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Laura Temime, Marie-Paule Gustin, Audrey Duval, Niccolò Buetti, Pascal Crepey, Didier Guillemot, Rodolphe Thiébaut, Philippe Vanhems, Jean-Ralph Zahar, David Smith, et al.

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Laura TEMIME
MESuRS laboratory, Conservatoire national des arts et métiers, Paris, France; PACRI Unit, Institut Pasteur, Conservatoire national des arts et métiers, Paris, France.

Marie-Paule GUSTIN
Institute of Pharmaceutic and Biological Sciences, University Claude Bernard Lyon 1, Villeurbanne, France; Emerging Pathogens Laboratory-Fondation Mérieux, International Center for Infectiology Research (CIRI), Inserm U1111, CNRS UMR5308, ENS de Lyon, Lyon, France.

Audrey DUVAL
Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, CESP, Anti-infective evasion and pharmacoepidemiology team, Montigny-Le-Bretonneux, France; Institut Pasteur, Epidemiology and Modelling of Antibiotic Evasion unit, Paris, France.

Niccolò BUETTI
INSERM IAME, U1137, Team DesCID, Paris, France.

Pascal CRÉPEY
UPRES-EA 7449 REPERES « Recherche en Pharmaco-Epidémiologie et Recours aux Soins » – EHESP – Université de Rennes, Rennes, France.

Didier GUILLEMOT
Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, CESP, Anti-infective evasion and pharmacoepidemiology team, Montigny-Le-Bretonneux, France; Institut Pasteur, Epidemiology and Modelling of Antibiotic Evasion unit, Paris, France; AP-HP Paris Saclay, Public Health, Medical Information, Clinical research, Le Kremlin-Bicêtre, France.

Rodolphe THIÉBAUT
INSERM U1219 Bordeaux Population Health, Université de Bordeaux, Bordeaux, France; INRIA SISTM team, Talence, France; Vaccine Research Institute, Créteil, France.

Philippe VANHEMS
Emerging Pathogens Laboratory-Fondation Mérieux, International Center for Infectiology Research (CIRI), Inserm U1111, CNRS UMR5308, ENS de Lyon, Lyon, France; Service d'Hygiène, Epidémiologie et Prévention, Hospices Civils de Lyon, F-69437, Lyon, France ; Inserm, F-CRIN, Réseau Innovative Clinical Research in Vaccinology (I-REIVAC), Paris, France.

Jean-Ralph ZAHAR
IAME, UMR 1137, Université Paris 13, Sorbonne Paris Cité, France; Service de Microbiologie Clinique et Unité de Contrôle et de Prévention du Risque Infectieux, Groupe Hospitalier Paris Seine Saint-Denis, AP-HP, Bobigny, France.

David R.M. SMITH
Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, CESP, Anti-infective evasion and pharmacoepidemiology team, Montigny-Le-Bretonneux, France; Institut Pasteur, Epidemiology and Modelling of Antibiotic Evasion unit, Paris, France; MESuRS laboratory, Conservatoire national des arts et métiers, Paris, France.

Lulla OPATOWSKI
Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, CESP, Anti-infective evasion and pharmacoepidemiology team, Montigny-Le-Bretonneux, France; Institut Pasteur, Epidemiology and Modelling of Antibiotic Evasion unit, Paris, France.

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Corresponding author:
Laura Temime
MESuRS laboratory
Conservatoire national des Arts et Métiers
292 rue Saint-Martin – 75141 Paris Cedex 03
France
Email: laura.temime@lecnam.net

ABSTRACT

To date, no specific estimate of R_0 for SARS-CoV-2 is available for healthcare settings. Using inter-individual contact data, we highlight that R_0 estimates from the community cannot translate directly to healthcare settings, with pre-pandemic R_0 values ranging 1.3-7.7 in three illustrative healthcare institutions. This has implications for nosocomial Covid-19 control.

Keywords: COVID-19; basic reproduction number; modelling; hospital; transmission

In the context of the current Covid-19 pandemic, the basic reproduction number R_0 has been recognized as a key parameter to characterize epidemic risk and predict spread of SARS-CoV-2, the causative virus of Covid-19 infection [1]. R_0 describes the average number of secondary cases generated by an initial index case in an entirely susceptible population. R_0 is determined not only by the inherent infectiousness of a pathogen, but also environmental conditions, host contact behaviours and other factors that influence transmission. Understanding the evolution of the effective reproduction number R_t, which describes R_0 as it varies over time, is also essential for epidemiological forecasting and to assess the impact of control strategies [2, 3].

