Emerging Evidence on COVID-19

Evidence Brief of COVID-19 Infectious Period in Immunosuppressed/Immunocompromised Individuals

Introduction

What is the length of the infectious period of SARS-CoV-2 in immunosuppressed and immunocompromised individuals?

The infectious period (also known as the communicability period) is defined as the time during which an infected person can transmit an infectious agent to another person. The infectious period is an important clinical and epidemiologic parameter to understand for the control of any infectious disease. Estimates of the average infectious period of SARS-CoV-2 for mild/moderately symptomatic immunocompetent cases is considered to start on average 2.5 days before developing symptoms, peak around day 4 of symptoms and decrease to low levels within 8-10 days after the start of symptoms for a total of 10-13 days (see Rapid Review on Infectious Period, Sep 2020).

In this brief, immunosuppressed and immunocompromised populations are considered. Immunosuppression may result from certain immune-mediated diseases and/or therapies (e.g. anti-cancer therapy, anti-rejection medication, etc.). Immunocompromised individuals may have an immune deficiency from infectious or genetic causes. Early case reports have documented longer periods (>14 days) during which replication-competent (i.e., culture positive) SARS-CoV-2 can be recovered in these populations and in severe cases of COVID-19. Further, immunosuppression has been shown to be associated with higher odds of persistent viral RNA shedding (>21 days) in two studies (1, 2), while another study found no significant association (3). Potential prolonged and recurrent infections in this population identified the need for further research on infectiousness and unique strategies for safe de-isolation to prevent further transmission.

This brief focuses on research conducted to document infectious period in immunosuppressed/immunocompromised cases of COVID-19 published up to February 5, 2021. They have been organized by underlying disease condition and type of study. Because of their preliminary nature, case reports were not included in this review. Infectious period estimates were determined by a combination of epidemiological and clinical investigations that together informed when an infected person could, or was likely to, no longer transmit the virus. Most studies used RT-PCR to diagnose cases of COVID-19 and to monitor viral RNA shedding over time. However, detection of viral RNA by RT-PCR does not provide proof of infectivity as this test also gives positive results when non-infectious virus particles are present. These particles are commonly shed from

infected tissue for a period of time after an infection has been cleared by the host immune system (4). Recovery of replication-competent virus has been used as an *in vitro* proxy for human-to-human infectiousness. To establish if viable virus has been isolated in a sample, replication of virus is established most reliably by cell culture. Unfortunately, few studies employed culture methods because they can be slow and expensive. Detection of subgenomic RNA has been recommended as a proxy for shedding of infectious virus (5), however there is not yet consensus on this application (6).

Key Points

- The review identified 19 studies including 1 bidirectional cohort, 1 prospective cohort, 10 retrospective cohort studies, and 7 longitudinal case series. Immunosuppressed populations included cancer (n=11) and transplant patients (n=6). Immunocompromised patients included those with HIV (n=2). Only two studies provided evidence of viable virus via cell culture while the others described the length of viral RNA shedding via RT-PCR or qRT-PCR.

Culture studies (n=2)

- Recovery of replication-competent SARS-CoV-2 has been reported in patients immunosuppressed due to hematologic cancers for at least 2 months. This is much longer than the infectious period estimated in the average immunocompetent populations (10-13 days, see Rapid Review on Infectious Period).

RT-PCR studies (n=17)

- RT-PCR conducted on respiratory samples from mildly symptomatic immunocompentent typically become negative within 14-20 days. As shown in the points below, time to viral RNA clearance was much longer in immunosuppressed/immunocomptent individuals. How long there was viral RNA shedding depended to some degree on the cause of the immunosuppression/immunocompromise.
    - In cancer patients, median time to viral RNA clearance ranged from 12-50 days with an overall range of 9-78 days. Systemic anticancer therapy (i.e., chemotherapy, hormonal therapy, targeted drugs, and immunotherapy), before or during COVID-19 positivity, was not significantly associated with viral clearance time.
    - In solid organ transplant patients undergoing immunosuppressive therapy, time to viral clearance ranged from 9-66 days. Mean viral RNA shedding was significantly

longer in kidney transplant patients than immunocompetent individuals (28.4 days vs. 12.2 days, $p<0.01$). Further, evidence from one study reported high viral loads at day 30 of infection in a group of transplant patients indicating high likelihood of SARS-CoV-2 transmission 30 days after symptom onset.

