An Inclusive supply chain model for the treatment of respiratory diseases based on Personalized medicine through modern biosensing devices.

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Abstract: The relentless escalation of healthcare costs and the ageing population process in industrialized countries threaten the long-term sustainability of modern healthcare systems. In particular, respiratory diseases, affecting around 500 million people globally, are a most relevant cause of inability and mortality worldwide and a main contributor to global healthcare spending. Increasing the coverage of healthcare systems in order to strengthen prevention and diagnostics is regarded as the only viable possibility to reduce the costs of treatment while maintaining or improving the quality of patient care. In such regard, the recent technological advances in biosensing and ICT technologies offer a substantial opportunity to implement advanced self-testing systems allowing for the provision of territorial servicers in coherence with the modern approaches to patient-centric and personalized medicine. Most of the testing operation in respiratory medicine, however, are currently performed in specialized labs, with costly and bulky equipment operated by professional personnel, thus making decentralized healthcare approaches a hardly viable and economically sustainable solution. The lack of effective screening and prevention programs, the significant incidence of underdiagnosed or late-diagnosed cases complicates the treatment of respiratory diseases and increases the overall costs. In such context this paper proposes a novel personalized testing method for respiratory diseases, and discusses the achievable benefits compared to traditional "Point of Care" (POC) and lab-based testing, thus offering an original contribution to the scientific debate on the effectiveness of decentralized healthcare Supply Chain (SC) models and some relevant insights on self-testing and community healthcare. Based on the results obtained, the proposed personalized testing method emerges a viable possibility to establish affordable screening and prevention of respiratory diseases, thus improving the inclusiveness of the services while preserving the economic sustainability of the healthcare system.

Keywords: Inclusiveness, Healthcare, Biosensing, Personalized medicine.

1.Introduction

The critical lack of responsiveness and inclusiveness of modern Healthcare Systems (HS), clearly emerged during the COVID-19 pandemic, has actually highlighted a structural inadequacy of the centralized hospital-based supply chain (SC) model in providing universal access to quality healthcare services to all individuals. Such inadequacy rises some fundamental concerns about the capability of the current healthcare SC in providing a response to the increase of the demand for healthcare services expected in the next future in consequence of the changing population demographics in industrialized countries. (Fatani et al., 2024).

In such regard, improving proximity services is considered a valid opportunity to increase the inclusiveness and economic sustainability of the traditional hospital-centric models. In the last two decades, the development of remote POC supply chain models, in alternative to centralized SC structures has animated a substantial scientific debate about their economic effectiveness. Several researchers indeed highlighted a higher service provision cost, while other studies reported clear evidence of successful applications of remotely provided healthcare services, for example in HIV testing or in diabetes. The recently renewed interest for remote healthcare service provision has led to the formulation of new SC models, such as homecare and community-services in addition to the traditional POC and hospital/laboratory models. In such regard, the development of new diagnostic systems and devices, based on advanced biosensing technologies allows for patients' self-testing and real time transmission of clinical data, thus opening a new spectrum of organizational and operational

possibilities within the context of Personalized Medicine (PM) (Tortorella et al., 2020; Wehde, 2019).

Based on such motivations, this research proposes an approach for evaluating the efficiency of PM SC models in comparison with traditional centralized and POC based schemes. In particular, in this research considers this topic referring to the scenario of respiratory diseases, which up to today affect approximately 500 million people globally and account for a total direct cost of approximately 6% of the total annual EU health care allocation, mostly related to Chronic Obstructive Pulmonary Disease (COPD) (Rehman et al., 2020).

Based on the recent literature on biosensing technologies (Radogna et al., 2020; Szunerits et al., 2023), this research proposes a new SC model for the provision healthcare services for respiratory diseases, through the employment of a novel smart device allowing for patients' self-testing, in alternative to traditional analysis method based on the analysis of the Exhaled Breath Condensate (EBC). The alternative method proposed involves a device for the measurement of the concentration of hydrogen peroxide (H_2O_2) in the exhaled breath (EB) without the need of condensation. The reliability of this method has been recently demonstrated (Bruno et al., 2024). This research thus contributes to the state of the art of PM SC models in e-health contexts, by means of a validated method, which, does not require costly and advanced equipment (Broza et al., 2018; Karnon et al., 2007) only available in specialized labs.

