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Research Paper

The cost of a late-detected outbreak among people who inject drugs. a modeling study

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ABSTRACT

Background: People who inject drugs (PWID) are at risk for human immunodeficiency virus (HIV) and hepatitis C virus (HCV). In 2009 and 2011, Athens, Greece experienced an HCV and an HIV outbreak among PWID, respectively. Of these, only the 2011 HIV outbreak was detected. However, the public health interventions implemented in response to the HIV outbreak tackled also indirectly the undetected HCV outbreak. The aim of this study is to highlight the potential benefits of an efficient notification system using as a case study the undetected 2009 HCV outbreak among PWID of Athens. More specifically, the study assesses whether an earlier implementation of the same public responses could diminish the scale of the HCV outbreak and estimates the potential cost-savings.

Methods: A previous dynamic, stochastic, individual-based model was used to simulate HCV transmission among PWID of Athens, Greece. We calibrated the model to reproduce the observed HCV prevalence. We examined the effect of the non-detection scenario, the 1- or 2-years earlier detection scenarios and compared them to the status quo scenario.

Results: Under the non-detection scenario, 2800 additional PWID would have been infected with HCV compared to the status quo by 2019. On the contrary, if the outbreak was detected 1- or 2- years earlier with immediate interventions, 440 and 970 HCV cases could be averted by 2019, respectively. Non-detection of the outbreak would cost an additional 43.2 (95% Credible interval: 2.7, 59.4) million euros to the healthcare system, compared to the status quo. On the other hand, if there was an efficient notification system to detect the HCV outbreak 1 or 2 years earlier, 6.8–15.6 million euros could have been saved by 2019.

Conclusions: An efficient notification system among PWID is a cost-saving investment that could detect on time and contain future outbreaks, and save valuable resources of the healthcare system.

Introduction

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection are efficiently transmitted through injecting drug use; therefore people who inject drugs (PWID) consist one of the major risk groups (Degenhardt et al., 2017; Polaris Observatory, 2017). It is estimated that around 8 and 2 million PWID have been infected by HCV and HIV worldwide, respectively. As HCV is about 10 times more infectious than HIV, it has a higher prevalence globally (Degenhardt et al., 2017).

Several studies have underlined the strong relationship between HIV and HCV prevalence among PWID (Akbarzadeh, Mumtaz, Awad, Weiss & Abu-Raddad, 2016; de Vos, van der Helm, Prins & Kretzschmar, 2012; Vickerman, Hickman, May, Kretzschmar & Wiessing, 2010). More specifically, it has been shown that in settings with baseline HCV prevalence>30%, if HCV prevalence increases, the community faces an increased risk of an HIV outbreak (Akbarzadeh et al., 2016; Vickerman et al., 2010). This relationship has been confirmed in the case of Athens, Greece. Specifically, in 2009 and 2011 two outbreaks emerged among the PWID population (an HCV outbreak in 2009 and an HIV outbreak about 2 years later). It is notable that only the 2011 HIV outbreak was detected (Gountas et al., 2019).

In response to the HIV outbreak, substantial and successful efforts

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were implemented to minimize the spread of HIV, including the expansion of harm reduction coverage (both needle & syringe programs (NSP) and opioid substitution therapy (OST)) and the implementation of a high-coverage seek-test-and-treat intervention (ARISTOTLE program) (Hatzakis et al., 2015; Sypsa et al., 2017). Those interventions managed to reduce significantly HIV incidence (Sypsa et al., 2017). As HCV and HIV share common transmission routes in this population, interventions implemented to limit the HIV outbreak, affected indirectly also the incidence of HCV; the HCV incidence among PWID in Athens in 2012 was 64.8% lower compared with 2009 (Gountas et al., 2019).