- In patients with HIV, RNA viral clearance occurred over a median of 18 days (IQR 7-28) but remained detectable in some patients >40 days post symptom onset. Severe HIV cases had a longer duration of viral RNA shedding compared to mild/moderate cases.

Overview of the Evidence

A total of 19 studies were included in this review, including cohort studies and longitudinal case series. Many of these are pre-prints and have not undergone a peer-review process. Prospective cohorts are of lower risk of bias and are considered higher quality research, but there are few of this study design contributing to this question. Case series suffer from low sample size, selection bias and recall bias (e.g., self-report symptom onset). In addition, many of the immunosuppressed/immunocompromised cases described in this review also had additional underlying chronic health conditions and it is difficult to determine if and how this affected the results. Overall, due to the risks of bias, these studies should be interpreted with caution, as results are likely to change with additional research.

Several knowledge gaps exist for the infectious period of SARS-CoV-2 in special populations. Few studies utilize cell culture and instead depend on detection of viral RNA as a proxy for potential infectious period. Such methods cannot distinguish between infectious and non-infectious viral particles, however, the relationship between viral load and probability of culture positivity has been covered in the literature. Additional research on immunity and how infectious period is impacted by immunosuppressive therapies for other immune-mediated diseases (e.g., rheumatoid arthritis, Crohn's disease, etc.) is needed. As well, further exploration into strategies for safely de-isolating these cases to prevent further transmission is warranted.

CONTENTS

INFECTIOUS PERIOD OF IMMUNO-SUPPRESSED/COMPROMISED INDIVIDUALS

Cancer/hematological disease patients (n=11):

- Only two studies provided evidence of replication-competent virus via cell culture:
    - Patients with immunosuppression due to hematologic cancers, that underwent allogenic or autologous hematopoietic cell transplantation or received cellular therapies, shed replication-competent SARS-CoV-2 for at least 2 months (7, 8). This was much longer than in immunocompetent patients (<7 days) (8).
- Many cases had additional underlying chronic health conditions (9, 10).
- Majority of cases required >14 days to achieve consecutive negative PCR results, with a median time ranging from 12-50 days and an overall range of 9-78 days (7-17).
- Anticancer therapy (i.e., chemotherapy, hormonal therapy, targeted drugs, and immunotherapy), before or during COVID-19 positivity, was not significantly associated with viral RNA clearance time (11, 12, 16).
- Severe cases had a longer duration of viral RNA shedding compared to mild/moderate cases, but this finding was not significant (13).

Solid organ transplant patients (n=6):

- The majority of patients were taking immunosuppressive therapy (18-21).
- No studies provided evidence of viable virus via cell culture.
- The majority of cases required >14 days to achieve consecutive negative PCR results, with an overall range of approximately 9-66 days (18-23).
- The mean time of SARS-CoV-2 viral RNA shedding in a group of kidney transplant patients was 28.4 ± 9.3 days, which was significantly longer than that of immunocompetent individuals (12.2 ± 4.6 days, $p<0.01$) (23).
- A study of kidney transplant recipients reported 43% of patients still had positive RT-PCR results at day 30 of follow-up with viral loads above 3 $\log^{10}$ copies per reaction, the threshold for which there is a risk of SARS-CoV-2 transmission (22).

- Severe cases had a longer duration of viral RNA shedding compared to mild/moderate cases, but this association was not statistically investigated (21).

Human immunodeficiency virus (HIV) patients (n=2):

- All patients were on antiretroviral therapy (24, 25).
- No studies provided evidence of viable virus via cell culture.
- RNA viral clearance occurred over a median of 18 days (IQR 7-28) post symptom onset (24).
- SARS-CoV-2 viral RNA may remain detectable in some HIV patients for >40 days post symptom onset (24, 25).
- Patients with longer times to viral RNA clearance had more severe disease, higher ICU admission, lower nadir CD4 cell counts, and a higher proportion of comorbidities than individuals with shorter times to viral clearance ($p<0.05$) (24).

