The European COVID-19 drugs calculation tool: an aid for the estimation of the drugs needed during the SARS-CoV 2 pandemic

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EAHP Statement 2: Selection, Procurement and Distribution.

ABSTRACT

Objective To create an informatics supportive tool, which can assist healthcare professionals in estimating potential requirements for essential drug supplies to respond to the current SARS-CoV-2 pandemic based on epidemiological forecasting.

Methods The tool was based on a Susceptible-Infected-Removed (SIR) epidemiological model in which the population is divided into three compartments and transmission parameters are specified to define the rate at which people move between stages. Appropriate data entry was guaranteed by the creation of structured guided paths. The drugs needed for the forecasted patients were estimated according to a list of critical care drugs compiled by consulting previous published scientific works, national and international guidelines. For each drug, an estimation was made of the percentage average ICU uptake for each therapeutic group and active principle.

Results The tool consists of a Microsoft Excel template that is based on the initial epidemiological situation, the non-pharmaceutical interventions applied, the risk of hospitalisation based on the population age distribution, and the hospital beds available. The tool provides a forecast of which patients with COVID-19 will need to be treated in a hospital setting. The number of patients is used to estimate the drugs needed based on the average daily dose and the treatment length of each drug. The possibility of editing the type of distribution (exponential or linear) of the number of patients at the beginning of the analysis, the percentage adherence with non-pharmaceutical interventions and their delayed effect, and all the key epidemiological parameters make the estimation tailorable to different clinical contexts and needs.

Conclusions This model might be an effective supporting tool that could be easily implemented within the workflow of health professionals. All the information reported in this paper could be useful in developing new strategies to tackle the COVID-19 pandemic.

INTRODUCTION

The COVID-19 pandemic has proved to be a global health threat, with approximately 100 million people infected and more than 2 million deaths worldwide.[1] The pandemic trend is influenced by multiple factors and each nation has adopted specific strategies to impede its spread. National health services have, therefore, been unprecedentedly challenged to assure adequate patient care, despite a constantly escalating demand for supportive drugs. This complex situation requires appropriate planning that is deeply affected by many aspects, such as the long-term unpredictability of the pandemic evolution, the disruption and vulnerability of the supply chains,[2] and the timeliness required by the decision-making process. All these aspects can generate misleading estimations, which can deeply impact the efficiency of the assistance provided by healthcare facilities, resulting in either a lack of therapies or placing further pressure on already constrained drugs and the supply chain. For this reason, health professionals should use adequate tools that can support the calculation of therapeutic needs, especially for those patients that require intensive care. With this regard, modelling of the pandemic appears to be crucial. As reported in a previous work,[3] every country, province or hospital should carry out proper pandemic modelling based on the epidemiological features and adapted to the local population in terms of number of people and age distribution in order to tailor and optimise the estimates to their specific situation.

AIM OF THE STUDY

We decide to create an informatics supportive tool, the European COVID-19 Drugs Calculation Tool (ECDCT). This tool is capable of assisting pharmacists, local healthcare institutions, governments, partners and other stakeholder to easily estimate potential requirements for essential drug supplies to respond to the current COVID-19 pandemic based on epidemiological forecasting.

We also wanted to share our methodological approach with other colleagues, so that our work might help to develop future strategies for the management of drug supplies during a pandemic emergency.