This research assesses the effectiveness of a PM SC model using a new method for testing respiratory diseases. It employs a low-cost and easy-to-operate device featuring a nanostructured electrochemical sensor that measures hydrogen peroxide levels in exhaled breath. Integrated into a mask with a chitosan layer, the sensor allows direct measurement without condensation, simplifying operations and enabling patient self-testing. Since hydrogen peroxide is a recognized biomarker for respiratory conditions, this system offers an accessible and effective testing approach. The high sensitivity of the sensor provides reliable measurements, opening new opportunities for screening and prevention.

2.Literature review

The decentralization of healthcare SCs is a topic discussed since the late 20th century, when the POC service provision model, became a relevant element of health policies in many European countries. Recently, the COVID-19 pandemic has dramatically fostered the research towards new and more efficient decentralized SC models, and the scope of remote service provision enriched with new possibilities including five distinct settings: homes, communities, clinics, peripheral laboratories, and hospitals. (Pai et al., 2012). The importance of proximity healthcare structures in the provision of primary care services has been recently discussed by several authors (Brambilla et al., 2023, 2021) within a new holistic view of territorial healthcare systems based on community homes and community hospitals and involving the medical staff to interact with the population to improve prevention and early diagnosis. Such approach ultimately aims at better exploiting the potential benefits of the decentralization in terms of efficiency, inclusiveness, and reduction of territorial inequalities through the establishment of interconnected proximity healthcare structures. Decentralization and connectivity thus become the technological pillars of new healthcare provision processes based on digitized patients' data, generating electronic medical records, and providing decision-support capabilities. The digitalization of the SC thus emerges as a transformation of organizations (Wang et al., 2020) towards more efficient and inclusive service provision models.

The above reported considerations highlight the need for the development of new decentralized HS in the context of PM. In such regard, finding application contexts where such an approach can produce substantial benefits becomes a challenging task. This research, in particular, proposes a possible application in the treatment of respiratory diseases such as asthma, COPD, etc. The World Health Organization (WHO) has recently estimated around 500 million people affected by these diseases globally (Bousquet and Kaltaev, 2007), which is likely to be an underestimated number, since a percentage between 45% and 65% of patients with COPD are not timely diagnosed due to the difficulties in successfully screening patients with the current technologies and testing methods. Based on the existing literature (Hortin, 2005; Melhuish et al., 2020), hence, this research aims discusses the development of a novel personalized service provision model and evaluates its economic effectiveness as compared to the current traditional practice. Following the methodologies proposed the literature for comparing traditional laboratory and POC testing processes, the approach proposed refers to the "Cost Of Illness" (COI) (Jo, 2014), methodology based on the evaluation of direct and indirect costs. For respiratory diseases, indirect costs have been reported to account for 61%, 82%, and 83% of the total cost per patient in Italy, the Netherlands, and the UK, respectively (Foo et al., 2016).

3. Methodology

This section discusses the methodology adopted for evaluating the efficiency of the proposed PM SC model for the treatment of respiratory diseases and compare them with the traditional clinical practice.

3.1 PM testing method for respiratory diseases

In the current clinical practice, the workflow of operations related to the treatment of respiratory diseases involves three main phases, namely: diagnostics, treatment and follow-up (Fig.1). The diagnostic process aims at determining the specific pathology of the patient, which is a crucial element for establishing the appropriate treatment. When the therapeutic treatment is completed, a follow-up program can be activated to periodically monitor the patient's conditions on a regular basis.