HIV and HCV infections can be asymptomatic and thus it is quite common outbreaks caused by those pathogens to be detected several years after the epidemic's emergence (Gonsalves & Crawford, 2018; Gountas et al., 2019; Mumtaz, Weiss, Vickerman, Larke & Abu-Raddad, 2015). However, this delay, apart from its adverse health effects for infected people, also poses significant financial challenges for the healthcare systems, as the additional budget needed to treat all new infections (both primary and secondary infections) is high. Furthermore, both HCV and HIV infections are associated with high societal cost (Degenhardt et al., 2016).

Although the 2012 HIV prevention measures were highly successful to minimize the spread of the HIV outbreak -and indirectly the HCV outbreak-, public health practitioners wondered what would happen and what would be the cost savings (both direct and societal), if there was an efficient notification system to timely detect the 2009 HCV outbreak. We define an efficient notification system as one that could reliably detect a potential outbreak early and would alert all parties involved in the fields of drug-related infectious disease monitoring, treatment, and harm reduction. The aim of this study is to highlight the potential benefits of an efficient notification system, using as a case study the 2009 undetected HCV outbreak among PWID of Athens, Greece. More specifically, the study assesses whether an earlier implementation of the same public responses (i.e., the interventions that began 2012 had been started in early 2011 or early 2010) could diminish the scale of the HCV outbreak and estimates the potential savings.

Methods

Description of the hcv mathematical model

To examine whether an earlier implementation of public health interventions could diminish the scale of the HCV outbreak, a previous discrete time, stochastic, individual-based model of HCV transmission among PWID was used (Gountas et al., 2017a; Gountas et al., 2019; Gountas, Sypsa, Blach, Razavi & Hatzakis, 2018). The model follows transitions concerning HCV infection between two mutually exclusive compartments of PWID: a) susceptible people including those who either have never been HCV infected, have cleared infection or have had successful treatment; and b) HCV-infected (due to the small proportion of PWID who have been treated for HCV in Athens, it was assumed the treatment coverage for HCV was negligible between 2002 and 2018 (Gountas et al., 2017a; Hatzakis et al., 2015)). The population of PWID was additionally stratified per sharing status (sharer or non-sharer). Initially, all new injectors are classified as sharers, since there is evidence demonstrating that PWID are at higher risk of infection during the first years of their injecting career (Sutton et al., 2008; Sweeting et al., 2009).

Every year, PWID enter in the susceptible group at rate θ and exit the various states through death (μ_1) or cessation of drug use (μ_2), equal to the entry rate to keep the population size at constant levels. The force of infection for susceptible PWID depends on HCV prevalence. After infection, PWID have a probability of clearing the disease spontaneously and are then at risk of re-infection. We conservatively assumed that the risk of re-infection was equal to the initial infection rate. PWID who do not clear the infection progress to the chronically infected stage.

The natural history of the model was simulated using METAVIR fibrosis scores. Fibrosis progression rates were obtained from a published meta-analysis specific for the PWID population (Smith, Combellick, Jordan & Hagan, 2015). Additionally, we used disease progression in HCV sequelae from published observational studies (Salomon, Weinstein, Hammitt & Goldie, 2002, 2003).

Model parameterization

The model was calibrated using HCV epidemiological data from Athens, Greece. The average injecting risk behavior (number of unsafe injections (NUI) is a time-dependent variable which was varied until the model reproduced the observed HCV prevalence in Athens) (Table 1). The model highlighted that two significant changes happened in the behavior of PWID living in Athens during 2002–2019. The first was in 2009 indicating the emergence of the outbreak and the second in 2012 reflecting the effect of HIV interventions [i.e. implementation of case finding interventions, increased HCV and HIV testing, expansion of opioid substitution (increased number of centers providing opioid substitution treatment by 50% during 2011–2012) and needles syringes provision (increased coverage from seven to 45 syringes per estimated PWID per year between 2010 and 2012), and provision of counseling and psychological support]. Additionally, the distribution of liver disease in 2019 was achieved by varying the disease progression rates. Further details about the description of the model and the calibration procedure are available in the appendix or in previously published studies (Gountas et al., 2018; Gountas et al., 2019).

