Tailored screening and dedicated funding for direct acting antiviral drugs: how to keep Italy on the road to hepatitis C virus elimination?

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Abstract
Background and aims. Hepatitis C virus (HCV) elimination for Italy is an ambitious, but achievable goal. In Italy, there is political will, which aims to achieve the World Health Organization (WHO) elimination goals recognizing the need to identify undiagnosed individuals in key high-risk groups and in the general population, however there is concern regarding HCV treatment implementation in Italian Regions.
Methods. A modelling analysis was conducted, using the "Italy Polaris" model, to forecast the impact of different HCV treatment rates in achieving the HCV elimination goals in Italy. The model assessed two treatment scenarios: 2018 Scenario and 2019 Scenario, using the annually HCV treatment rate in Italy.
Results. Considering a high treatment rate, as assumed by the 2018 Scenario, all HCV elimination targets would be achieved. Considering the 2019 Scenario, in which a decreasing number of newly diagnosed individuals and as consequence, a decline in the number of treated patients, were assumed, only the 65% HCV mortality reduction would be an achievable goal in Italy. The other elimination targets could be achievable over 7 years later than the year 2030.
Conclusions. Establishing an *ad hoc* fund for DAAs for each Italian Region, binding resources both for case finding, through active screening and activities for rapid linkage to care and treatment, is of paramount importance, in order to keep Italy on track to achieve the WHO elimination targets by 2030.

ORIGINAL ARTICLES AND REVIEWS

INTRODUCTION

Viral hepatitis is not just a clinically relevant disease, but it is a major public health problem that requires an urgent response. As a life without HCV is now an achievable target, it is crucial to define health policies that seek to identify undiagnosed infections but also guarantee access to treatment to all infected individuals. Thus, achieving the World Health Organization (WHO)'s Global Health Sector Strategy (GHSS) goals for the elimination of HCV by 2030 has reinvigorated public health initiatives aimed at identifying patients with HCV related disease [1]. The limitation of HCV therapy is no longer treatment efficacy or adherence, but the identification of the available patients to treat.

Initially in Italy, HCV treatment with direct acting antivirals (DAAs) was prioritized to patients with severe, progressive liver disease. In 2017, however, a Universal treatment strategy was introduced, meaning all diagnosed patients were eligible for treatment [2]. Since 2015, a large proportion of the HCV-infected population has been treated and eradicated their infection, which was possible thanks to a dedicated Fund for Innovative Drugs, which guaranteed the release of DAAs without any kind of budget restriction. However, access to treatment has not been homogeneous throughout the country. Italy is divided into twenty Regions with their own broad discretion in planning, organizing, and financing health care services within their territory, while the State is limited to formulating general principles. The Constitutional Reform of 2001 transformed the Italian National Health Service (NHS)

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from a substantially centralized system into a highly regionalized one. As a consequence of this decentralization, although a National Hepatitis Plan exists, individualized models of HCV care persist and there are no uniform strategies across regional networks. Only two (Sicily and Veneto) of 20 Regions throughout Italy have developed adequate organizational and operational policies regarding HCV elimination [3].

Considering these health systems challenges and the economic burden of HCV chronic infection, is it possible to achieve the HCV elimination targets and what barriers will be faced?

METHODS

A modelling analysis was conducted using the "Italy Polaris" model, grounded in the natural history of HCV progression to forecast the impact of HCV in the disease burden in the general population as previously described [2-6]. Briefly, an Excel-based Markov disease burden model was populated with HCV prevalence data in Italian general population, stratified by age and sex, to quantify the annual HCV-infected population by liver disease stage, sex, and age. The model simulates the natural history of the disease and forecasts disease burden annually, assessed under two scenarios, 2018 Scenario and 2019 Scenario, using the annually, reported DAA treatment rate in Italy [7, 8]. The inputs of each scenario are reported in *Table 1 (A, B)*. 2018 Scenario assumes that the same number of people are treated each year beginning in 2018, and that at least 30 000 patients are diagnosed per year [7]. 2019 Scenario assumes that without an extensive screening policy the number of newly diagnosed individuals each year will decrease. Additionally, as the number of newly diagnosed decreases, it is estimated that the number

of treated patients will also decline. To evaluate the progress of each scenario, the WHO elimination targets were calculated for Italy (Targets: 90% reduction in incidence of chronic HCV infections between 2015 and 2030, 65% reduction in HCV-related deaths due to chronic HCV infection between 2015 and 2030, 90% diagnosis coverage of the HCV-infected population and 80% treatment coverage of the eligible HCV-infected population by 2030) [1].