Over recent months, numerous estimates of R_0 for SARS-CoV-2 have been computed through analysis of reported infections from countries all over the world [2, 4-6], as well as in specific subpopulations, such as individuals aboard the Diamond Princess cruise ship [7]. Published estimates mostly range from 2-4.

However, to date, no estimates of R_0 specific to healthcare settings have been published.

Healthcare institutions are confronted with several urgent and overlapping challenges linked to Covid-19. Acute care facilities face unprecedented demand for beds and resources to accommodate Covid-19 patients, particularly in intensive care units in high-prevalence regions. Introduction of SARS-CoV-2 to healthcare settings can further result in nosocomial outbreaks, with superspreading events already reported in some hospitals [8], as was also observed for SARS-CoV and MERS-CoV. In addition to risks for patients, whose underlying conditions put them at greater risk of severe infection, there is also an important risk of infection among healthcare workers [8].

Contacts between individuals are fundamental to the spread of respiratory pathogens like SARS-CoV-2, and contact patterns in healthcare settings are highly context-specific. Contacts between patients and healthcare workers tend to be simultaneously more frequent, longer and more at-risk than contacts occurring in the community. This could translate to higher R_0 values, as underlined in earlier

work on other coronaviruses, in which R_0 was estimated to be much higher in hospitals than in the community [9].

Here, using detailed individual-level contact pattern data from both the community and three healthcare institutions in France, we explore how the reproduction number estimated in the community may translate to these institutions, and discuss potential consequences for public health.

METHODS

Under simplifying assumptions, R_0 can be estimated as follows:

$$R_0 = p \times d_{Ctc} \times n_{Ctc} \times d_{Inf}$$

where p is the probability of transmission per minute spent in contact, d_{Ctc} is the average contact duration (in minutes), n_{Ctc} is the average number of contacts per person per day, and d_{Inf} is the average duration of infectivity (in days): approximately 10 days for Covid-19 [10].

Assuming that p and d_{Inf} are the same for individuals in the community and in healthcare settings, we can translate the previous expression into setting-specific R_0 values computed as:

- In the community: $R_0^C = p \times d_{Ctc}^C \times n_{Ctc}^C \times d_{Inf}$
- In the healthcare settings: $R_0^H = p \times d_{Ctc}^H \times n_{Ctc}^H \times d_{Inf}$

where superscripts *C* and *H* denote values for community and healthcare settings, respectively.

The healthcare setting-specific reproduction number may then be estimated from the community-specific reproduction number and the contact pattern characteristics in both settings, as:

$$R_0^H = R_0^C \times \frac{d_{Ctc}^H \times n_{Ctc}^H}{d_{Ctc}^C \times n_{Ctc}^C}$$

NUMERICAL APPLICATION IN THE FRENCH CONTEXT

Based on detailed inter-individual contact data from France [11], in the community the median number of inter-individual contacts per person is n_{Ctc}^{C} = 8 contacts/day and the median duration of these contacts ranges from 15 minutes to 1 hour. For simplicity, in the following we use d_{Ctc}^{C} = 30 minutes.

The reproduction number for SARS-CoV-2 has been estimated in the French community at values ranging from $\mathrm{R}_0^{\mathrm{C}}$ = 2 to 4 [2, 12, 13]. In the following we use $\mathrm{R}_0^{\mathrm{C}}$ = 3.

These translate to an average transmission risk per minute spent in contact of:

$$p = 3 / (8 \times 30 \times 10) = 0.00125$$

Table 1 provides estimates of the healthcare setting-specific reproduction number $\mathrm{R}_0^{\mathrm{H}}$, depending on the average number of daily contacts within the healthcare setting n_{Ctc}^{H}, and the actual value of $\mathrm{R}_0^{\mathrm{C}}$. The mean duration of daily contacts within the healthcare setting d_{Ctc}^{H} is assumed to range from 10 to 40 minutes.