Economic part of the model

Regarding the economic part of the model, we computed treatment and societal costs of the HCV outbreak.

Universal access of Greek patients to direct-acting antivirals (DAAs) treatment was granted in September 2018. The decision followed a period of 6 years of restrictions based on liver-disease severity, which excluded the vast majority of PWID patients (Papatheodoridis et al.,

Table 1
Model Parameters and references.

Parameters	Value	References
PWID population size in Athens	9000	(Greek Reitox focal point, 2018)
Proportion acutely infected spontaneously clearing infection	20%	(Sypsa et al., 2004)
Duration of injecting carrier among PWID in Athens (years)	12	(Hatzakis et al., 2015)
Overall PWID mortality per annum	2%	(Cornish, Macleod, Strang, Vickerman & Hickman, 2010; Gountas et al., 2017b; Stoove, Dietze, Aitken & Jolley, 2008)
Proportion of sharers PWID	23%	(Hatzakis et al., 2015)
Disability weights		
F0–2	0.012	(Scott et al., 2019)
F3–4	0.068	(Scott et al., 2019)
DC	0.194	(Scott et al., 2019)
HCC	0.508	(Scott et al., 2019)
Progression rates		
F0→F1	0.176	(Smith et al., 2015)
F1→F2	0.082	(Smith et al., 2015)
F2→F3	0.100	(Smith et al., 2015)
F3→F4	0.161	(Smith et al., 2015)
F4→Decompensated cirrhosis	0.04	(Salomon et al., 2002, 2003)
F4→ Hepatocellular carcinoma	0.021	(Salomon et al., 2002, 2003)
Decompensated cirrhosis→HCC	0.021	(Salomon et al., 2002, 2003)
Decompensated cirrhosis→Death related to HCV	0.306	(Salomon et al., 2002, 2003)
Hepatocellular carcinoma → Death related to HCV	0.433	(Salomon et al., 2002, 2003)
Antiviral treatment costs of DAAs (€)	13,000	(Gountas et al., 2019)

2019). In our analysis, we optimistically assumed that all PWID infected from the HCV outbreak during 2009–2018 are treated by 2019. The average cost per direct acting antiviral agents (DAA)-treated patient in Greece in 2017 was estimated by a previous cost-effectiveness study (13, 000 € per treated patient) (Gountas et al., 2019).

The societal cost was used to approximate loss of productivity due to HCV-related disabilities and loss of life. Specifically, the disability-adjusted life year (DALY) metric was applied to estimate the societal costs of the disease (Murray & Lopez, 1996). One DALY can be thought of as one lost year of "healthy" life. DALYs are computed by combining years of life lost (YLLs) and years lost due to disability (YLDs) and weighted by the severity of the disease (WHO, 2016). The cost per DALY was assumed to be equal to the Gross Domestic Product per capita (GDP) per capita in 2019 (€18,150) (Eurostat, 2020). DALYs were discounted at rate of 3% per year. The societal cost caused by the outbreak was calculated by subtracting the cumulative DALYs of each scenario from the corresponding one in the status quo scenario and multiplying it by the GDP per capita. Several previous studies have used the assumption to value 1 DALY as a function of economic indicators such as GDP or GNI (Gross National Income) (Benzaken et al., 2019; Estes et al., 2015; Gountas et al., 2019; Sanai et al., 2020)

Examined scenarios

The time horizon of our analysis was 18 years (2002–2019). Specifically, during the first 11 years (e.g. 2002–2012) the model describes the pre- and the HCV outbreak era, followed by 7 years follow up (e.g. 2013–2019), in order to capture the long-term effects of the outbreak (i.e. secondary infections caused by the outbreak). We extended our analysis until 2019, as this was the first year that the majority of PWID were eligible for treatment with DAAs (Papatheodoridis et al., 2019).

A 'status quo' scenario was used to generate predictions regarding the actual HCV incidence during 2002–2019. In addition, three additional scenarios were considered. Specifically, two scenarios where all interventions were implemented 1- or 2- years before the original launch of preventive interventions and a counterfactual scenario in which we assumed that all HIV-related interventions were removed to estimate how the HCV epidemic would have unfolded if nothing had been done.