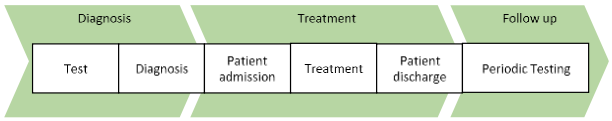

Figure 1 – Workflow of operation for the treatment of respiratory diseases.

As stated before, the current clinical practice for testing patients affected by respiratory diseases mostly relies on the measurement of the concentration of specific biomarkers (e.g. hydrogen peroxide, lipid mediators, purines, and cytokines) in the EB. For such purpose, the EB is collected through a non-invasive sampling method involving the patient to breathe into a single-use mask connected to the expiratory circuit of a mechanical ventilator. The samples collection involves their condensation into a refrigerating unit until the dew point is reached. The EBC samples can thus be analyzed immediately or stored for delayed processing. EBC samples storage, however, may result in the degradation of the biomarkers, therefore, for delayed processing, the samples are sealed in a tube and frozen at temperatures approx. −80°C. The concentration of relevant biomarkers is then measured in centralized labs using a Gas Chromatographer in tandem with Mass Spectrometer (GC-MS). Portable GC systems based on Ion Mobility Spectrometry (IMS) (Covington et al., 2015) can also be found on the market for POC breath analysis (Zhou et al., 2015), however their limited Volatile Organic Compound (VOC) separation capability may affect the accuracy of the tests. Finally, referring to the POC setting, hence, a common practice is to collect the samples at the patient's place by means of portable sampling devices (e.g. R-Tube by Respiratory Research, USA), and bring them to the centralized lab for the analysis.

Summing up, referring to the current clinical practice, the lack of standardized collection procedures is a most relevant drawback of the current EBC sampling method, which may affect the quality of the analysis.

Differently from existing approaches, the self-testing PM method here proposed relies on a smart device capable of measuring of the hydrogen peroxide concentration in the EB, without condensation thus avoiding possible alterations due to sample handling and delayed processing. This device has been scientifically validated (Bruno et al., 2024) and consists of a carbon nanocluster mask compliant with the 93/42 EEC bacteriostatic directive and equipped with an integrated electrochemical sensor for detecting the concentration of hydrogen peroxide in the EB. This sensor consists of three electrodes (reference, counter and working electrodes) obtained from the silver layer of Compact Discs (CDs). The counter electrode is coated with a carbon conductive ink, while the pseudo-reference electrode is covered with an Ag/AgCl paste. A thin chitosan absorbent layer is then electrodeposited on the top of the three electrodes to trap the aerosol phase, ensuring the contact of the analyte with the sensitive element. The use of chitosan as absorbent is advisable not only for its high absorbent capacity, but also because it makes the whole system biocompatible and biodegradable(Khalid et al., 2002; Ren et al., 2005). Similar recent studies (Güder et al., 2016), report the use of a paper absorbent layer with a potassium chloride as electrolyte; however, the effects of evaporation in normal ambient conditions requires continuous moistening of the paper and the changes in humidity alter the conductivity of the cell thus affecting the quality of the measured signals.

By employing novel nanostructured electrodes in conjunction with a Linear Sweep Voltammetry (LSV), the proposed method allows for the quantification of hydrogen peroxide concentrations from 100 to 500 μM with a sensitivity of 0.110 $\mu A\ \mu M^{-1}\ cm^{-2}$ and Limit Of Detection (LOD) of 30 μM (Bruno et al., 2024). This unprecedented sensitivity allows to overcome a main limitation of similar studies based on traditional electrochemical sensors (Połomska et al., 2021; Radogna et al., 2020; Szunerits et al., 2023).

3.2 Healthcare supply chain efficiency

The performance of the SC has been measured referring to the COI method, a widespread evaluation technique generally employed in the healthcare sector and to prioritize health-care policies and SC decisions. The COI classifies the costs of provision of healthcare services into two main categories: direct and indirect costs. Direct costs refer to the expenses directly attributable to treatment and typically involve:

- cost of labor, referred to the time spent by the medical and paramedical staff and estimated considering to their average salary;
- cost of equipment, referred to a share of the cost of the equipment employed in the treatment, and evaluated considering the equipment acquisition cost, its salvage value, useful lifespan and additional calibration, maintenance, and repair expenses;
- cost of consumables, referred to the cost of reagents, and other consumables.