RESULTS

The results of each scenario for each elimination target are reported in *Figure 1*.

All WHO elimination targets would be achieved considering the 2018 Scenario. This means that considering a high treatment rate, as it was reported during the year 2018, Italy could eliminate HCV infection by 2030. Considering the 2019 Scenario, in which it was assumed the number of newly diagnosed individuals each year would decrease and as consequence the number of those treated will also decline, only the 65% HCV mortality reduction would be an achievable goal. The other elimination targets could be achievable over 7 years later than the year 2030. If screening/diagnosis increases from the screening guidelines but treatment does not, then the outcomes will not change substantially from the 2019 Scenario outcomes.

For each elimination target, the overall results are schematically reported in *Figure 2*.

DISCUSSION

Italy, a country that in 2018 was on track for achieving the elimination goals [7], is no longer estimated to achieve these targets, except the goal for liver mortality reduction [8]. Previously, Italy was estimated to have

Table 1
Key inputs by treatment scenario

(A) 2018 Treatment scenario						
Years	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**
Treated	56 300	56 300	56 300	56 300	56 300	56 300
Newly diagnosed	30 400	30 400	30 400	30 400	30 400	30 400
Fibrosis stage	≥F0	≥F0	≥F0	≥F0	≥F0	≥F0
New infections	7200	7200	6000	5400	4800	4300
Treated age	15-85+	15-85+	15-85+	15-85+	15-85+	15-85+
SVR*	98%	98%	98%	98%	98%	98%

(B) 2019 Treatment scenario						
Years	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**
Treated	56 300	35 800	32 100	31 400	31 200	31 200
Newly diagnosed	30 400	27 800	25 800	23 800	22 000	15 400
Fibrosis stage	≥F0	≥F0	≥F0	≥F0	≥F0	≥F0
New infections	7200	6500	6100	5700	5300	4900
Treated age	15-85+	15-85+	15-85+	15-85+	15-85+	15-85+
SVR*	98%	98%	98%	98%	98%	98%

*SVR: sustained virological response.

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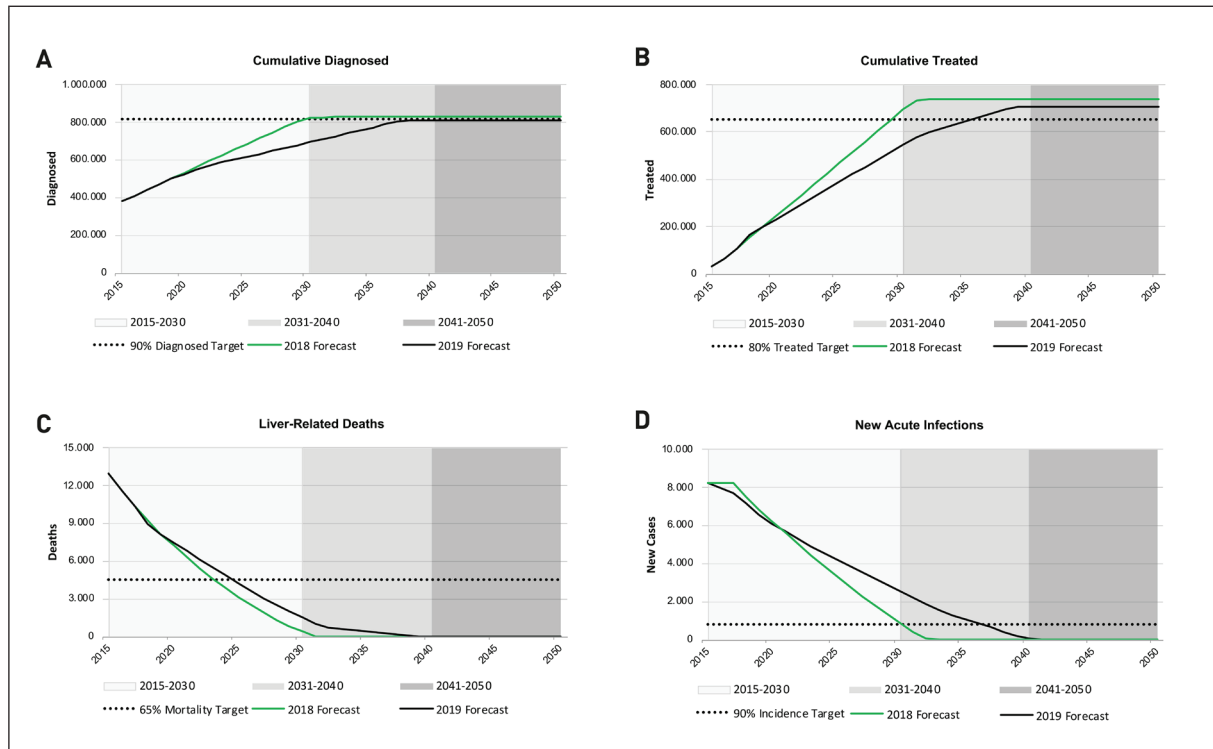How to keep Italy on the road to hepatitis C virus elimination?