THREE ILLUSTRATIVE EXAMPLES

As an illustration, we used detailed contact data from three different healthcare settings in France during the pre-pandemic period to estimate $\mathrm{R}_0^{\mathrm{H}}$ in the absence of control measures specific to Covid-19:

- For a 170-bed rehabilitation hospital [14], where n_{Ctc}^{H} = 18 contacts/day and d_{Ctc}^{H} = 34 min, the pre-pandemic $\mathrm{R}_0^{\mathrm{H}}$ is estimated as

$$\mathrm{R}_0^{\mathrm{H}} = 0.00125 \times 34 \times 18 \times 10 = 7.65$$

- For an acute-care geriatric unit [15], where the cumulative time spent in contact with others per individual per day was $n_{Ctc}^{H} \times d_{Ctc}^{H}$ = 104 min, the pre-pandemic $\mathrm{R}_0^{\mathrm{H}}$ is estimated as

$$R_0^H = 0.00125 \times 104 \times 10 = 1.3$$

- For a 100-bed nursing home [16], where the cumulative time spent in contact per individual and per day was $n_{Ctc}^H \times d_{Ctc}^H$ = 615 min, the pre-pandemic R_0^H is estimated as

$$R_0^H = 0.00125 \times 615 \times 10 = 7.7$$

DISCUSSION

Estimating R_0 has been an important focus of epidemiological work to understand the transmission dynamics and pandemic trajectory of SARS-CoV-2. We highlight here that reproduction numbers estimated in the community cannot be translated directly to healthcare settings, where inter-individual contact patterns are specific to and variable between institutions.

Health care institutions are at high risk of SARS-CoV-2 importation, from admission of infected patients or from visitors or healthcare workers infected in the community. Our estimates of R_0^H suggest that, depending on a healthcare facility's size and structure, the risk of nosocomial spread may be much higher or lower than in the general population, with values ranging from 0.4 to 13.3 (Table 1).

Our results have implications for Covid-19 infection prevention and control. In healthcare settings with estimated low values of pre-pandemic R_0^H, it is expected that classical barrier measures – reducing *p*, the probability of transmission per minute of contact – may suffice to prevent a majority of cases. On the contrary, in healthcare settings where the estimated pre-pandemic R_0^H is high, it is critical to implement additional control measures. These measures could include reducing the frequency (n_{Ctc}^H) and duration (d_{Ctc}^H) of contacts (e.g. through limiting patient-patient contacts by cancelling social activities and gatherings), limiting patient transfers, or reorganizing human resources and provisioning of care within the institution.

It should be underlined that this work's aim is to present a conceptual discussion about R_0 in healthcare settings. Hence, the elements presented here, and in particular the numerical estimates, should be interpreted in light of the following over-simplifications.

First, Covid-19 infection was simplified by assuming the same duration of infectivity, irrespective of the setting. However, in the community, individuals presenting symptoms may isolate themselves and stay at home whereas patients of healthcare settings will stay hospitalized. Considering such differences would lead to higher estimates of R_0^H.

Second, we assumed the same per-minute probability of transmission, irrespective of the setting and nature of contacts. However, some hospital contacts, such as those involving close proximity or invasive procedures, may pose greater transmission risk than others. Also, a higher concentration of severe infections, which may shed more virus [17], and the presence of immunosuppressed individuals, may entail a higher transmission probability in hospitals, therefore increasing R_0^H.

Third, R_0^H may differ according to individual characteristics, notably for patients vs. healthcare workers. In addition, some individuals may be super-contactors or super-shedders, with a greater probability of generating secondary cases if infected.

Fourth, contact duration and frequency measured during distinct studies in the community and in specific healthcare populations are not necessarily comparable.

Last, our R_0 formula assumes random homogenous mixing between individuals in the population. However, contact patterns in the general population may depend on age. In addition, hospital networks are highly clustered due to ward structure and occupational hierarchies. Computing R_0^H values using contact information at the ward level and age structure data should facilitate more accurate estimates. Additionally, our formula makes the assumption that transmission risk increases linearly with contact duration, which may not be correct, especially for very long contacts. For

instance, censoring contacts longer than 1 hour in the data from the first example gives an average contact duration within the facility of 15 min, leading to a lower estimated R_0^H of 3.37.