For each scenario, 500 runs were performed, and the results were summarized using the median over all simulations. To include the appropriate uncertainty (stochastic variability), the credible interval (i.e., the 2.5 and 97.5 percentiles of the simulations) were also shown. Increasing further the number of runs left median and credible interval practically unchanged.

Sensitivity analysis

To examine the impact of different assumptions of the model on cumulative infections caused by the outbreak, series of univariate sensitivity analyses was implemented. More specifically the impact of shorter/longer average duration of injecting carrier (10 or 14 versus 12 years), greater/smaller annual mortality rate (1%, 4% versus 2%), higher/lower PWID population (8000, 10,000 vs. 9000) and greater/smaller proportion of sharers PWID (15% or 30% versus 23%) were explored (Table S3).

Results

Epidemiological outputs

Chronic hepatitis c (CHC) prevalence

Fig. 1 shows the trend in chronic hepatitis C (CHC) prevalence over time under different scenarios depending on when the outbreak was detected. The status quo scenario showed that the 2012-interventions halted the increasing trend of the CHC prevalence post-2013. On the contrary, under the counterfactual scenario, that assumes no-detection

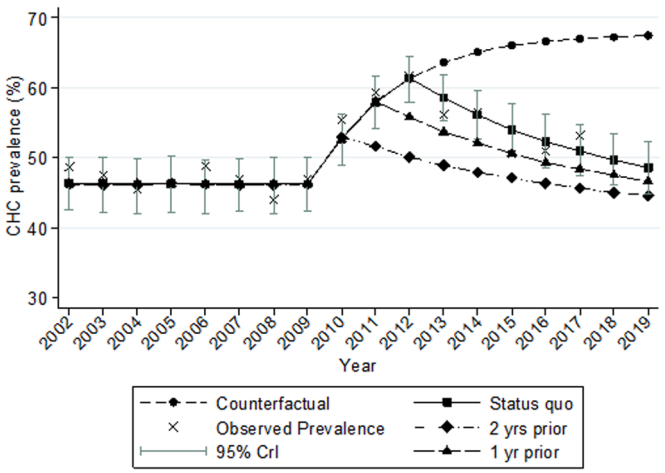

Fig. 1. Model predictions for chronic hepatitis C virus (HCV) prevalence for the 4 different scenarios (status quo scenario, counterfactual scenario, one-year earlier implementation of interventions and 2-years earlier implementation of interventions). The solid black line and shaded gray error bars show the median and 95% credible intervals (95% CrI) for the model projections. For comparison, asterisks indicate the observed chronic hepatitis C virus (CHC) prevalence data.

of the HCV outbreak and thus no interventions, the CHC prevalence would continue to increase until 2019. More specifically, in 2019 the estimated relative CHC prevalence under the counterfactual scenario was 38.9% higher compared to the corresponding CHC prevalence under the status quo (48.6% vs 67.5%; Fig. 1).

If we had implemented the same public responses a year ago, CHC prevalence in 2019 would have been relatively reduced by 4.1% compared to the status quo scenario (48.6% vs. 46.6%). Similarly, if we had launched the interventions in 2010, the expected prevalence in 2019 would be relatively reduced by 8.2% compared to the status quo scenario (48.6% vs. 44.6%; Fig. 1, Figure S7-S9).

HCV incidence

Fig. 2 displays the trends in HCV incidence among PWID in Athens, Greece. It is notable that HCV incident cases post-2012 were lower compared to the pre-outbreak levels. Under the status quo, the model computed that 6480 (95% Credible interval: 6000, 6900) PWID were infected, during 2009–2019 (Table 2, Fig. 2, Figure S10-S12).

