ORIGINAL ARTICLE

The Gibraltar COVID-19 Cohort: Determining the True Incidence and Severity Rate During an Outbreak

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ABSTRACT

Objective: COVID-19 is a new infectious disease with an unclear incidence and an unknown rate of progression to severe disease. The Gibraltar COVID-19 Cohort utilises two distinct cohorts - a clinical cohort and a random population based cohort -, to provide an accurate assessment of case severity rate. **Design:** Retrospective analysis of a SARS-CoV2 RT-PCR point prevalence study and a RT-PCR confirmed positive clinical case cohort to calculate case severity rates. **Settings and Participants:** Over a three day period nasopharyngeal swabs were sampled from a randomly selected 1.2% of the population of Gibraltar and then analysed via RT-PCR to determine the background incidence of COVID-19 infection. The results were then analysed and compared to the clinical case cohort. The rate of progression to severe COVID-19 disease in those with COVID-19 infection was then calculated. **Results:** Gibraltar tested 1500 suspected COVID-19 cases over a 35 day period. Of these, 125 cases were confirmed positive for COVID-19 via RT-PCR analysis. The rate of progression to severe disease in this clinical cohort was 7.2% (95% CI 3.3 - 13.2%). 25 days into the initial surge of cases, 400 members of the public were randomly selected from the electoral register and over a subsequent three days were tested for COVID-19 by nasopharyngeal swab RT-PCR analysis. 2.5% of this total population sample were confirmed as positive for the infection (95% CI, 1.2 to 4.6%). Combining both clinical case detection with random case detection, at first using an ultraconservative model of infectivity, readjusted rate of progression to severe COVID-19 disease to 0.93% (95% CI, 0.43-1.8%). A secondary analysis adjusting for projected number of cases over 35 days and correcting for the sensitivity of the RT-PCR analysis via nasopharyngeal swab led to a readjusted rate of progression to severe COVID-19 disease of 0.18%. **Conclusion:** From the Gibraltar COVID-19 Cohort, at a population level, the rate of progression to severe COVID-19 disease in those with COVID-19 infection is estimated at between 0.1% and 1%.

Key words: COVID-19, SARS-CoV2, Severity, Incidence, Mortality

INTRODUCTION

The novel coronavirus 2019 is a new infectious disease to humans. Initially, the disease severity rate was reported as high as 20%.[1] Subsequently, as the outbreak has developed, various case severity rates have been reported (e.g., 18%,[2] 17%,[3] and 11%).[4]

The uncertainty relating to the disease severity rate pertains to the absence of population testing.[5] During an outbreak, limited testing capacity leads to an inability to detect the background or milder infections.

There has been ongoing suspicion that there is a high background rate of infection with coronavirus disease (COVID)-19.[6] The challenge to capture the true incidence rate of infection with COVID-19 relates also to the logistical challenges of testing a sufficient proportion of the population to give credence to the rates detected in a random sample. Even more challenging is to conduct a sufficient number of

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tests over a short enough period of time to provide a true "snap-shot" of how the infection is behaving in the population.

The Gibraltar COVID-19 Cohort overcomes many of these hurdles. Early and extensive contingency plans and public health control measures meant that the health-care system was not overwhelmed. This gave capacity for extensive testing for COVID-19 and the capacity to undertake a population sampling of over 1% of the total population over only 3 days, mainly to help direct how and when to ease up restrictions to day-to-day life.

Combined with the clinical cohort data, the random population sampling data are analyzed. The true incidence and true disease progression rates are then calculated.

METHODS

There were two arms to the current study. The first involved a retrospective analysis of the data collected on the 125 COVID-19-positive cases detected through the usual clinical pathways. The pathway and data collection are described below. The second arm was a population sampling of 1.2% of the population during the latter stages of the current outbreak. The technique for sampling, polymerase chain reaction (PCR) analysis, and data collection was the same as that for the clinical cohort.

Technique for sampling

The mainstay of diagnosis was through real-time Polymerase Chain Reaction (RT-PCR) analysis of nasopharyngeal swabs. At the onset of the outbreak, the infection control team determined suitability for testing and conducted the tests. The swabs taken at this time were likely well performed. As the level of sampling increased, seconded staff and local nursing staff undertook more and more swabs. Training was of a high quality and easily accessible, and as such the sampling technique was likely good.

RT-PCR analysis

The technique remained the same throughout the surge described here. The method for RT-PCR is as described previously.[7]

Early in the outbreak the RT-PCR analysis of the swabs sampled were undertaken in a reference lab (Colindale or Basingstoke) in the UK. This involved collecting the swab in a suitable medium and transporting via plane to the UK. Delays between sampling and analysis typically ranged from 3 to 5 days. During the second phase of the initial surge of infections the RT-PCR analysis was undertaken in two laboratories in Spain (Eurofins and Synlabs). This shortened the time between sample collection and analysis, and improved turn around time. Latterly the in-house testing facility came into operation at St Bernard's Hospital, Gibraltar. Turn around time improved from around 48 hours to around 12 hours.