MATERIALS AND METHODS

The ECDCT was developed using Microsoft Excel software and was structured as a user-friendly interactive application that allows users, through a series of guided paths, to enter data about the current epidemiological situation in various countries and geographical areas. Based on the data provided, the tool will output a drug needs estimation derived from an epidemiological forecasting model.
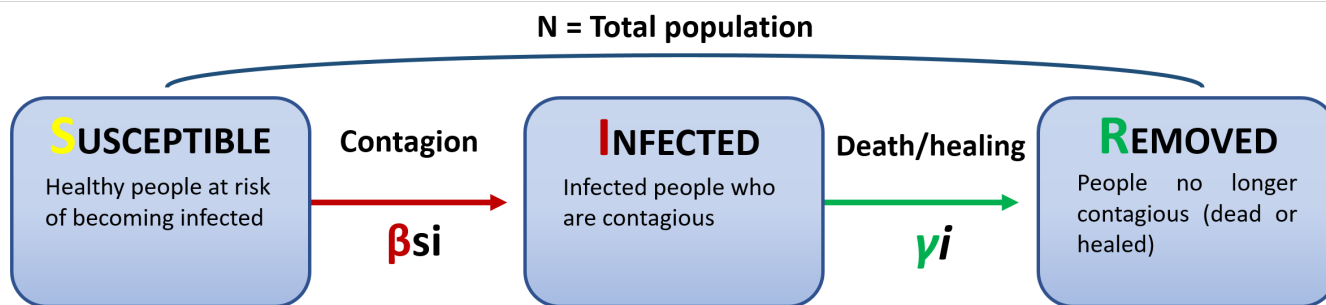
Figure 1 Schematic visualisation of susceptible-infected-removed (SIR) compartments. The total population (N) is given by the sum of S+I+R compartments. At the early stage of an unprecedented pandemic, S can be approximated to N.

Forecasting model

Epidemiological forecasting was based on a susceptible-infected-removed (SIR) model,[4] which describes the transmission dynamics as the flow over time of individuals of a given population (N) through three mutually exclusive population compartments (figure 1):

► Susceptible (S): healthy individuals at risk of becoming infected.
► Infected (I): individuals who have already been infected by the virus and can transmit it to susceptible individuals.
► Removed (R): individuals who recovered from the virus and are assumed to be immune, or those who have died.

Given the short timespans involved, it is assumed that the total population does not change significantly during the forecasted period as the births and deaths unrelated to the infection can be neglected and the number of deaths from the virus is small compared with the living population. Moreover, no immigration and emigration phenomena were considered, since movements between countries are restricted during outbreaks. We also assumed that the population is well mixed and every person interacts with one another. Finally, we assumed that all infected people are infectious and are spreading the disease among the susceptible population, and that people who are immune will not become susceptible again.

Defining s=S/N, i=I/N, r=R/N as the fraction of the population in each compartment, the rates of change of the three populations are governed by the following system of ordinary differential equations:

$$\frac{ds}{dt} = -\beta si \tag{1}$$

$$\frac{di}{dt} = \beta si - \nu i \tag{2}$$

$$\frac{dr}{dt} = \nu i \tag{3}$$

where β represents the rate of spread of infection by an infected person per day when they interact with the susceptible population, and ν is the rate of removal that governs the number of removed people. As β and ν can be difficult to obtain by the average user, we calculate the expected infected individuals based on the basic reproduction number (R_0), which can be calculated as:

$$R0 = \tau \cdot c^- \cdot d \tag{4}$$

where τ=infection/contact, c=contact/time, d=time/infection. Since β and ν can be respectively defined as $\beta = \tau c$ and d = ν −1, we calculated β as:

$$\beta = \frac{R_0}{d} \tag{5}$$

We augmented our SIR model by including the effects of Non-Pharmaceutical Interventions (NPIs), a series of public health containment measures, on the R effective (R_t) value, as reported by the Covidactnow Response Simulator,[5] and by correcting the number of infected people according to the testing capacity, as shown by the WHO COVID-19 Essential Supplies Forecasting Tool.[6] Finally, we set the default tuning values of the ECDCT based on what reported in the scientific literature,[6–13] as illustrated in table 1.

Although many more complex epidemiological models exist, we adopted the SIR because:

► it is easier for users with limited epidemiological competences as it requires fewer variables, easily obtained through official sources;
► it allows removal of many of the complexities associated with the real-time evolution of the virus' spread, while still providing a good estimation, both quantitatively and qualitatively[14];
► our forecasting needs did not require a highly accurate model on a short-time period, but one that could capture the fundamental human-to-human transmission dynamics of the pandemic, as the final aim of the ECDCT is estimation of drugs needs throughout the whole COVID-19 surge;
► it is widely adopted in the scientific literature[14 15] and other similar forecasting tools,[6 7] although with some ad-hoc variations.

