypted, secure and meets standards for transmission of protected health information.

The reliability of MSU-based telestroke assessment has been evaluated. Remote stroke assessment through telemedicine by a vascular neurologist has been shown to be reliable and comparable to in-person assessment (94). Further treatment decisions for thrombolysis showed strong agreement between an on-board vascular neurologist and a telemedicine vascular neurologist (84). The level of agreement is comparable to two vascular neurologists evaluating the same patients face-to-face in the emergency department (97). Importantly, the time to treatment decision and thrombolysis administration has been shown to be comparable between on-board and telemedicine vascular neurologists (98).

Limitations

While MSU-based telestroke approaches are promising, there are limitations to the management tasks which can be carried out remotely. The treatment of acute stroke in an MSU is a complex exercise involving multiple parallel tasks being carried out by several healthcare professionals within the confined space of an MSU. This includes neurological assessment, monitoring of vital signs, patient positioning, management of patient comfort, and possible restraint, CT scanning, point-of-care laboratory testing, and medication preparation and administration (86). Furthermore, the clinical decision on whether to administer thrombolysis requires training, experience, and careful clinical judgment. As such, there may be a limit to clinical decisions which can be carried out in the physical absence of a vascular neurologist via telemedicine. Looking beyond the first hour's hyperacute care, stroke patients require ongoing care from physiotherapists, occupational therapists and speech and language therapists. When considering the extension of stroke care to rural and underserved areas with MSUs, further work is required to determine optimal models for integration of these services.

EMS response varies worldwide, including between many European and US MSU settings. In the United States, ambulances are typically not staffed by physicians. As a result, in developing an MSU programme, a decision has to be made as to whether to include an on board physician. Early experience from Houston suggests the ratio of MSU alerts from EMS dispatch to tPA treatments is up to 10 to 1, suggesting that it may be impractical to have a vascular neurologist aboard the MSU for all calls (86).

IMPROVING PREHOSPITAL STROKE CARE IN LOW AND MIDDLE-INCOME COUNTRIES

With rapid advances in prehospital stroke care primarily in high-income countries (HIC), it is important to consider opportunities, challenges and the applicability of these approaches to low and-middle income countries (LMIC) as

well. There is a growing disparity in the burden of stroke between LMIC and HIC. About 75% of deaths from stroke and more than 80% of disability-adjusted life years (DALYs) occur in LMICs (99–103). Further, in the last four decades, there has been a 42% decrease in stroke incidence in high-income countries and a 100% increase in LMIC (104). Cerebrovascular diseases in sub-Saharan Africa are increasingly frequent and associated with a poor outcome (2, 105–111). Unfortunately, there is very limited data on the organization of prehospital stroke services in such settings. For example, only 3 African countries (South Africa, Egypt, and Morocco) have reported experiences on thrombolysis (112).

There are multifactorial barriers to implementing effective prehospital stroke care in the LMIC setting. Prehospital barriers include unavailable/inadequate transportation and a lack of trained stroke specialists (101, 102, 113). Considering transport, in many cases, the ambulances are not well-equipped and do not have trained personnel (114). Further, most patients in these settings use their personal or hired vehicles, rather than ambulances, to seek medical help (113, 115). In these settings, patients who are transported by ambulances are predominantly those with trauma injuries and obstetric emergencies (113).

The global deficit in skilled healthcare personnel is most pronounced in rural areas, especially in LMIC (114, 116). In India, 80% of specialists live in urban areas. Consequently, 700 million people living in rural India have to travel a distance of 75 to 100 km for a tertiary consultation (117). There remains a paucity of neurologists worldwide, especially in the LMIC setting. The global median of adult neurologists is 0.43 per 100 000 population, with the number of adult neurologists ranging from 0.04 (in LIC) to 4.75 (in HIC) per 100,000 population (118). In India, nearly 1 billion people live in regions lacking access to a practicing neurologist (119).

With limited specialized personnel and transport available, telemedicine could be helpful to address gaps in stroke service delivery. Remote teleconsultations would allow the few, existing specialists, primarily situated in urban areas, to provide expertise to a greater number of patients who are situated in rural settings. To overcome infrastructure and connectivity hurdles, satellite-based telemedicine has been effectively employed in rural India (120).

A telemedicine-capable MSU could provide specialized care in the regions with limited hospital emergency departments and lacking EMS systems. MSUs could function as mobile clinics when not in use in emergencies. As such, they could provide hospital-caliber imaging and laboratory services to underserved areas.

Encouragingly there are a growing number of MSU programmes in LMIC settings. For example, in Thailand, a stroke fast track programme, telestroke, and two MSUs in Bangkok are improving stroke care (121). Inclusion of MSUs should be considered as part of long-term planning for stroke service improvement in these settings.

MSU operation is influenced strongly by setting—be it urban or rural, or high- or low-income. In metropolitan settings, factors such as traffic congestion and existing emergency response configurations as well as geo- and socio-spatial determinants of

emergency service utilization impact transport modeling (122). In LMIC, road conditions impact both transport planning and may necessitate physical upgrades to the MSU vehicle. However, data in these settings remains limited. As the preponderance of MSU studies to date have been conducted in HIC, further research is required better understand the implementation and optimization of MSU transport models in the LMIC setting.

Considering the prehospital phase as a whole, there are alternative strategies for early identification and preclinical selection of stroke patients which may have applicability to rural patients and those in resource-limited settings. Several prehospital stroke screening scales have been developed and employed in an effort to assist dispatchers in identifying stroke patients with high specificity and sensitivity (123–125). Additionally, there are several prehospital scales assessing stroke severity with the potential to help identify patients with LVOs (126–128). Nevertheless, prehospital stroke scales vary in their accuracy and may be influenced by levels of stroke scale training and provider educational standards (124, 129). Public awareness campaigns, training of dispatchers, and paramedics are also effective methods of early identification of stroke which may be complementary to other prehospital strategies (130–135). The quality of stroke care varies across the world depending upon location, local hospital facilities, ability to pay, education, and

cultural, social, or religious beliefs (136). As such, prehospital strategies should be tailored to local health needs, affordability and existing stroke services.

FUTURE DIRECTIONS

Future MSU service planning may involve integration of multiple concepts. Further adaptation will allow MSUs to better integrate into local and regional emergency medical services. Remote locations may eventually benefit from a combination of the Air MSU and rendezvous model. Specialized training of on board personnel may further alleviate the need for an on board vascular neurologist. Improvements in technology may allow for smaller, lighter and more robust units CT scanners. The MSU concept can be expanded to treat other emergencies in underserved areas. Further studies are required to better understand the medical and health-economic benefit of each model.

AUTHOR CONTRIBUTIONS

SM and KF contributed to the conception and design of the work, literature search, analysis and interpretation, and article drafting. SM, SW, IQG, SAH, ML, and KF contributed to critical revision. All authors gave final approval of the version to be published.

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