Eligibility criteria

The initial eligibility for undertaking RT-PCR testing in cases required a history of travel or contact with a known positive case and a documented fever. Typically, any individual from a high-risk country with a fever was swabbed for COVID-19. After 2 weeks from Gibraltar's index case, the eligibility criteria changed to remove the necessity for travel or contact with known infection.

Testing eligibility criteria changed again after a further week. All patients with any "viral" symptoms were considered possible COVID-19 even in the absence of fever. Any person with "viral" symptoms were advised to self-isolate and contact a newly implemented "111" telephone service. The public were encouraged to contact '111' if they displayed any viral symptoms.

The testing eligibility then changed as the number of suspected cases increased. Around 3 weeks into the outbreak, suspected cases were not routinely swabbed unless high risk for complications (e.g., over 70 years of age or immunosuppressed), a health care worker or the person required admission to hospital. The public were still instructed to contact '111' if there were any symptoms that could be COVID-19.

Random sampling

During the third week of the outbreak, a random stratified point prevalence study was undertaken as part of the public health monitoring strategy. The medical register was utilised to generate a computer randomised list of 400 members of the public. Each were contacted by phone and a nasopharyngeal swab was undertaken and analysed via RT-PCR. Any positive case was included within the total count and subject to the same review procedure as all positive cases.

Data collection

At the outset a database was created for all patients who tested positive for COVID-19 via RT-PCR analysis of nasopharyngeal swabs as part of the public health response. Patients who were positive were followed-up via phone until a clinician determined 'recovery'. Demographics, symptoms, co-morbidities and contact with healthcare services such as '111' were recorded.

Classification of severity was based on the presence of lung disease (severe) or the absence of lung disease (mild), determined by a clinician. The presence of lung disease was confirmed either through chest imaging or through a documented oxygen requirement considered directly related to COVID-19 disease.

Statistical Analysis

Poisson Distribution was preferred to Binomial Distribution for incidence rates as the testing related to a single variable,

likely uncommonly represented, and took place over a specified and discrete time period. Binomial distribution was preferred for progression rates as the progression was a single variable and a percentage calculation.

RESULTS

The first case was confirmed on February 26, thought related to recent travel to Italy. There were no other confirmed cases until March 12. March 24 saw the peak of 22 new cases [Figure 1].

The solid line indicates the true numbers of new cases day by day. The broken line indicates the best-fit polynomial line. Positive cases from the random sampling are excluded from this illustration.

A total of 125 cases were reported as of April 9, 2020. At the point of data recording, 102 had recovered, and there were no patients meeting the criteria for a severe case and no patients admitted to hospital with confirmed or suspected COVID-19 infection. The mean age was 43 years with a range of 1.2 to 89 years of age. Male-to-female ratio was 1.17. The commonest symptoms were Coughing, Fatigue, Headache, Myalgia and Fever.

The vast majority of patients had mild disease. Out of the 125 cases, 11 were admitted to hospital. Of those 11 admitted, 9 were considered severe with 6 requiring oxygen and one requiring a period of mechanical ventilation. There were no deaths and no inpatients at the time of writing.

Random sampling

Between the 1st and 3rd of April, 400 nasopharyngeal swabs were taken from 400 randomly selected members of public. 10 were positive. Of those 10 positive cases, 8 had symptoms. None of the ten cases had contacted "111" or any health-care professional. The mean age was similar to the clinical cohort at 39 years of age (range 19–73 years). In this small cohort of 10, 3 were male and 7 female.

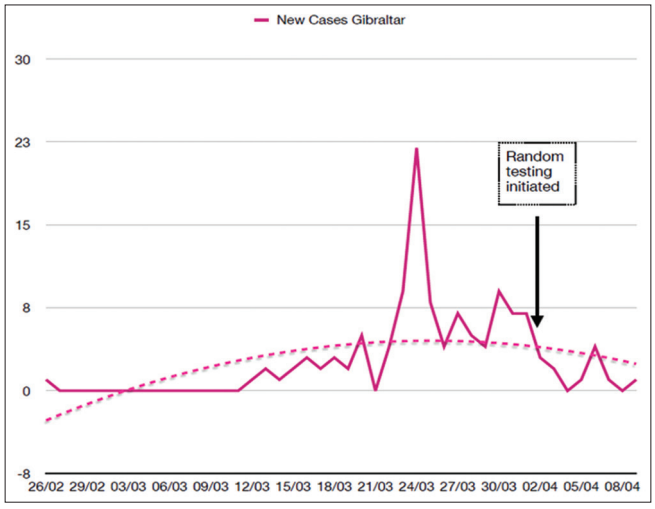

Figure 1: COVID-19 new case detection over time (n = 115)

DISCUSSION

Gibraltar has maintained one of the highest testing rates per head of capita reported. In total 1500 swabs were taken and analysed for COVID-19 via PCR from a population of 33,691 over 35 days. 125 cases were positive for COVID-19 over a period of 35 days. This equates to 44,522 tests per million inhabitants and an infection rate of 3,710 per million inhabitants. Based on this clinical cohort the incidence rate for COVID-19 in Gibraltar would be 3 per 1000 every 35 days (95% CI, 3.1 - 4.4).