Drugs selection

The drugs included in the ECDCT were selected by reviewing published scientific works, national and international guidelines,[3 6 16–21] and adjusted according to local practices.

As the treatment guidelines for patients with non-critical disease, at the time of writing, are still not exhaustively defined and most of the drugs are used when needed and depending on the patient's clinical features, such as the need for oxygen supplementation, it is hard to accurately quantify the demand for drugs in this patient population. For this reason, we provide specific drugs need estimations only for patients requiring critical care (ICU).

The calculation method adopted was informed by a previously published scientific work[17] considering the patient and treatment characteristics assumptions, such as the percentage uptake of a drug group, treatment duration for each drug, drug dosages and percentage usage within a drug group.

Table 1 List of assumptions made to tune the susceptible-infected-removed (SIR) model

Assumptions group	Specific parameter	Value	Additional notes	References
R_0	C	12,5	Average rate of contact between susceptible and infected individuals	6
	τ	2,68%	Probability of infection given contact between a susceptible and infected individual	
	d	7	Duration of infectiousness	
Hospitalisation details	Length of stay of hospitalised non-ICU patients	8		7 8
	Length of stay of hospitalised ICU patients	16		
	Length of stay in ICU	10		
Clinical features	% of ventilated ICU patients	70%		9
	% of intubated ICU patients	50%		
	% of shock ICU patients	35%		10
	Average days until hospitalisation	6		11
	% of mild and moderate cases	80%		6
	Hospitalisation rate	Inferred	Depending on the population's age group and the corresponding risk of hospitalisation according to Imperial College data	8
	% hospitalised in ICU	Inferred	Depending on the population's age group and the corresponding risk of critical care need according to Imperial College data	
Testing	% mild/moderate cases detected by test	10%	Percentage of infected individuals with mild or moderate symptoms that will be detected by testing	6 12
Non-pharmaceutical interventions	Min R_t with 100% mask compliance	0.40	Minimum R_t value achieved with all the population wearing masks	5
	Mask spread reduction	0.80	% reduction of infectious spread by those infected wearing masks	
	Mask protection level	0.40	% protection of those susceptible wearing masks	
	Min R_t with complete shelter in place	0.30	Minimum R_t value achieved with all the population sheltering in place	
	Susceptible shelter in place efficacy	0.70	Proportion of susceptible who will actually shelter in place	
	Infected shelter in place efficacy	0.90	Proportion of infected who will actually shelter in place	
	Closure NPI min R_t	0.60	Minimum R_t value achieved with the closure of all the activities, not taking into account masks and sheltering in place	
	Schools and universities (R_t impact)	0,2	Maximum contribution provided by the closure of each specific activity (100% compliance) on the Rt value	
	Large events (Rt impact)	0.04		
	Bars/restaurants (Rt impact)	0.18		
	Offices and factories (Rt impact)	0.13		
	House of worship (Rt impact)	0.04		
	Personal care (Rt impact)	0.06		
	Non-essential retail (Rt impact)	0.15		
	Essential retail (Rt impact)	0.13		
	Entertainment (Rt impact)	0.04		
	Outdoor recreation (Rt impact)	0.03		
	Lag time before NPIs impact the Rt (days), suggested values 14–21	21	Delay between the date of NPI implementation and the date of their observable maximum impact on the Rt value	13

NPI, non-pharmaceutical intervention; R_t, R effective.

The dosages entered were chosen on the basis of the most likely daily dosages according to what is reported in the scientific literature. When there was uncertainty or in the case of emergency medications for which the dosage ranges can vary widely (eg, naloxone, flumazenil), the Lexicomp maximum dosages were used as reference.

Some of the assumptions made for the drugs needed that are influenced by local practices and availability of drugs (dosages, duration of treatments for specific indications, and others) have been designed to be modifiable by the users in order to better adapt the estimation to their different clinical needs.