In conclusion, pandemic Covid-19 continues to overwhelm healthcare institutions with critically ill and highly infectious patients, and nosocomial outbreaks pose great risk to patients and healthcare workers alike. Understanding how transmission risk varies between community and healthcare settings, and within and between different healthcare institutions such as hospitals and long-term care facilities, is fundamental to better predict risks of nosocomial outbreaks and inform appropriate infection control measures.

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Potential Conflicts of Interest

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REFERENCES

1. Anderson RM, Heesterbeek H, Klinkenberg D, Hollingsworth TD. How will country-based mitigation measures influence the course of the COVID-19 epidemic? Lancet **2020**; 395(10228): 931-4.
2. Flaxman S, Mishra S, Gandy A, et al. Report 13: Estimating the number of infections and the impact of non-pharmaceutical interventions on COVID-19 in 11 European countries, **2020**.
3. Pan A, Liu L, Wang C, et al. Association of Public Health Interventions With the Epidemiology of the COVID-19 Outbreak in Wuhan, China. Jama **2020**.
4. Kucharski AJ, Russell TW, Diamond C, et al. Early dynamics of transmission and control of COVID-19: a mathematical modelling study. Lancet Infect Dis **2020**.
5. Li R, Pei S, Chen B, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2). Science **2020**.
6. Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R. High Contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome Coronavirus 2. Emerg Infect Dis **2020**; 26(7).
7. Zhang S, Diao M, Yu W, Pei L, Lin Z, Chen D. Estimation of the reproductive number of novel coronavirus (COVID-19) and the probable outbreak size on the Diamond Princess cruise ship: A data-driven analysis. Int J Infect Dis **2020**; 93: 201-4.
8. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Jama **2020**.
9. Hsieh YH. 2015 Middle East Respiratory Syndrome Coronavirus (MERS-CoV) nosocomial outbreak in South Korea: insights from modeling. PeerJ **2015**; 3: e1505.
10. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature **2020**.

11. Béraud G, Kazmercziak S, Beutels P, et al. The French Connection: The First Large Population-Based Contact Survey in France Relevant for the Spread of Infectious Diseases. PLoS One **2015**; 10(7): e0133203.

12. Alizon S, Bénéteau T, Choisy M, et al. Estimating the basic reproduction number of the COVID-19 epidemic in France, **2020**.

13. Di Domenico L, Pullano G, Sabbatini C, Boëlle P-Y, Colizza V. Expected impact of lockdown in Île-de-France and possible exit strategies, **2020**.

14. Duval A, Obadia T, Martinet L, et al. Measuring dynamic social contacts in a rehabilitation hospital: effect of wards, patient and staff characteristics. Sci Rep **2018**; 8(1): 1686.

15. Voirin N, Payet C, Barrat A, et al. Combining high-resolution contact data with virological data to investigate influenza transmission in a tertiary care hospital. Infect Control Hosp Epidemiol **2015**; 36(3): 254-60.

16. Assab R, Temime L. The role of hand hygiene in controlling norovirus spread in nursing homes. BMC Infect Dis **2016**; 16: 395.

17. Xu K, Chen Y, Yuan J, et al. Factors associated with prolonged viral RNA shedding in patients with COVID-19. Clin Infect Dis **2020**.

Table 1 – Range of estimated reproduction numbers (R_0^H) values obtained when d_{Ctc}^H ranges from 10 to 40 minutes, for different assumed values of R_0^C (rows) and n_{Ctc}^H (columns)

		Average number of daily contacts in the healthcare setting (n_{Ctc}^H)				
		5	10	15	18	20
Assumed value for basic reproduction number in the community (R_0^C)	2	0.4-1.7	0.8-3.3	1.3-5	1.5-6	1.7-6.7
	2.5	0.5-2.1	1-4.2	1.6-6.3	1.9-7.5	2.1-8.3
	3	0.6-2.5	1.3-5	1.9-7.5	2.3-9	2.5-10
	3.5	0.7-2.9	1.5-5.8	2.2-8.8	2.6-10.5	2.9-11.7
	4	0.8-3.3	1.7-6.7	2.5-10	3-12	3.3-13.3