Of the 125 positive cases, 11 were admitted. In total there were 9 cases classified as severe COVID-19. One patient required a period of mechanical ventilation. All patients were successfully discharged. Based on this clinical cohort the rate of progression to severe COVID-19 disease from COVID-19 infection would be 7.2% (95% CI 3.3 - 13.2%).

As has happened in most regions around the world, the criteria for testing individuals have changed overtime. In Gibraltar, at day 20 of the outbreak, patients who were likely to have COVID-19 but were considered mild or at low risk of progression were not tested. As such, the true rate of infection is unknown and crucially the pathogenic potential of COVID-19 was not able to be calculated.

To offset this inaccuracy, a random sampling of the population for the presence of COVID-19 was undertaken, as part of a random stratified point prevalence study. 400 members of the public were randomly selected via computer programme and tested via nasopharyngeal swab over a three day period. The swabs were analysed via PCR for COVID-19. 2.5% (or 10) of the randomly sampled population were positive for COVID-19 (95% CI, 1.2 to 4.6%). Of these, 2% (or 8) were symptomatic, but had not contacted any healthcare professional. 0.5% (or 2) were asymptomatic.

Ultraconservative modeling

Projecting for the total population, on the 3 days measured, 842 people (2.5% of the population) were infected with COVID-19. As expected, most people seemed to have mild illness and did not consider it appropriate to contact the health-care services. Based on this random sampling the background incidence rate for COVID-19 infection over 3 days is 25 per 1000 (95% CI, 18.6 - 40.5). Applying an ultraconservative model of infectivity (whereby the 842 background infections were the total background infections), the calculated rate of progression to severe disease for COVID-19 infection in Gibraltar is 0.93% (95% CI, 0.43-1.8%).

The temporal trend in PCR positivity remains unknown. Based on the current available literature, the mean time to transition from positive to negative in PCR analysis of nasopharyngeal swabs is 7 days[7,8]. Conservative estimation of total cases in Gibraltar over a 28-day time period (where daily rates of infections detected were at least as high as they were during the random sampling), and considering the mean time to negative swab results is 7 days, then the total number of background cases in Gibraltar would be 3,368 over the 28 day period. That is, if the entire population of Gibraltar were tested every three days, the estimated total number of individuals detected with COVID-19 infection would be 3,368. The incidence rate is then 104 per 1000 over 28 days, and the rate of progression to severe COVID-19 for those with COVID-19 infection is 0.26%.

Most studies give a sensitivity rate of nasopharyngeal swabs at 60%.[8,9] Adjusting the total figure for this would equate to a total case level of 4,905. At this level of infections the incidence rate is 146 cases per 1000 inhabitants over 35 days, and total severity rate for COVID-19 infection in Gibraltar would be 0.18%.

Rate of infection dictates mortality

Even at these much lower levels of case severity rates than previously predicted, in the absence of public health controls, the Gibraltar health system would have struggled. At the ultraconservative model of infectivity, a total of 313 cases would have developed severe disease within the space of a few weeks. With an acute medical capacity of 34 beds and an ITU capacity of 12 beds and an average length of admission of (a conservative) 5 days, the service would have been saturated early on in the outbreak and individuals would have gone without the medical intervention they needed.

Limitations

The severity rate for COVID-19 infection may have been underestimated in relation to elderly population. The protective measures for the over 70s were put in place early and led to a clear reduction in infections in those over 70 years of age. As such, the progression to severe COVID-19 disease as assessed here is within the context of social distancing and proactive protection of elderly population.

CONCLUSION

The Gibraltar COVID-19 Cohort provides a useful insight into the epidemiology of this new pathogen. The cohort benefits from a high rate of testing, a relatively contained population and the addition of a random sampling of over 1% of the total population over three days. Our results are similar to the reported background population infection level in Iceland of 0.8%.[10] The Iceland study tested 0.7% of their population over four days. Here, the Gibraltar's random stratified point prevalence study attained a population testing rate of 1.2% over three days.

125 clinical cases were confirmed by RT-PCR analysis via nasopharyngeal swab to have COVID-19 infection over a 35 day period. 2.5% of the population were also confirmed to be positive for COVID-19 by RT-PCR analysis via nasopharyngeal swab over a 3 day period of random testing (95% CI, 1.2 to 4.6%). Based on an ultraconservative model, the rate of progression for COVID-19 infection to severe COVID-19 Disease is 0.93% (95% CI, 0.43-1.8%). Based on an estimation of confounder influences, we estimate the case severity rate for COVID-19, within a proactive clinical management, and protecting the vulnerable approach, to be between 0.1 to 1%.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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