Additional data sources

To aid the ECDCT compiling process, we included data about the population and the number of hospital beds by country, extrapolated by the World Bank.[22] [23] Moreover, the number of people was stratified by age groups based on the age distribution by income, with data extrapolated from the United Nations,[24] and the specific income group of each country. These values were used to infer the percentage of patients with symptoms who would require hospitalisation and critical care in the population considered, based on the standard percentages reported by Imperial College.[8]

RESULTS

The final version of the ECDCT consists of an Excel template in which it is possible, through a guided and structured user form, to enter all the epidemiological data required to perform the forecasting, such as population selection, R_0 value, initial epidemiological situation, NPIs and availability of hospital beds. In particular, the population considered can be either chosen from a specific country or manually entered. For the R_0 value, it is possible to enter the whole value, or to specify the single epidemiological parameters described in equation 4.

Information about the initial epidemiological situation refers to the total number of patients who tested positive for COVID-19 and those who were admitted to hospital and were logged on the day of the analysis. Because some of the forecasted values (eg, patients admitted to hospital) depend on the epidemiological situation of the previous few days, we achieved better modelling of the early stages of the analysis by including the epidemiological data relating to either 14 days prior to, or the day of the start of the pandemic (when the first cases occurred), if it happened less than 14 days earlier. This last option is especially useful in case there is a resurgence of the SARS-CoV2 infection after a period of no new detected cases. We considered a maximum threshold of 14 days because it corresponds to the
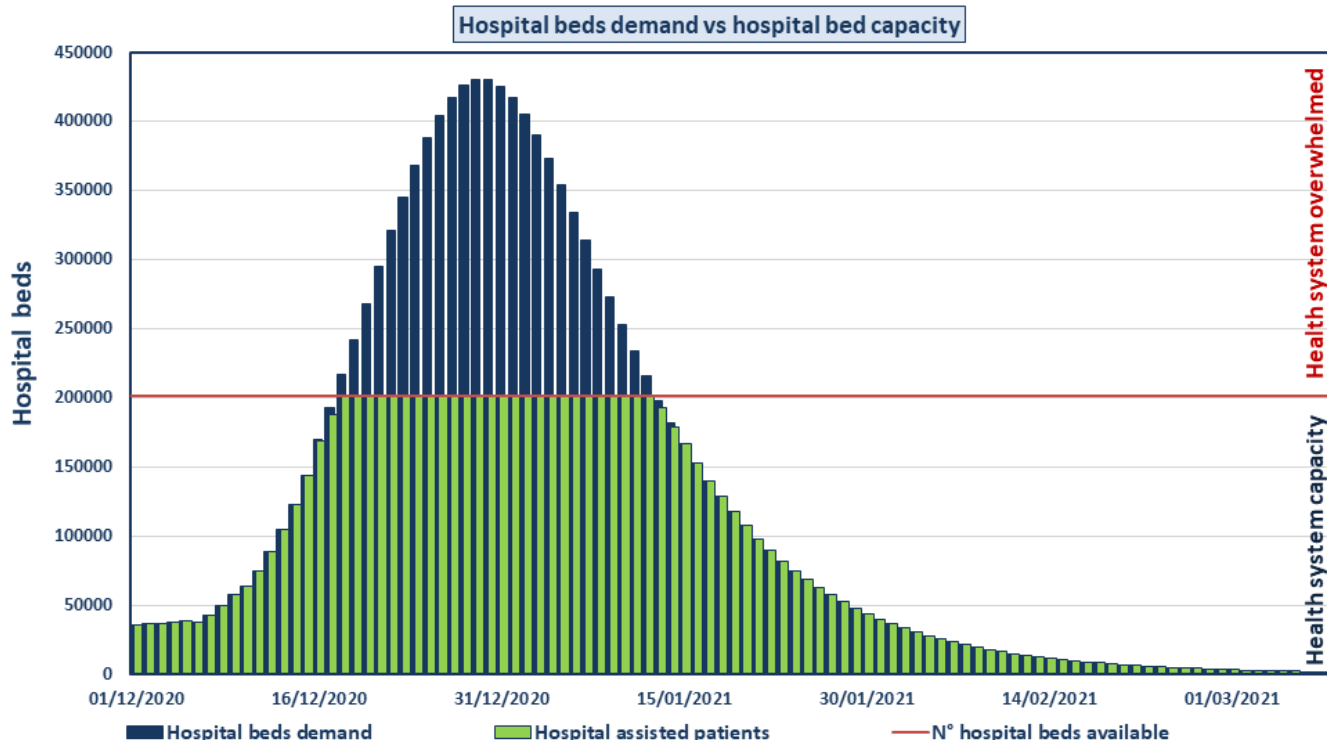
Figure 2 Comparison between the predicted hospital bed demand and the real hospitalisation capacity simulated using the European COVID-19 drugs calculation tool (ECDCT). For this simulation, the following values were used: population=59 132 073, R_0=2.35, total number of cases=1 400 000, active cases=700 000, patients in hospital=35 000, new cases=23 000, total number of cases 14 days previously=600 000, new cases 14 days previously=20 000, total hospital beds available=201 049, percentage of mild/moderate cases detected by test=33%. No NPIs (non-pharmaceutical implementation) was considered.