In the counterfactual scenario, the HCV incidence would have increased between 2009 and 2011 and then would have decreased, even

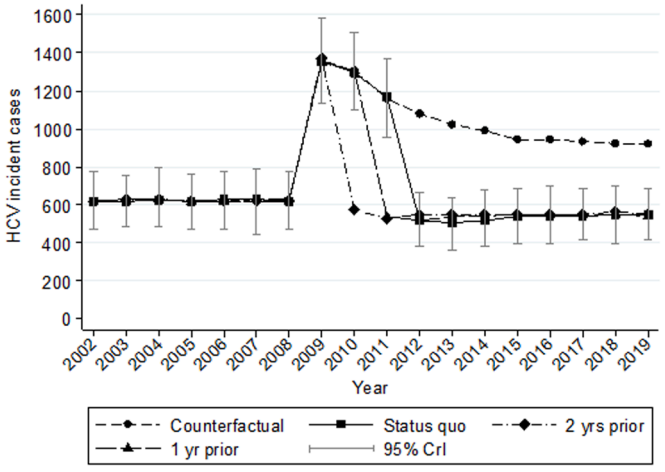

Fig. 2. Estimation of the number of incident cases of HCV infection under the status quo, counterfactual scenario and earlier implemented scenarios.

Table 2
Cumulative infections amongst people who inject drugs for different scenarios and relative difference compared to the status quo scenario. Ranges in the brackets correspond to the 95% credibility intervals.

Scenarios	Cumulative number of new infections (95% Credible interval)	Relative difference compared to the Status quo (95% Credible interval)
2009–2011		
Status quo	3060 (2740, 3380)	NA
One-year earlier implementation	2555 (2250, 2870)	−16.4% (−27.8%, −0.1%)
Two years earlier implementation	1970 (1690, 2270)	−35.6% (−46.7%, −23.0%)
Counterfactual	3060 (2740, 3380)	0%
2009–2019		
Status quo	6480 (6000, 6900)	NA
One-year earlier implementation	6040 (5550, 6520)	−6.8% (−16.8%, +0.2%)
Two years earlier implementation	5510 (5070, 6000)	−15.0% (−23.0%, −0.5%)
Counterfactual	9280 (8790, 9770)	+43.2% (+30.1%, +56.4%)

in the absence of any intervention, due to the saturation effect of the outbreak (Fig. 2). Compared to the status quo, 2800 (2100, 3400) additionally HCV cases would have occurred during 2009–2019 (Fig. 2, Table 2).

If we had diagnosed the outbreak 1 year earlier and had started the interventions in 2011, 440 (−100, 1100) fewer HCV cases would have been observed during 2009–2019, compared to the status quo scenario. Similarly, if we had diagnosed the outbreak 2 years earlier, 970 (300, 1550) HCV cases could have been averted during 2009–2019, compared to the status quo scenario (Table 2).

Treatment cost

Under the status quo scenario, it was estimated that 6480 (6000, 6900) PWID were infected, during 2009–2019, which equates to a treatment cost of 84.2 (78.0, 89.7) million euros to heal all infections. If we had not detected the outbreak at all (i.e. counterfactual scenario), the additional direct costs for the healthcare system would have been 36.4 (27.3, 44.2) million euros.

On the contrary, if we had detected the outbreak in 2011, the additional saving for the healthcare system, compared to the status quo would have been 5.7 (1.3, 14.3) million euros. Finally, if we had diagnosed the outbreak in 2010, the corresponding saving, compared to the status quo, would have been 12.6 (3.9, 20.1) million euros (Table 3).

Societal cost

Concerning societal costs, the counterfactual scenario would have caused 360 more DALYs than the status quo scenario, which equates to an additional 6.5 million cost (Table 3, Figure S5). If we had detected the outbreak 1 or 2 years earlier, 58 and 158 DALYs could be averted compared to the status quo scenario, corresponding to an averted cost of 1.05 and 2.9 million euros, respectively.