Figure 1
The number of years needed to achieve the WHO elimination goals in Italy, by scenario.
A) Target: 90% diagnosed by 2030
    2018 Scenario: by 2030, 90% of viremic patients will be diagnosed.
    2019 Scenario: by 2030, less than 90% of viremic patients will be diagnosed. It will take more than seven years, given the scenario-specific diagnosis and treatment rates, to achieve the treatment target.
B) Target: 80% treated in 2030
    2018 Scenario: the model estimates 80% of patients will be treated by 2030.
    2019 Scenario: the model estimates 65% of patients will be treated by 2030. It will take an additional seven years, given the scenario-specific diagnosis and treatment rates, to achieve the treatment target.
C) Target: 65% reduction in HCV correlated deaths
    This target is achievable in Italy with both scenarios.
    2018 Scenario: the target is achievable by 2022.
    2019 Scenario: the target is achievable 5 years later, by 2027.
D) Target: 90% reduction of new HCV infections
    2018 Scenario: the 90% reduction of new infections will be achieved by 2030.
    2019 Scenario: the target is achievable 7 year later, in 2037.

the highest HCV prevalence in Europe, which was most likely attributed to a wave of nosocomial transmission occurring in the 1950s, followed by intravenous drug use in the 1980s [9-11]. These earlier epidemics would have resulted in a large number of HCV-infected individuals progressing to more severe liver disease, such as cirrhosis. However, due to the extensive roll-out of treatment in 2015 delaying further progression to death, the 65% reduction of liver related deaths target was forecasted to be an achievable reality for Italy by 2022 [3]. Though a constantly high treatment rate, as observed in the 2018 Scenario, would permit to achieve the WHO targets, reducing the number of patients treated each year, beginning in 2019 (the 2019 Scenario), would mean the
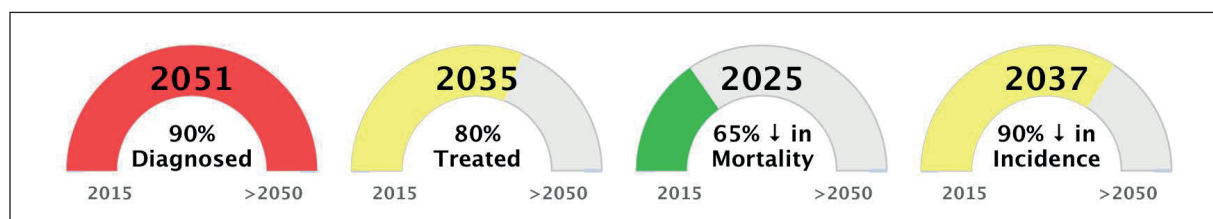

Figure 2
Year of achieving elimination targets (extrapolated from 2019 data). Current WHO Target is 2030.
The Center for Disease Analysis Foundation. Picture available from: https://cdafound.org/dashboard/polaris/dashboard.html.

opposite [7, 8]. Italy would not be able to maintain the treatment rate necessary to achieve the set targets. According to the 2019 Scenario, which does not consider an extensive screening strategy of the population, the pool of treated patients is predicted to run out by the year 2025 [3], leaving a large burden of HCV-infected individuals undiagnosed, nor cured. However, if screening and diagnosis increases due to new screening guidelines but treatment does not, then the outcomes will not change substantially from the 2019 Scenario outcomes. As reported by mathematical models, Italy will be able to achieve the elimination goals if at least 40 000 patients are treated annually, which is achievable only through an active screening campaign and consistent access to treatment for newly diagnosed patients [7]. To address this issue, a recent modelling analysis determined if universal and birth cohort screening (those born between 1948-1987, with the highest HCV prevalence and proportion of undiagnosed patients), were cost-effective measures to improving diagnosis [12]. The analysis found that both scenarios were cost-effective compared to the status quo (treatment of linked-to-care patients only). The incremental cost-effectiveness ratio (ICER) varied from 3,552-6,758/quality adjusted life year (QALY), far lower than the Willingness to Pay threshold of 25 000 Euros/QALY, under which the strategy is considered cost-effective in Italy.