Indirect costs are a much less agreed upon cost category (Ernst, 2006), involving the economic burden of a disease borne by the society (Halpin, 2006; Ramsey and Sullivan, 2003). These costs are generally measured through the human capital method considering the evaluation of the productivity losses associated with morbidity and mortality. Based on the above cost scheme, in this research the Average Cost per test (ACt) and the Average Annual Cost per patient (AACp) (Hortin, 2005; Howanitz and Jones, 2004) indicators are employed to compare the efficiency of the supply chain models considered. The aforementioned cost indicators are defined as:

$$AC_t = \frac{(E + S + L)}{N} \quad (1)$$

$$AAC_p = AC_t\ n \quad (2)$$

, where E is the annual cost of equipment, S is the annual cost of supplies, L is the annual labor cost, N is the total number of tests performed per year, and n is the average number of tests performed per patient per year.

The cost of labor per test is calculated referring to the duration of the testing cycle. In such regard, the approach commonly employed in the literature (Kaso et al., 2022) is to classify the overall logistic time of healthcare supply chains that distinguishes the following relevant delays:

- Time to diagnosis (or diagnostic delay): period between the onset of symptoms and confirmation of the pathology.
- Time-to-treatment initiation: period between diagnosis and the start of treatment.
- Time to-recovery: period between the admission and patient recovery, calculated as the difference from the start of the treatment and the patient discharge.

The diagnostic delay is further classified into patient delay and health system delay, referred to the time from the appearance of symptoms to the consultation with the referring physician, and the period from the first consultation to the date of diagnosis. Finally, the workflow model of a laboratory test first outlined by Lundberandg (1981), divides the testing cycle in three phases: pre-analytical, analytical, and post-analytical, involving nine sub-operations. The Pre-analytical Phase which starts when the consultant orders a test and a sample is received in the laboratory, the analytical phase involving sample segregation operations and association with the patient, and the post-analytical phase including the approval of reports and the issue of the result. The total turnaround time (TAT) of the testing operations, defined as the time between ordering a test or submitting a specimen to the lab to reporting results (Dawande et al., 2022), is generally employed as a benchmark for laboratory performance and timeliness (Dawande et al., 2022; Goswami et al., 2010).

4. Results and discussion

This section discusses the results of the comparison of the traditional centralized lab-testing medicine (CM) model and decentralized (POC) model, and the novel PM model. Specifically, the CM model refers to the scenario where the patient moves to the specialized lab and performs the test with assisted by a professional caregiver. The traditional POC testing model refers to a scenario where the caregiver that moves to the patient's place, collects the sample, and brings is to the lab for the subsequent analysis. Finally, in the proposed PM scenario the patient can self-test using the smart medical device. In each scenario the cost of equipment, labor and consumables have been analytically evaluated. In the CM scenario, the fixed annual equipment cost is calculated referring to the price of an EBC condenser unit and a GC-MS equipment, and the Turnaround Time (TAT) is considered equal to half hour. In the POC scheme the additional cost of the portable sampling and storage system is considered, and the overall TAT considered is one hour. In both cases, the non-discounted annual depreciation is considered, with a useful life of 5 years and no salvage value. The labor cost for the CM and POC schemes is referred to their respective TAT. In the PM scenario, each patient is supposed to receive a personal testing device, and its cost ultimately influences the annual testing cost per patient. The costs obtained are reported in Tab. 1.

Testing Costs in traditional centralized/decentralized HS models		
	CM scenario (TAT=30 min)	POC scenario (TAT=60 min)
Fixed Annual equipment cost (€/year)	25.000	28.000
Variable (per test) Labor cost (€)	17,5	35
Variable (per test) Cost of consumables (€/test)	0,5	1

Table 1 - CM and POC testing costs.