average duration of the infection, with an incubating period of 4 days,[11] a contagious period of 5 days[25] and a convalescence period of 5 days.[7] This epidemiological information is used to automatically distribute the number of cases occurring in the aforementioned interval according to an exponential or linear growth, based on the user's preferences. As reported by Cooper and colleagues,[14] at the beginning of the epidemic, when $R_t >1$ and $S \approx 1$, the rate of infection obtained through a SIR model can be described by an exponential increase, and thus equation 2 can be approximated to:

$$\frac{di}{dt} = i\left(\beta - \nu\right) \qquad (6)$$

$$i\left(t\right) = i\left(0\right) e^{\left(\beta - \nu\right) t} \qquad (7)$$

which can be rewritten as

$$i\left(t\right) = i\left(0\right) e^{\lambda t} \qquad (8)$$

In ECDCT, because the number of people with infection at the beginning and at the end of the interval considered are known, we inferred λ as:

$$\lambda_{fit} = \ln\left[i\left(t_d\right)/i\left(t_0\right)\right]/t_d \qquad (9)$$

Where t_0 and t_d are, respectively, the beginning and the end of the interval.

Finally, we fitted the exponential growth of the infected population as:

$$i\left(t\right) = i\left(t_0\right) e_{fit}^{\lambda} t \qquad (10)$$

The linear growth uniformly distributes the number of cases occurring in the interval considered, and can be used when the exponential growth is not reliable, such as in extremely short timespans or in the mid-late stage of the pandemic surge.

The tool also includes a set of NPIs, such as the closure of activities, the use of masks and the sheltering in place of the population. Concerning the type of closure, the users are allowed to choose between a default set of activity closures or assigning each of them individually. As reported in other works,[5 26] we included a factor (that we called percentage of closure and adherence), which represents the percentage of compliance with the public health measures on a scale from 0 (no intervention) to 1 (maximum measure's compliance). We also included an additional parameter relating to the lag time before the NPIs' full impact on R_t, which is the delay between the date of NPIs' implementation and the date of their observable maximum impact on the R_t value. In fact, as has been previously reported in another work,[26] there are a series of factors (eg, virus incubation and delay in lab testing) that generate a delayed detection of the NPIs' effect. Therefore, the evaluation of the NPIs' effect may require an observational period of 2–3 weeks.[13] During this time frame, the R_t reduction is step-wisely achieved by subtracting an increasing percentage of the total NPI effect, calculated as follows:

NPI reduction on R_t * (number of days that have passed since the NPI implementation date / the total number of lag days).

