Modelling the SARS-CoV-2 vaccination campaign in Italy: the fundamental role of unreported cases

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\begin{abstract}
In Italy and around the world, the year 2021 was dedicated to vaccination campaigns against the COVID-19 epidemic arising after the outbreak of SARS-CoV-2 in China in 2019. In December 2020, we proposed a model prediction for the effects of vaccination, and now, after more than 9 months of the vaccination campaign, a comparison of those predictions with the actual data is mandatory. Surprising evidences emerge suggesting new strategies to consider regarding the spread of the virus and to protect frail people. After several months of the immunization campaign in Italy, it is estimated that approximately 20,000 deaths were avoided during the year 2021.
\end{abstract}

\section{Introduction}
At the end of 2020, a model study was performed to predict severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections as a function of time during the year 2021, including different scenarios for the vaccination rate in the Italian population (see Section 5.1 Traini et al. (2021a)). The model incorporates appropriate compartments relevant to interventions such as quarantine, isolation, and treatment. The population was stratified into susceptible (S), exposed (E), asymptomatic infected individuals (A), infected with symptoms (I), hospitalized in a large sense (detected infected, reported cases) (H), and recovered (R). Further stratification included quarantined susceptible (Sq) and isolated exposed (Eq) compartments. The use of the asymptomatic compartment was crucial in order to obtain a reliable estimate of the unreported cases (Traini et al., 2021b) (for a previous attempt see Maugeri et al. (2020)). The main parameters of the model can be found in Table 2 in (Traini et al., 2021a). A Markov chain Monte Carlo (MCMC) method was used to fit the values (and statistical uncertainties) onto the data of the outbreak in Italy during the period up to April 6, 2020. The procedure was implemented through an adaptive Metropolis–Hastings algorithm used for four concatenated runs with 100,000, 50,000, 25,000, and 10,000 iterations within the MCMC toolbox in MATLAB. A particular aspect of the model is the time-dependence of the key parameters related to the contact rate and the quarantine rate (Tang et al., 2020a; Tang et al., 2020b). Following the control measures adopted in Italy, the flexibility of the model was such that it was possible to adapt the values of some parameters to the actual social situation (Traini et al., 2020).

\section{Model predictions}
The predictions of the model study for vaccination effects are summarized and simplified in Figure 1. The predicted values of the infected reported cases were investigated within two different scenarios: a scenario with no vaccination during 2021 (magenta curves) was compared with the scenario that incorporates the actual (average) rate of vaccination realized in Italy during the first 9 months of the year 2021 (blue curves). The inset in Figure 1 is a graphical representation of the second scenario where the average immunization fit used in the model study (dotted lines) is shown together with the actual bar plot of the immunization data in Italy (Ministero della Salute, 2021). The assumed vaccine efficacy was 95% (see, for example Polack et al. (Polack et al., 2020)); therefore the number of immunized persons per day is given by the number of vaccines administered per day divided by 2 and multiplied by 0.95.

Also in Figure 1, the model predictions are compared with the official data collected during the year by the Italian Ministry of Health (Ministero della Salute, 2021). They documented the third wave of the pandemic in Italy, basically due to the presence and spread of the SARS-CoV-2 variants (see Burki and Fontanet et al. (Burki, 2021; Fontanet et al., 2021)), the rapid decrease in May and June, and the new increase starting in July (currently stabilized). Despite the massive increase in infections due to the new highly transmissible variants (basically the Delta variant in Italy), the actual number of reported cases from June onwards (i.e., after more than 6 months of the vaccination campaign, at the time of the highest rate of inoculations) is in very close agreement with the order of magnitude of the model predictions (between 15% and 25% of the initial value).

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When the predictions in Figure 1 were generated for the first time in December 2020, they had a mathematical value only. Now the same figure has another relevance and one has to investigate (and justify) the origin of the actual predictive power of the model.

3. Discussion and perspectives

The model discussed herein (Traini et al., 2021a) has been tested in a serological survey by the Italian National Institute of Statistics (Istat, 2020). The unreported cases in Italy, as evaluated within the model, were compared with the survey analysis for the period May–July 2020. The results, corrected for the sensitivity of the serological tests (Deeks et al., 2020), showed that the ratio of the total infected individuals to the reported cases was roughly 6:1, a quite large fraction, which agrees (within 20%) with the results of the serological testing performed by Istat (Istat, 2020). Extension of the calculation to a more recent period and comparison with the data showed that the ratio remained stable, also allowing an estimate of the asymptomatic population (Traini et al., 2021b).