Concerning the cost of the equipment, the additional cost of the sample collection unit must be considered. Additionally, the TAT is higher due to the sample transport time which is not considered in the CM scenario since it is assumed that in this case patient moves to the centralized infrastructure at his expenses. In the PM scenario the industrial cost of the system must be calculated referring to the cost of the sensor and to the cost of the smart device. The overall industrial cost of the sensor can be estimated at approx. 2 €, while the self-testing device, designed to interact with a common smartphone, results from the assembly of a Micro-Controller Unit (MCU), a potentiostat, a communication module, a power supply unit, and some minor components. The overall industrial variable cost, including the cost of the Printed Circuit Board (PCB) system can be estimated at around 115 €/pc. Additional initial costs to consider are referred to research & development costs, the patenting operations, the development of the firmware, the compliance with the EU Medical Device Directive 93/42/EEC (EU 1993) and the CE certification required for the introduction in market. The corresponding fixed industrial cost can be estimated at around 145 € per unit (assuming a minimum production of 1000 units per year). The final selling price, considering a reasonable profit margin to the developer, can be estimated at approximately 300 € per unit. Assuming a useful life of the device of 3 years, the corresponding annual cost results in 100 €/year per patient. The variable cost per test (i.e. the cost of the mask with the integrated sensor) is roughly estimated at 20 €/year assuming a monthly testing base of 10 tests per year, in coherence with the current clinical practice for COPD treatment, involving 6-month intervals for mild diseases, and 2-week to 1-month intervals (Yawn and Kim, 2018) for severe exacerbations. Based on such

assumptions, the cost per patient referred to the SC models considered is reported in Fig. 2.

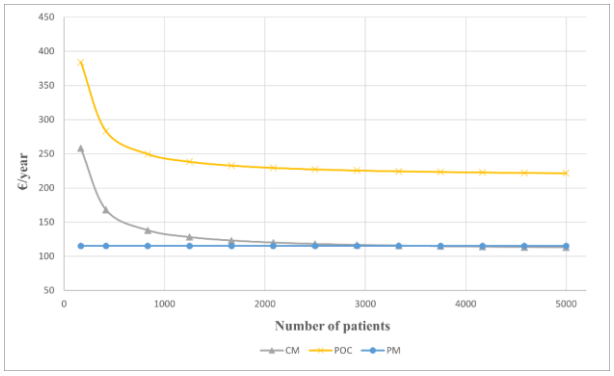

Figure 2 - Comparison of the cost per patient in CM, POC and PM SC models.

Personalized testing offers a capital saving in the investment related to the equipment which makes it more convenient for a limited number of tests (patients), however as the number of smart devices increases, the higher scale economies of the lab-based system emerges, thus originating a break-even at approximately 12.500 tests per year as given in Fig. 3.

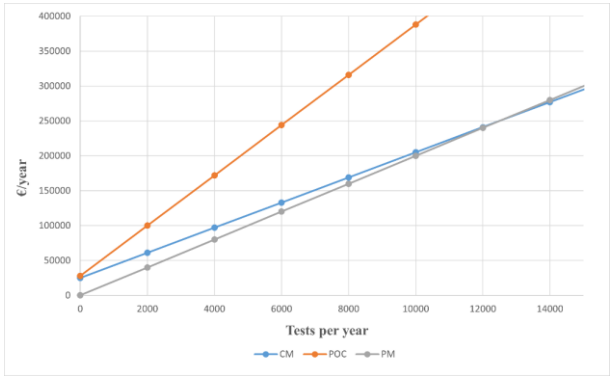

Figure 3 - Comparison of the cost per year in CM, POC and PM SC models.