Table 1: Studies reporting infectious period estimates in immunosuppressed and immunocompromised COVID-19 patients (n=19)

STUDY	METHOD	KEY OUTCOMES
IMMUNOSUPPRESSED PATIENTS		
Cancer patients (n=11)		
Roedl 2020 (8) *LTE* Retrospective cohort study Germany Nov 2020*	Studied patients with malignancies being treated with allogenic hematopoietic stem cell transplant (HSCT) recipients or chimeric antigen receptor T-cell (CAR-T) therapy who also required ICU treatment for COVID-19 (n=6). Outcomes were compared with COVID-19 patients without a history of malignant disease (n=18). SARS-CoV-2 was detected by RT-PCR and viral isolation was performed using cell culture. After 48–72 hours of incubation, infected Vero cells (CCL81; American Type Culture Collection) were monitored for cytopathic effect.	Bronchoalveolar and plasma samples -In patients with history of HSCT or CAR-T, viral loads remained high until end of follow-up, day 28 (in both respiratory and plasma samples). In contrast, SARS-CoV-2 RNA was below the limit of detection after 21 and 11 days in respiratory and plasma samples, respectively, in immunocompetent patients. -Infectious virus was isolated from five samples from four patients with a history of HSCT or CAR-T therapy, obtained 4-28 days post ICU admission. In immunocompetent patients, infectious virus could not be detected after Day 7.

Aydillo 2020 (7) *LTE* Longitudinal case series USA Mar-Apr 2020	Analyzed longitudinal samples collected from immunocompromised cancer patients with COVID-19 (n=20). Cell culture was used to detect viable virus and whole-genome sequencing was used to detect genetic variants. Inoculated Vero E6 cell monolayers were incubated for a week and monitored daily for cytopathic effect. Time from symptom onset to negative RT-PCR was also measured.	Nasopharyngeal and sputum swabs -There were 18 recipients of allogenic (n=6) or autologous (n=10) hematopoietic stem-cell transplants or chimeric antigen receptor (CAR) T-cell therapy (n=2). Fifteen were receiving active treatment or chemotherapy. -Viral RNA was detected up to 78 days after the onset of symptoms (IQR: 24-64 days). -Viable virus was isolated from follow-up samples from five patients for 8, 17, 25, 26, and 61 days after the onset of symptoms. -The patients with viable virus for more than 20 days had received allogeneic hematopoietic stem-cell transplants or CAR T-cell therapy within the previous 6 months and remained seronegative for antibodies to viral nucleoprotein. Two of these patients had severe COVID-19. -Whole-genome sequencing showed no major changes in the consensus sequences of the original serial specimens or cultured isolates, consistent with persistent infection.
Wong 2020 (15) Bidirectional cohort study USA Dec 2020*	Cancer patients positive for SARS-CoV-2 that had undergone cancer-directed therapy (n=26) were tested every two weeks by PCR (targeting N2 and ORF1a) until two successive negative PCR results were obtained.	Nasopharyngeal swabs -Various cancer cases were included, 15 of which (58%) had advanced stage IV disease. -Mean time to consecutive negative PCR results was 32 days. -Twenty (77%) patients required >14 days to achieve consecutive negative PCR results.
Nakamura 2020 (10) *Preprint* Retrospective cohort study Japan Jan-May 2020	Analyzed data from COVID-19 patients with a history of cancer (n=32). Measured the time between illness onset and the first of two consecutive negative SARS-CoV-2 RT-PCR results.	Nasopharyngeal swab -Twenty-five patients (78%) had solid tumors, while 7 (22%) had hematologic malignancies. Nineteen (59%) also had at least one comorbidity (e.g. hypertension, 41%). Thirteen patients (41%) received cancer treatment within the last 30 days. -The median period between illness onset and the first of two consecutive negative SARS-CoV-2 RT-PCR results was 22 days (IQR: 18–25) in survivors (n=224).
Fox 2020 (11)	Analyzed data from COVID-19 patients with a hematological disorder, mostly cancers (n=55). The duration of viral RNA	Nose and throat swabs -94% (52/55) of patients were currently on or had previously received systemic anti-cancer therapy (chemotherapy or immunotherapy).