Total cost

Summing the above, the non-detection of the outbreak (i.e. the counterfactual scenario) would cost the healthcare system 43.2 (95% CrI: 2.7, 59.4) million euros more than the status quo scenario (Figure 3). If there was an efficient notification system to detect the HCV outbreak 1 or 2 years earlier, 6.8–15.6 million euros could be saved, compared to the status quo scenario (Table 3). Although HCV is a disease with high societal costs, in the short term, direct costs to treat primary and secondary infections that were produced by the outbreak are the dominant costs of the disease.

Sensitivity analysis

The sensitivity analysis revealed that the variation in the average injecting duration substantially affected the projected cumulative infections caused by the outbreak (Figure S6). Specifically, for longer injecting duration (14 years instead of 12 years), and under the status quo, the cumulative incidence decreased by 10.5%, while for shorter injection duration (10 years instead of 12 years) increased by 18.8%. Furthermore, potential changes in the number of PWID also affected model predictions. Specifically, if PWID of Athens were 8000 rather than 9000, the cumulative incidence would decrease by 11% whereas if PWID were 10,000 the cumulative incidence would increase by 11%.

Finally, compared to base case, lower or higher annual death rate resulted in 7.4% decrease and 9.6% increase in the cumulative incidence, respectively. Changes in the proportion of sharers had only a marginal effect on the estimated cumulative infections (Figure S6).

Discussion

Our model highlights that the 2009 HCV outbreak in Athens, Greece might have been mitigated with an earlier response. It is important that years after the emergence of the epidemic, it was not recognized, and an indirect response was implemented only after the detection of the HIV outbreak in early 2012 (Gountas et al., 2019). More specifically, under the status quo scenario, during 2009–2012, 3060 PWID were infected, of which 16.4–35.6% could be averted with an earlier response. In Greece, like in many developed countries, monitoring of HIV infection is given priority compared to HCV infection, although their impact on public health is quite similar. Our study highlights that an efficient notification system that accurately monitors both diseases is a cost-saving investment maintaining valuable resources of the healthcare system. To our

Table 3
Cumulative costs (millions of euros), DALYs and absolute difference in the total cost between each examined scenario and status quo scenario. Ranges in the brackets correspond to the 95% credibility intervals.

Scenarios	New infections	Treatment cost to heal all new infections	DALYs	Societal cost	Total cost	Absolute Difference compared to status-quo scenario
Status quo	6480 (6000, 6900)	84.2 (78.0, 89.7)	2260 (1665, 3100)	41.0 (30.2, 56.2)	125.2 (113.8, 142.1)	NA
1-year earlier implementation	6040 (5550, 6520)	78.5 (72.1, 84.7)	2200 (1595, 3150)	39.9 (28.9, 57.1)	118.4 (107.4, 138.2)	−6.8 (−22.2, +9.2)
2-years earlier implementation	5510 (5070, 6000)	71.6 (65.9, 78.0)	2100 (1515, 3330)	38.1 (27.5, 60.4)	109.7 (98.6, 129.4)	−15.6 (−30.0, +1.5)
Counterfactual	9280 (8790, 9770)	120.6 (114.3, 127.0)	2630 (2070, 3610)	47.7 (37.6, 65.5)	168.3 (157.9, 187.5)	+43.2 (+2.0, +62.2)

+Treatment cost is calculated by multiplying the cost of one treatment (13,000 € per treated patient) by the number of the treated patients. Societal cost is calculated by multiplying the DALYs index by the GDP per capita (€18,150).

knowledge, our study is the first analysis that examined what would be the savings if we detected an unnoticed HCV outbreak.