Sum of New hospitalized	Sum of New Hospitalized non-ICU	Sum of New ICU patients	Sum of Ventilated patients	Sum of New Intubated patients	Sum of New shock patients
33327	28313	5015	3510	2507	1755

Date

feb 2021

[DAYS] [MONTHS] [QUARTERS] [YEARS]

2020 | 2021
GEN FEB MAR APR MAG GIU LUG AGO SET OTT NOV DIC | GEN FEB MAR APR MAG GIU LUG AGO SET OTT NOV DIC

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Non-ICU patients

For 28313 patients start synthomatic tretment, in case of pneumonia and need for oxygen therapy it is advisable to use remdesivir (200mg first day + 100mg for the next 4 days) and dexamethasone (6mg for 10 days or until discharge)"

ICU patients

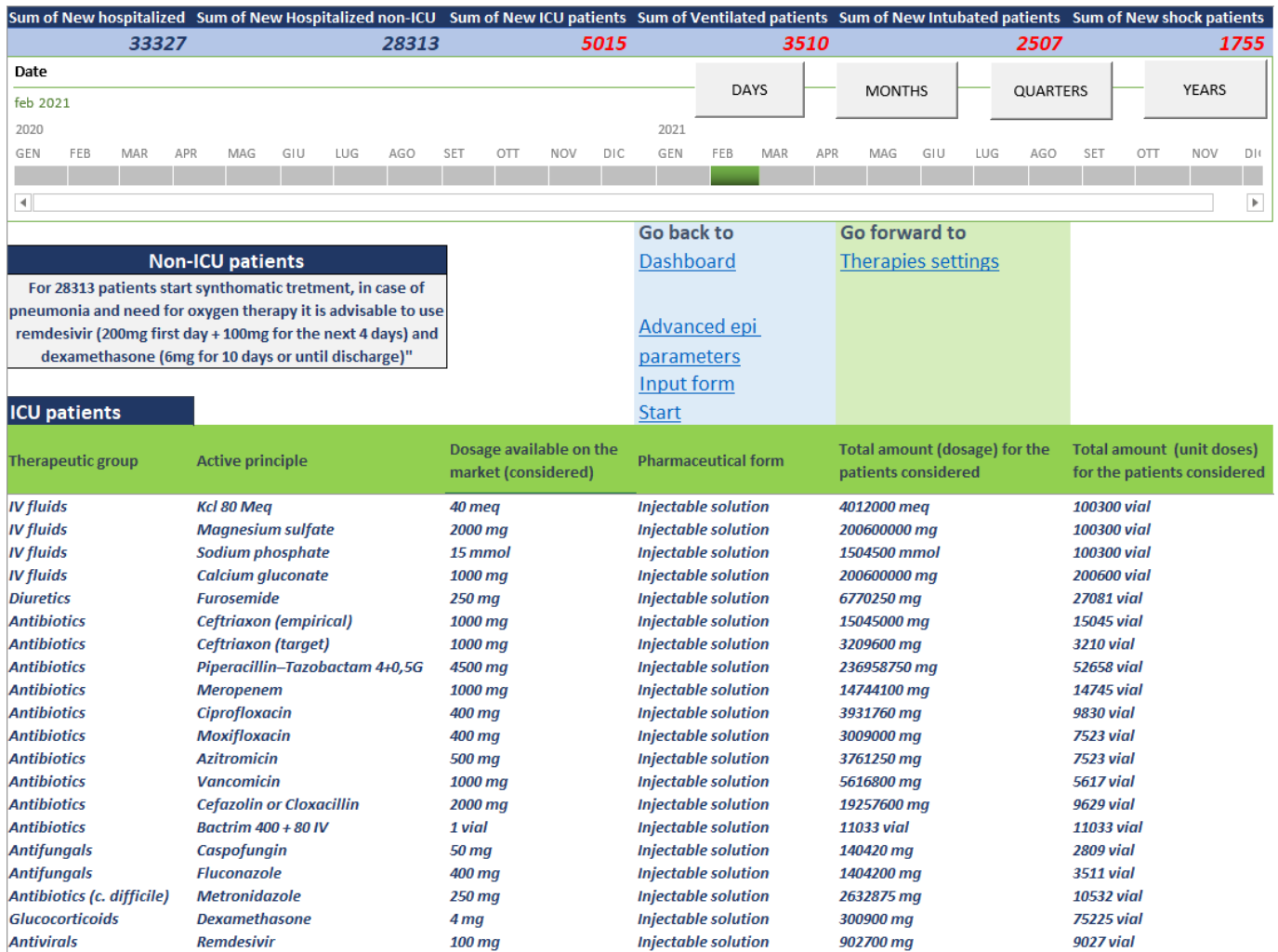| Therapeutic group	Active principle	Dosage available on the market (considered)	Pharmaceutical form	Total amount (dosage) for the patients considered	Total amount (unit doses) for the patients considered
IV fluids	Kcl 80 Meq	40 meq	Injectable solution	4012000 meq	100300 vial
IV fluids	Magnesium sulfate	2000 mg	Injectable solution	200600000 mg	100300 vial
IV fluids	Sodium phosphate	15 mmol	Injectable solution	1504500 mmol	100300 vial
IV fluids	Calcium gluconate	1000 mg	Injectable solution	200600000 mg	200600 vial
Diuretics	Furosemide	250 mg	Injectable solution	6770250 mg	27081 vial
Antibiotics	Ceftriaxon (empirical)	1000 mg	Injectable solution	15045000 mg	15045 vial
Antibiotics	Ceftriaxon (target)	1000 mg	Injectable solution	3209600 mg	3210 vial
Antibiotics	Piperacillin–Tazobactam 4+0,5G	4500 mg	Injectable solution	236958750 mg	52658 vial
Antibiotics	Meropenem	1000 mg	Injectable solution	14744100 mg	14745 vial
Antibiotics	Ciprofloxacin	400 mg	Injectable solution	3931760 mg	9830 vial
Antibiotics	Moxifloxacin	400 mg	Injectable solution	3009000 mg	7523 vial
Antibiotics	Azitromicin	500 mg	Injectable solution	3761250 mg	7523 vial
Antibiotics	Vancomicin	1000 mg	Injectable solution	5616800 mg	5617 vial
Antibiotics	Cefazolin or Cloxacillin	2000 mg	Injectable solution	19257600 mg	9629 vial
Antibiotics	Bactrim 400 + 80 IV	1 vial	Injectable solution	11033 vial	11033 vial
Antifungals	Caspofungin	50 mg	Injectable solution	140420 mg	2809 vial
Antifungals	Fluconazole	400 mg	Injectable solution	1404200 mg	3511 vial
Antibiotics (c. difficile)	Metronidazole	250 mg	Injectable solution	2632875 mg	10532 vial
Glucocorticoids	Dexamethasone	4 mg	Injectable solution	300900 mg	75225 vial
Antivirals	Remdesivir	100 mg	Injectable solution	902700 mg	9027 vial