The study determined that a tailored, graduated birth cohort screening strategy, which first identified young populations (1968-1987 birth cohorts) at risk of transmitting HCV and then expanded to identify older populations (1948-1967 birth cohorts) before disease progression, had the highest cost-effectiveness profile in Italy [12]. With specific regard to the 1968-1987 birth cohort, the phenomenon of transmission through injecting drug use needs to be mentioned. In Italy, injecting drug use has been a less important mode of transmission when compared to other European countries, although it was mainly responsible for the 1980-1990 wave of infections. Most individuals who have acquired HCV through injection drug use were born between 1968 and 1987. Because these individuals are younger than those who acquired infection through iatrogenic means, a higher proportion of them are in the F0-F3 fibrosis stage and thus, more likely to have gone undiagnosed [13]. Screening these younger cohorts first would likely detect individuals at higher risk of infectiousness, decreasing the potential to transmit new infections compared to screening older patients who are more likely already diagnosed and cured for their symptomatic disease. Considering also that more than 20% of treated patients in 2019 had cirrhosis or very advanced liver disease and similar estimates of advanced disease could be found in undiagnosed individuals, DAAs should still be considered as life-saving drugs [2, 12, 13]. Additionally, numerous studies have shown that HCV-related disease inflicts a huge economic and clinical burden as a result of HCV related extra-hepatic comorbidities. Early eradication of HCV before it progresses to advanced liver disease could reduce these burdens [14, 15].

The tailored screening strategy, coupled with the results of a previous study that reported HCV treatment has important medium to long-term health and economic benefits for the NHS [16], were well received by Italian policymakers, resulting in important political action to achieve the elimination goals. An amendment to the *Milleproroghe Decree* concerning HCV screening has recently been approved [17]. With this provision, 71.5 million Euros are allocated in 2020-2021, to introduce a screening program at no cost to the patient, with the final goal of identifying undiagnosed individuals with chronic HCV infection. These screening strategies will focus on the free of charge screening of key populations (current intravenous drug users) in the public services for drug addiction (SerT), people detained in prison, and general population screening, first, of those born between the years 1969-1989.

In light of these efforts, it seems as though programmatic structures are in place and would support Italy to once again be on track for the elimination of HCV by 2030. However, identifying undiagnosed HCV-infected individuals and patients not yet on treatment requires close partnership between the scientific, health, and political worlds at central and regional levels. This would involve uniting the local medical structures, general medicine doctors, and prescribing centers around one goal: the elimination of HCV infection by the year 2030. However, the roll-out of an active screening campaign could be considered as a starting point, as efficient screening should be supplemented with rapid linkage-to-care and treatment of newly diagnosed patients. To ensure rapid linkage-to-care means appropriate diagnostic and therapeutic paths that focus diagnoses on patients not yet on treatment must be constructed. An "*ad hoc* fund for HCV elimination" should be part of each regional elimination strategy. However, providing HCV treatment to diagnosed individuals will be a challenge. The "Innovative Drugs Fund", through which the State guarantees the necessary funds for DAAs, expired in April 2020. This means that Italy's 20 individual Regions will be faced with the challenge of finding a way to pay for the drugs, yet to date, no regional plans for eliminating HCV infection exist. Though the new HCV screening policies address one bottleneck to the elimination of HCV, the lack of a dedicated fund for DAAs will stress an already overburdened regional budget. This could result in discordant actions with little chance of success. In most Regions, in the absence of regional elimination plans, the treatment curve will drastically decrease and Italy will move further and further away achieving HCV elimination targets. In other words, if Italy is to achieve the WHO's HCV elimination target, screening alone will obviously not be sufficient. A commitment is needed by the state to support the WHO elimination goals for chronic HCV infection, which remains a silent public health threat in Italy. It is of fundamental importance that a national plan for providing treatment for HCV infection be an integral part of regional elimination plans.

CONCLUSIONS

Italy can once again be "on track" for achieving the WHO targets for HCV elimination which can be maintained if adequate screening strategies are adopted to

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identify undiagnosed individuals (as a starting point), and immediately link them to a cure for viral eradication (an end point and of equal priority). The establishment of an *ad hoc* fund for hepatitis treatment within the National Plan for the Prevention and Treatment of hepatitis C is necessary and should be supplemented by regional elimination plans that could make the WHO's HCV elimination targets attainable in Italy by 2030.

Conflict of interest statement

The Authors declare that there is no conflict of interest regarding the publication of this paper.

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