Successful surveillance and/or notification systems are fundamental for the implementation of timely public health interventions, as early detection can limit epidemic size, reduce the associated morbidity and preserve valuable resources of the healthcare system. It is noteworthy that, during the last decade, many HIV and HCV outbreaks among PWID had emerged globally (Des Jarlais, Kerr, Carrieri, Feelemyer & Arasteh, 2016; Gountas et al., 2019; Maisa et al., 2019; Ramachandran et al., 2018; Sypsa, 2019; Van Handel et al., 2016). Additionally, in 2016, the US Centers for Disease Control and Prevention (CDC) declared that 220 US counties in 26 states are at high risk for future HCV or HIV outbreaks among PWID (Van Handel et al., 2016). Nevertheless, it is quite common that HIV or HCV outbreaks among PWID population are detected years after the epidemics' emergence, due to the generally hidden nature of this marginalized population (Akbarzadeh et al., 2016; Gonsalves & Crawford, 2018; Mumtaz et al., 2015). This highlights the crucial need for even better tools that are able to timely detect infectious disease outbreaks. Developing automated systems of early detection and notification of outbreaks using mathematical modeling and/or artificial intelligence could be an interesting method both to timely recognize outbreaks prior to their emergence and to suggest potential healthcare interventions to mitigate them. For example, in the contemporary era of big data, an unsupervised machine-learning model, that could be fed with data from different sources, would be potentially able to timely detect an unusual bump of HIV or/and HCV infections and predict the potential future course of the outbreak.

In our analysis, we also assessed the effect of a counterfactual scenario, in which the HCV outbreak was never been detected and thus no action was taken We acknowledge that this is definitely the worst case -but at the same time not a very unlikely- scenario. This scenario was examined to emphasize that under the absence of an efficient notification system, undetected outbreaks may emerge which will cause increases the disease burden and will cost a substantial amount of money in the healthcare system. In our case study, the cost of non-detection of the HCV outbreak (i.e. the counterfactual scenario) would cost an additional 43.2 (95% CrI: 2,7, 59,4) million euros, compared to the status quo (in a horizon of a decade, which includes the long-term effects of the outbreak as well).

In this analysis, we used as a case study the undetected HCV outbreak of Athens (Gountas et al., 2019). It is important that If we had missed or delayed to detect the HIV outbreak -instead of the HCV outbreak-, the cost will be much higher. Although the price of antivirals for HCV are higher than those for HIV, the treatment for HCV is relatively short, while the treatment for HIV patients is lifelong. Thus, delayed detection of an HIV outbreak would be more expensive than a delayed detection of an HCV outbreak.

Our analysis estimated that 6.8–15.6 million euros could be saved with an earlier response to the epidemic. To compute this estimation, we assumed that all the new and secondary infections caused by the 2009 outbreak would be immediately treated in 2019 (the first year when universal access to DAA treatments was granted).

There is a 1-year lag between the increase in incidence and prevalence (i.e. Incident cases increased in 2009 while prevalence started to increase in 2010). This is because prevalence data are reported per year, thus to observe an increase in a particular year, an increase in the incidence should have occurred in the previous year.

When analysing the impact of an intervention, which tackles an outbreak, it is important to take into consideration the saturation effect of the epidemic. In Athens, the saturation effect of the epidemic is high (Figure S1, Figure S2). For example, even without any intervention (e.g. counterfactual scenario), HCV incidence in Athens would decline post 2009 (Fig. 2). The reason lies in the velocity that the uninfected susceptible population is running out in each scenario. The population size of PWID of Athens is renewed slowly, since the average injecting duration is relatively high (about 12 years) and additionally most high-risk PWID became infected very soon at the start of the HCV epidemic. This is why the effects of the 1- or 2-years earlier detection scenarios are fading over time, compared to the status quo (Table 2).

An efficient detection and notification system will have broader implications, apart from the timely detection of unusual bumps of HIV or/and HCV infections. In Greece, similarly to the majority of western countries, the incidence of HCV is solely limited to the PWID population (Degenhardt et al., 2017; Papatheodoridis et al., 2019). As the country is committed to meet the World Health Organization (WHO) targets (WHO, 2015), HCV incidence in this population should be accurately monitored over time. This highlights the crucial need for accurate estimations concerning the incidence of HCV infection. However, as the methods to estimate incidence are complex or/and expensive, HCV prevalence among PWID could potentially be a good proxy to track progress toward the incidence reduction (van Santen et al., 2020). Therefore, an efficient notification system could assess whether the HCV incidence target of WHO's elimination is on track. Likewise, the trend of HIV prevalence could be a proxy of the course of the HIV incidence in this population.