Figure 3 A representative example of the drug estimation output. The drugs amount displayed in the ICU table refers to 5015 patients in ICU, as reported in the 'sum of new ICU patients' field above the timeline.

Hospital beds were inferred for each country by considering the average number of beds/1000 inhabitants and adjusted by the country's total population. When calculating critical care bed numbers, or when data were missing, we used the average number of beds/1000 inhabitants for the appropriate country's income group, as reported by the Imperial College.[8]

If the forecasting is performed based on a manually entered population, the ECDCT allows one to specify the number of beds available, and whether those beds are used to assist the whole population or just a percentage of it. Using the latter option, drug estimation will be performed only for the specified percentage of the total number forecasted to be infected, which could be useful for single hospitals that are likely to assist only a fraction of all patients who will need hospitalisation within the area considered.

Hospital bed availability is a key parameter in our calculation because it is used to set the maximum amount of drugs needed since the total number of hospital beds corresponds to the maximum number of patients that will be therapeutically assisted (figure 2).

The ECDCT also includes a series of editable epidemiological parameters that are useful to finely tune the tool, as reported in table 1. Among them, the percentage of patients with mild to moderate severity of symptoms that are detected by tests is

of particular note because it is used to calculate the number of patients admitted to hospital. According to scientific evidence, the percentage of undocumented infections (not tested) at the beginning of the outbreak ranged between 82% and 90%.[12] Because patients with severe to critical symptoms are the least likely to remain undetected, we decided to consider the percentage of undocumented infections as relating exclusively to patients with mild to moderate symptoms. Therefore, the default percentage of mild to moderate cases detected by test is set equal to 10%,[6] but it will be updated according to the latest scientific evidence.