Retrospective cohort study UK Mar-May 2020	shedding was analyzed using Kaplan-Meier methods from date of illness onset to first of consecutive negative SARS-CoV-2 RT-PCR results (targeting the N gene).	-The median duration of SARS-CoV-2 viral RNA shedding was 34 days in survivors (n=27, 95% CI, 27–47). The longest duration of shedding (still positive at the end of follow-up) was 49 days. -The duration of viral RNA shedding was not prolonged in patients treated with chemo- or immuno-therapy in the last 14 or 28 days.
Ramaswamy 2020 (16) Retrospective cohort study India Apr-Jun 2020	Cancer patients undergoing systemic therapy with laboratory confirmed COVID-19 (n=230) were tested every 3-4 days until RT-PCR negativity. Logistic regression analysis was conducted to evaluate factors affecting delayed conversion to RT-PCR negativity.	Oropharyngeal or nasopharyngeal swab -Patients had various cancer diagnoses, the most prevalent malignancies were acute leukemia (20%) and gastrointestinal malignancies (17%). -53% of patients had evidence of remission or controlled cancer status, while 14% had uncontrolled cancer status or were on active symptom control. -The median time to SARS-CoV-2 seroconversion was 17 days (IQR: 17-28). -Duration of viral RNA shedding was ≤14 days for 52 patients (30%; n=182), 52 patients (30%) tested negative between 15 and 21 days, and 50 patients (29%) were still positive >21 days of follow-up. -None of the factors evaluated, including age, gender, diabetes mellitus, hematolymphoid malignancies, uncontrolled cancer status, and nonmyelosuppressive systemic therapy were found be significantly associated with prolonged viral RNA shedding.
Infante 2020 (9) *LTE* Retrospective cohort study Spain Mar-Apr 2020	Analyzed data from COVID-19 patients with hematological malignancies (n=41). Time to viral clearance was measured by RT-PCR but start/end points were not defined.	Nasal swab -Twenty-nine (70%) of patients had a lymphoid malignancy. Twenty-one (51%) were under active treatment at the time of COVID-19. -The majority of patients (93%) had additional chronic medical conditions. -The median duration of viral RNA shedding was 32.7 days (range 10-70) in surviving patients (n=26). A patient with acute myeloid leukemia under induction therapy at the time of infection was still positive by RT-PCR after 70 days of follow-up.
Xu 2020 (12) *Preprint* Retrospective cohort study USA	Analyzed all patients at a tertiary care hospital with confirmed COVID-19, who had a cancer-related clinical visit within 3 years, and at least one follow-up SARS-CoV-2 assay (n=32). Time to viral clearance was analyzed using Kaplan-Meier methods, for which	Nasopharyngeal swab -Sixteen patients had metastatic disease, 17 were on active treatment at the time of COVID-19 diagnosis, with 8 receiving cytotoxic chemotherapy. -The median time to viral clearance was estimated at 50 days (95% CI, 33-58 days). -Using the UK-NICE guidelines, median time to clearance was 31 days (95% CI, 26-42 days).

Mar-June 2020	data was censored at the time of the last known RT-PCR assay. This method was compared with other guidelines for viral clearance: • UK-NICE guidelines: measured as time to one negative RT-PCR test. • CDC criteria: Symptom/time based strategy measured as 10 days after first positive RT-PCR and 3 days after last symptoms.	-Using a symptom/time-based strategy per CDC criteria, median time to clearance was 13 days (95% CI, 10-17 days). -Cox proportional hazards models showed symptomatic patients had longer viral RNA shedding than asymptomatic patients (HR 0.25 for negative PCR, 95% CI 0.08-0.76, p=0.01). -Anticancer therapy (chemo-, immuno-, targeted- or hormonal therapy), before or during COVID-19 positivity, was not significantly associated with viral clearance time.
Berghoff 2020 (17) Retrospective cohort study Austria Mar-May 2020	Patients with cancer (n=1,016) were routinely tested for SARS-CoV-2 RNA by RT-PCR. Measured time from first positive test to first negative RT-PCR test.	Nasal or pharyngeal swab -SARS-CoV-2 infection was confirmed in 4 of 1,016 (0.4%) patients. Cancers included stomach (n=1), sarcoma (n=1) and head and neck cancer (n=2). Two of the patients were under active anticancer therapy. -Viral clearance was achieved in three patients 14-56 days after testing positive. One patient had still not achieved viral clearance 28 days after first positive at time of this report.
Sanchez-Pina 2020 (13) Retrospective matched cohort study Spain Mar-Apr 2020	Analyzed patients with COVID-19 and haematological malignancies (n=39). Outcomes were compared to a matched control group of 53 non-cancer patients with COVID-19. Follow-up COVID-19 PCR testing was performed in a subset of the cancer patients (n=20) to measure time to viral clearance.	Nasopharyngeal swab -The most frequent haematological diseases were lymphoma (n=12), multiple myeloma (n=12), and chronic lymphocytic leukaemia (n = 6). -In the 20 follow-up cases, median time to achieve PCR negativity was 14 days. -Five patients experienced prolonged viral RNA shedding with a median duration of 23 days (range 16-31 days). -Severe cases had a longer duration of viral RNA shedding compared to mild/moderate cases (22 vs. 14 days), but this finding was not significant (p=0.441).
O'Nions 2020 (14) *Preprint* Longitudinal case series UK Apr-May 2020	Analyzed longitudinal samples from hospitalized COVID-19 patients with aggressive hematological malignancy on systemic anti-cancer treatment (n=10). Measured days from symptom onset to negative PCR result.	Nose and throat swabs -Hematological malignancies included acute myeloid leukaemia, B-lymphoblastic leukaemia, T lymphoblastic leukaemia, and diffuse large B cell lymphoma. -All patients received systemic anti-cancer treatment within 28 days of developing COVID-19. - Eight patients seroconverted and developed antibodies to the major SARS-CoV-2 antigens (S1 and N) with six producing neutralising antibody responses.