Sensitivity analysis

The model projections are sensitive to the uncertainty of some of the underlying parameters. Sensitivity analyses provide evidence that under shorter injecting duration or higher death rate i.e., if the population of PWID was renewed more rapidly, the cumulative infections would be higher, because more PWID would be at risk of infection. On the other hand, if injecting duration was higher or death rate was lower, i.e., PWID population was renewed slowly, the cumulative number of infections would shrink (less PWID would be at risk of infection). Thus, the extent of an outbreak is strongly dependent on the speed of the population renewal. In settings where the population renews slowly, the cumulative number of infections because of the outbreak are lower compared to a setting where the population is renewed relatively fast.

The number of PWID is also a significant parameter that affects model's projections; In our case, under larger number of PWID, the estimated cumulative infections would be 11% higher. More accurate estimation of the number of PWID would reduce the uncertainty in the model's projections.

Comparison with other studies

Assessing the impact of an earlier public health response to an outbreak

A recent mathematical modeling study also explored the potential impact of a potential earlier public health response to an outbreak. The study examined the setting of Scott County, Indiana, USA -a similar to Athens setting- in which HCV prevalence started to increase, and some years after an HIV outbreak occurred (Gonsalves & Crawford, 2018). Gonsalves et al. concluded that the HIV epidemic might have been prevented with an earlier public health response (Gonsalves & Crawford, 2018). Overall, this study as well as our analysis, underlined the vital role of an effective surveillance system to timely detect potential outbreaks that would allow rapid integrated public health responses.

Limitations

Our analysis has some limitations. First, the model ignores the impact of social networks on HCV transmission and assumes that the population is totally mixed i.e. sharing injectors have equal contact with all other sharing injectors in the population. Second, we assumed that all reductions in high-risk behaviors was attributed to the prevention measures. Third, the model did not take into account the potential for increased coinfection mortality (HCV/HIV). However, the additional coinfection mortality risk among HIV-infected PWID is likely to be small, as most HIV-infected PWID were infected recently. Fourth, the analysis

has not considered the averted costs attributable to the HIV prevented cases. If the 2-years earlier public health response strategy could prevent also the 2011 HIV outbreak, the potential averted costs would be much higher. Fifth, we assumed that PWID would not change their risk behavior after a potential spontaneously clearing of the infection. Another limitation is that the model does not take into account issues related to identifying HCV-infected PWID and harm reduction costs. We have not addressed this issue in this analysis since in short-term (assuming that all PWID would be treated in 2019) treatment costs would be the dominant cost among all direct costs. For example, the cost of treating all new infections, under status quo scenario, would be 84.2 million whilst the cost of the ARISTOTLE program (the seek-test-and-treat program implemented in Athens in 2012) was estimated at about 975.000€ (Sypsa, 2015). Finally, we did not consider the cost of setting up an effective detection system. In European countries HCV surveillance systems have been established, but they suffer from serious under-reporting (Klevens, Liu, Roberts, Jiles & Holmberg, 2014). However, in Greece the vast majority of PWID are followed in the Hellenic Organization Against Drugs (OKANA). A model-based effective detection system, of relative low cost, could be implemented in the OKANA database.

Conclusions

Our model estimated that if we had detected the outbreak 1- or 2-years earlier, the epidemic would have been substantially blunted and 6.8–15.6 million euros could have been saved.

The analysis highlights that an efficient notification system among PWID is a cost-saving investment, as it could detect on time and contain future outbreaks, and save valuable resources of the healthcare system.

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Conflict of interest statement

KS, NG, GT: No conflicts of interest

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Author contributions

Gountas I: Conceptualization, Methodology, Modelling, Writing - Original Draft **Hatzakis A, Nikolooulos G., Touloumi G, Souliotis K:** Writing- Reviewing and Editing

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2020.103032.

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