To improve data visualisation about the epidemiological progression and hospital bed availability, we introduced a summary dashboard where the information is displayed through both charts and tables.

Finally, the estimation of drugs based on the number of patients obtained with the SIR model is performed considering the list of drugs selected. This list includes 51 drugs belonging to 19 therapeutic groups (online supplemental table). For each drug we specify the active principle, the daily dose, the pharmaceutical form, the percentage uptake of the drug group, the percentage usage within a drug group and the treatment duration for each drug. In case of therapeutically equivalent alternatives, the users are allowed to select their preferred choice. As reported

by Hogg and colleagues,[17] the total amount of drug is calculated as follows: the adjusted amount of a specific drug used=daily dose * % of use in ICU (according to therapeutic group) * % of use in ICU (according to each active principle) * average treatment length (days). This adjusted amount is then multiplied by the total number of patients in the timeframe considered.

In our tool, the value obtained is then divided by a specific dosage available on the market (editable by the users) to calculate the total amount of unit doses required. In figure 3 an example of drug estimation output is reported.

DISCUSSION

As previously stated, predictive models for epidemics are fundamental to understand the course of the epidemic and to plan effective strategies.[27] In particular, as outlined in a previously published paper,[9] some of the features of a forecasting model should be:

► pragmatic and focusing only on the relevant question for surge capacity;
► taking into account the most relevant data such as R_0 of the virus, the expected or observed rate of hospitalisation, need for ICU, need for mechanical ventilation, ICU length of stay;
► incorporating the impact of installing social distancing measures in society and their delayed impact on case detection.

In the ECDCT, we sought to implement all these features to create a tool that could represent a useful aid to estimate potential requirements for essential drug supplies to respond to the current COVID-19 pandemic.

The main goal of our work was to find a compromise between the creation of an accessible and user-friendly interface and an adequate capacity to capture the fundamental dynamics of the pandemic and thus capable of performing reliable drugs estimation. This aim has informed every developmental decision, such as the choice of basing our epidemiological forecasting on a SIR model, and the adoption of a well defined drugs calculation methodology, which can be easily personalised according to the users' needs, through a series of editable parameters.

However, it should be considered that the reference values used to tune our model, as with every other model, are often the result of data of questionable quality and homogeneity. As suggested by Casella,[26] there can be remarkable differences between countries' standards and capacity for swab testing, data lost due to clerical errors, and the NPIs' effectiveness that is still quite uncertain.

Particularly, the NPIs' effectiveness, in order to be statistically significant, is evaluated by grouping together countries with very different social habits and interpretations of the same measure (eg, lockdown) in the same dataset. Additionally, it should be noted that the impact of NPIs can differ according to a country's income group.[28]

Another critical aspect to consider is the fast evolution of available data, which require constant updating of the relevant parameters to ensure that the forecasting always mirrors the current epidemiological and clinical situation. This is particularly true for the lab testing capacity, which has increased since the beginning of the pandemic,[29] and the list of drugs included because the therapeutic guidelines and protocols for patients with SARS-CoV-2 have extensively changed over time.[30]

CONCLUSION

Despite its intrinsic limitations, we believe that the ECDCT can still be an effective aid for the health professionals' workflow. Moreover, all the information reported in this paper can

represent a useful aid to guide our colleagues in the development of their own methods and tools to tackle the COVID-19 pandemic. The evaluation of the possible benefits derived from the introduction of ECDCT in daily drug management will be an interesting subject for future works.

What this paper adds

What is already known on this subject
► the COVID-19 pandemic represents a global health emergency that has exacerbated pharmaceutical demand
► the emergency aspect of the pandemic makes it necessary to estimate pharmaceutical needs in a short time
► considering that it is a new virus, it is not possible to use historical consumption data as a reference

What this study adds
► the description of an informatics tool that allows users to make a timely estimate of pharmaceutical needs
► a drugs forecasting method based on an epidemiological model that can be customised to different settings, needs or other future pandemics

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