The results obtained demonstrate that the CM scenario achieves the lowest cost per patient, but it is substantially influenced by the fixed costs of equipment, therefore the cost per test drastically increases when the number of tests per year is low and scale economies are not effective. This makes it not suitable for small communities and demonstrates its poor inclusiveness. In the POC scenario, the cost per test increases because there are additional costs referred to the sampling equipment and to the higher labor cost due to the longer TAT. Finally, in the PM scenario, the patient can self-test without involving medical staff, thus the direct cost of the test is only related to the consumables, but all the patients must be provided with the testing device. As mentioned before, this scenario can only be compared to the others assuming an average number of tests per year. In the case considered here, with 6 test per patient per year, the PM testing model shows a slightly higher cost per patient compared to the CM model. However, as the number of patients decreases, PM becomes substantially more cost-efficient than CM due to the lack of the fixed laboratory costs.

A final underlying assumption is that all the testing approaches have the same quality, therefore the diseases diagnosis and treatment processes are not influenced by the testing method, and no impact is generated on the indirect costs. However, in the POC scenario the risk of alteration of the sample during the collection or transportation phases may lead to sample corruption, while in the PM scenario besides the validation of the sensor, additional scientific evidence of the equivalence of the electrochemical sensing method with the traditional EBC analysis should be provided.

5. Conclusions

Respiratory diseases are a main cause of disability and mortality and significantly contribute to the healthcare expenses in modern healthcare systems. In addition, with the ongoing population ageing process in industrialized countries, the economic and social burden of respiratory diseases is expected to further increase. In such context, the development of new approaches to treat respiratory diseases is necessary to improve the sustainability and inclusivity of healthcare systems. For respiratory diseases, in particular, the lack of effective prevention and screening processes results in a considerable number of undiagnosed or late-diagnosed cases. Furthermore, the reliability and cost efficiency of the testing methods employed in the current clinical practice are questioned by researchers. In particular, this study demonstrates that traditional POC testing methods based on compact portable devices do not improve the cost effectiveness of the testing services, while they introduce additional sample alterations problems which may originate during the handling phases.

In such context, the advent of smart clinical devices based on bio-sensing technologies, and their applications in personalized medicine context are opening a wide landscape of new decentralized testing methods capable of providing timely and accurate diagnostic information to healthcare professionals. The proposed research analyzes a new testing method for respiratory diseases based on the analysis of the exhaled breath through a low-cost and easy to operate device featuring a novel nanostructured electrochemical sensor for the measurement of hydrogen peroxide concentration in the EB. Considering the superior sensitivity of the nanostructured sensor and the consolidated scientific evidence confirming the validity of hydrogen peroxide as a biomarker of respiratory diseases, the system proposed allows an easy to use and cost-effective approach for testing respiratory diseases. The development of a cost-effective and easy to use self-testing device thus allows for the development a new PM SC model for respiratory diseases in addition to traditional centralized and POC testing methods. Following the existing literature on the cost effectiveness of centralized vs

decentralized SC models for the provision of healthcare services, this research provides a preliminary cost analysis of the traditional testing methods for respiratory diseases in comparison with the proposed PM model.

The reported results demonstrate how centralized and decentralized SC models do not allow for territorial and inclusive provision of services for respiratory diseases, while a PM can substantially improve the performance of the Healthcare SC at a much lower service provision cost, particularly in small communities. In such regard the research proposed also represents a substantial contribution to the scientific literature on PM SC models.

Ultimately, this research aims at demonstrating that modern decentralized SC models for the provision of healthcare services are arguably the only possibility of providing inclusive healthcare services while ensuring economic sustainability. In such regard, the study proposes substantial managerial insights concerning the implementation of modern concepts of territorial medicine, e-health, and patient centric medicine. This approach enables proximity services to people based on a new concept of integrated treatment path starting from the patient's home as the first point of care and proceeding with proximity infrastructure (Community Homes) and finally reaching the hospital network.

Finally, a main limitation of this study is that it does not take into to account the indirect costs therefore it provides only a partial representation of the economic efficiency. In addition, the assumption of the same quality of the treatment obtained with the new testing methods should be validated. Referring only to direct costs is however a common approach adopted in the literature, most likely due to the lack of reliable estimates of the indirect costs.

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