		-The median duration of PCR positivity was 12 days (IQR 24). -Days from symptom onset to negative PCR ranged from 9-62 days.
Solid organ transplant patients (n=6)		
Benotmane 2020 (18) Retrospective cohort study France Mar-Apr 2020	Studied kidney transplant recipients with COVID-19 (n=40). qRT-PCR was used to detected SARS-CoV-2 nucleic acid (targeting two regions on the RNA dependent RNA polymerase gene). Patients were followed up weekly until discharge then tested at 30, 45, and 60 days after symptom onset. Viral clearance was defined as at least 1 negative RT-PCR test.	Nasopharyngeal swabs and plasma samples -The median time after kidney transplantation was 6.6 years (IQR: 2.8-14.6 years). At the time of COVID-19 diagnosis, 35 (87.5%) patients were taking immunosuppressive therapy. -The viral load of most patients (74.4%) peaked at the time of diagnosis. -No patient showed a viral clearance before day 21. Ten patients (24.4%) showed persistent viral RNA shedding after 31 days. -Patients receiving immunosuppressive therapy tended to have more positive RNAemia, but this finding was not significant (p=0.29).
Zhu 2020 (23) Retrospective cohort study China Jan-Mar 2020	Analyzed data from renal transplant recipients with laboratory-confirmed COVID-19 pneumonia (n=10). Also collected and compared clinical data from immunocompetent family members with COVID-19 pneumonia (n=10). Time of virus shedding, defined as illness onset to negative RT-PCR test, was monitored.	Throat swabs -The mean time of virus shedding in the transplant patients was 28.4 ± 9.3 days. This was significantly longer than that of the immunocompetent family members (12.2 ± 4.6 days , p<0.01).
Caillard 2020 (22) *LTE* Longitudinal case series France Oct 2020*	Prospectively monitored kidney transplant recipients with COVID-19 (n=42). RT-PCR was used to detect SARS-CoV-2 nucleic acid (targeting two regions on the RNA dependent RNA polymerase gene).	Nasopharyngeal swab, saliva, and respiratory specimens -At day 30, 15/35 (43%) patients tested still had positive RT-PCR results, with viral loads above the threshold for which there is a risk of SARS-CoV-2 transmission (>3 log10 copies per reaction). -At day 45, 12 patients (34%) still had positive RT-PCR results. -At 60 days, 6 patients (17%) had low but still detectable SARS-CoV-2 loads.
Gaston 2020 (19) Longitudinal case series	Analyzed data from solid organ transplant recipients on maintenance immunosuppression with symptomatic COVID-19 infection (n=25). Viral positivity	Nasopharyngeal and oropharyngeal swabs -Only 5 patients had serial testing. -4/5 patients had RT-PCR results longer than 21 days post symptom onset.