In Figure 2, the (average) model predictions for the reported cases in Figure 1 are compared with the analogous predictions of the reported + unreported cases. Results for both vaccination scenarios are shown: the ones due to a scenario with no vaccination (solid lines) and those due to a scenario including the actual fit of immunizations realized until now in Italy (dotted lines). At the time of writing, on October 13, 2021, the official total number of infected in Italy (reported cases) was 4 707 087. The results of the present analysis suggest that this number should be multiplied by a factor 5.94 to also add the effect of the unreported component (compare with equation 8 in Traini et al. (Traini et al., 2021b) and the discussion in Section 3 of the same reference); i.e. total estimated recovered (TER) is approximately 27 900 000, with an uncertainty of 20%, which includes statistical errors in the serological survey (Istat, 2020), corrections due to the sensitivity and specificity of the tests (as discussed in Section 3.1 of Traini et al. (Traini et al., 2021b)), and the additional corrections due to the time dependence of the antibody tests (Section 3.2 of Traini et al. (Traini et al., 2021b)).

The comparison of the TER with the number of immunizations attained until today in Italy through vaccination (43 546 872 as of October 13, 2021) emphasizes the crucial role of the unreported cases to obtain the decrease in the reported ones in the first 9 months of the year 2021. The rapid decrease in the reported population cannot be ascribed to vaccination only but to the combined effect of vaccination, social restrictions, and the crucial effect of the (hidden) unreported recovered. In addition, it is evident from Figure 1 that the present number of infected is particularly similar to the predictions of a scenario without vaccines. The presence of the new variants that can also be transmitted (at least with some probability) by immunized people (Subarum, 2021; Riemersma et al., 2021), introduces an unusual situation for the spread of the virus, and the recovered and immunized population tends to remain (partially) active. At the same time, immunized people are often excluded from tests utilized to admit people to specific activities within a ‘green pass’ system, and the immunized asymptomatic infected remain unreported. Within this complicated scenario of post-vaccination and active variants, the large number of unreported helps to stabilize the situation producing the recent behaviour (beginning of October 2021) as documented in the present study.

In particular one could guess that a large number of unreported cases would be found among young people (Rumain et al., 2021) who remain asymptomatic or pauci-symptomatic (Maltezou et al., 2020). The investigation of Traini et al. (Traini et al., 2021b) combined with the results of the Istat survey (Istat, 2020), suggest that within the unreported cases, the proportion of asymptomatic is as high as 8:1. A detailed survey based on serological tests aimed at investigating the seroprevalence of SARS-CoV-2 among young people and in the general Italian population could help gain an understanding of the role of unreported individuals in Italy. An information which becomes discriminating to orient vaccination, specifically for the youngest in the population (5–11 years old) and to protect the frail persons in Italy and in other countries.

Vaccination campaigns remain crucial to limit the spread of SARS-CoV-2 and in particular to moderate the most severe effects in older and frail people. To reinforce the last statement in a quantitative way, Figure 3 shows the rate of daily and weekly averaged deaths due to coronavirus in Italy, as a function of time in the year 2021, with respect...
Figure 3. The rate of the daily (asterisks) and weekly (green diamonds) averaged deaths due to COVID-19 in Italy as a function of time in the year 2021, with respect to the (reported) infected population on the same day. At a fixed average probability of death, the rate would show a constant behaviour; the evident decrease in the rate (on average) is an unambiguous indication of the effects due to vaccination.

to the (reported) infected population on the same day. At the beginning of the year, the rate was roughly 0.9 deaths per 1000 reported infected per day. The minimum value was reached at the beginning of August after 7 months of the vaccination campaign: approximately 0.2 deaths per 1000 reported infected per day. During the last 2 months, the rate increased to 0.4 per 1000 reported infected. Obviously, at a fixed average probability of death, the rate would be independent of the number of infected fluctuating during the year. The visible decrease in the rate (on average) is an unambiguous indication of the effects due to vaccination. The increase in the rate, after an interval of 5–6 months from the first vaccinations, can also be interpreted as a signal of the need for a ‘booster’ inoculation (see Figure 3). The data in Figure 3 support the estimate of at least 20,000 deaths saved in Italy during 2021.

The relative contribution of the unreported cases in the vaccination scenarios is amplified by a low rate of vaccination. Accelerating vaccine administration would result in a decrease in the relevance of the unreported cases.

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