USA Mar-May 2020	was assessed by RT-PCR (targeting N1 and N2 SARS-CoV-2 gene).	-Two patients were still positive ≥27 days post symptom onset. -One patients was still positive at day 38.
Christensen 2020 (20) Longitudinal case series USA Mar-May 2020	Analyzed data from symptomatic kidney/liver transplant recipients with COVID-19 (n=6). Viral positivity was assessed by qRT-PCR.	Nasopharyngeal swabs -The median time from transplant was 1.9 years (range: 0.21-9.3). All six patients had hypertension (100%) and 5 had diabetes (83%). -All patients had been on immunosuppressant medication prior to COVID-19 diagnosis. Five had their immunosuppressant medication stopped at time of hospital admission while the other patient who was managed as an outpatient had their medication reduced by 50%. -Four of 5 patients (80%) were positive for SARS-CoV-2 viral RNA, while 1 patients only had a positive SARS-CoV-2 neutralizing antibody test. -One patient had a positive RT-PCR result for 28 days of follow-up, despite presence of SARS-Cov-2 IgG.
Silvano 2021 (21) Longitudinal case series Portugal Mar-Jun 2020	Analyzed data from kidney transplant patients with COVID-19 (n=6). Duration of viral RNA shedding measured and defined as the time between the first and the last positive RT-PCR SARS-CoV-2 test.	Nasopharyngeal and oropharyngeal swabs -The median time from transplant to COVID-19 diagnosis was 161 months (range: 8-235). Only one patients had undergone transplantation in the past year. All patients were on immunosuppression therapy. -Duration of viral RNA shedding was measured for five of the patients. -For the two patients with moderate severity, the duration of viral RNA shedding was <9 days. -For the three patients with severe disease, the duration of viral RNA shedding was >40 days, persisting despite symptom resolution. Two still had positive RT-PCR swabs at the end of follow-up (>44 and >66 days).
IMMUNOCOMPROMISED PATIENTS		
People with HIV (n=2)		
Vizcarra 2020 (24) Prospective cohort study Spain	Studied consecutive HIV-infected adults who had suspected or confirmed COVID-19 as of April 30, 2020 (n=51). SARS-CoV-2 was detected by qRT-PCR.	Nasopharyngeal swabs, sputum, or lower respiratory tract aspirates -54% (19/35) of individuals with laboratory-confirmed SARS-CoV-2 infection had follow-up qRT-PCR assays conducted. -All patients were on antiretroviral therapy. -Viral clearance occurred over a median of 18 days (IQR 7-28) post symptom onset for 68% (13/19) of

May 2020*		individuals. For the other six individuals, SARS-CoV-2 remained detectable for a median of 40 days (IQR 13–45) post symptom onset. These patients had more severe disease, higher ICU admission, lower nadir CD4 cell counts are a higher proportion of comorbidities than individuals with shorter times to viral clearance ($p<0.05$).
Mondi 2020 (25) Longitudinal case series Italy Mar-May 2020	Analyzed data from HIV-positive patients hospitalized with COVID-19 (n=5). Viral clearance was defined as two consecutive negative RT-PCR tests for SARS-CoV-2 (targeting the E and RNA-dependent RNA polymerase genes).	Nasopharyngeal swab -All five patients were virologically suppressed on antiretroviral therapy. -Serial testing results were only available for two patients. For these two patients, viral clearance occurred on day 29 and 43, from symptom onset.

*Date estimated from publication date

LTE=Letter to the editor

Methods:

A daily scan of the literature (published and pre-published) is conducted by the Emerging Science Group, PHAC. The scan has compiled COVID-19 literature since the beginning of the outbreak and is updated daily. Searches to retrieve relevant COVID-19 literature are conducted in Pubmed, Scopus, BioRxiv, MedRxiv, ArXiv, SSRN, Research Square and cross-referenced with the COVID-19 information centers run by Lancet, BMJ, Elsevier, Nature and Wiley. The daily summary and full scan results are maintained in a refworks database and an excel list that can be searched. Targeted keyword searching was conducted within the excel database to identify relevant citations on COVID-19 and SARS-COV-2. Search terms used included: (immunosup* OR immunocomp* OR transplant OR cancer) AND (persist* OR prolonged OR viable OR shed* OR culture OR dynamics OR clearance). This review contains research published up to February 5, 2021. Each potentially relevant reference was examined to confirm it had relevant data and relevant data is extracted into the review.

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