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SARS-CoV-2 infection: use and effectiveness of antigenic swab for the health surveillance of healthcare workers

Maurizio Coggiola[1], Rossana Cavallo[2], Eugenio Grillo[1], Roberto Frammartino[1], Giuseppe Clemente[1], Cristina Costa[2], Ida Marina Raciti[3], Carlo Silvestre[4], Gitana Scozzari[4], Ettore Paradisi[1], Alessandro Tuffanelli[1], Maria Carolina Alfonso Pensamiento[1], Alessandro Godono[1], Enrico Pira[1]

[1] Department of Occupational Medicine, University Hospital Città della Salute e della Scienza of Turin, Italy
[2] Microbiology and Virology Unit, University Hospital Città della Salute e della Scienza of Turin, Italy
[3] Quality, Risk Management and Accreditation, University Hospital Città della Salute e della Scienza of Turin, Italy
[4] Health Management Molinette Hospital, University Hospital Città della Salute e della Scienza of Turin, Italy

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Abstract

Background: *The gold standard to identify SARS-CoV-2 infections is the Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) on rhino-pharyngeal swabs, but faster and cheaper methods such as antigenic swabs have been developed. A retrospective observational study on antigenic swabs included in the extraordinary health surveillance protocol of a large Hospital in Turin was aimed to assess their performance validity.* **Methods:** *From 30 October 2020 to 4 May 2021, 4000 antigenic swabs were carried out in three groups of healthcare workers (HCWs), respectively (i) asymptomatic, (ii) cohabiting with a positive case, and (iii) not recently exposed to the virus.* **Results:** *Overall sensitivity and specificity associated with a prevalence of 1.30% were 26.9%, 97.2%, respectively, the corresponding positive (PPV) and negative predictive value (NPV) being 11.29% and 99.02% [95% IC (99.00 - 99.04)] respectively; a prevalence of 0.29% was observed in the asymptomatic group, among whom sensitivity and specificity were 25.0% and 98.9%, respectively, the corresponding PPV and NPV being 6.25% and 99.78% [95% IC (99.76 - 99.81)], respectively; the cohabitant group showed a prevalence of 21.11%, sensitivity and specificity were 47.4%, 81.7%, respectively, giving rise to a PPV of 40.91% and NPV of 85.29% [95% IC (85.18 – 85.41)] respectively. The prevalence in the not exposed group was 0.77%, sensitivity and specificity were 29.2%, 97.4%, respectively, and PPV and NPV 8.05% and 99.44% [95% IC (99.42 - 99.46)] respectively.* **Conclusions:** *Antigenic swabs reduced costs and provided reliable diagnostic results. In the cohabitant group, the higher-prevalence groups showed poor test performances, likely because of the high prevalence of pre-symptomatic illness in this group. Owing to the relatively low NPV, a negative result would still require confirmation with a molecular test to be acceptable for a surveillance program that effectively reduces the virus's intra-hospital spread.*

Introduction

The recognition of a cluster of patients affected by pneumonia of unknown cause in Wuhan led to the identification, in December 2019, of a new Coronavirus responsible for Coronavirus Disease 2019 (COVID-19). This new virus was initially referred to as 2019-nCoV1 (1) and was later renamed

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Corresponding author: Maurizio Coggiola, Department of Occupational Medicine, University Hospital Città della Salute e della Scienza of Turin, Italy. E-mail: maurizio.coggiola@unito.it

"Severe Acute Respiratory Infection Coronavirus 2" (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (2). Globally, the virus had infected more than 150 million cases when writing this article (3). The uncontrolled spread of the virus forced the World Health Organization (WHO) to declare a pandemic status on March 11th 2020 (4); in this dramatic scenario, a major increase in diagnostic and therapeutic tools was required.

Real-time Polymerase Chain Reaction (RT-PCR) tests on samples collected through nasopharyngeal swabs are generally considered to be the gold standard for SARS-CoV-2 infection diagnosis. This type of test requires laboratories equipped with the instruments necessary for viral RNA extraction, amplification, and identification. Usually, this procedure takes a few hours, but transporting samples to laboratories and the limited number of samples processed daily (mainly due to the need for highly specialized personnel, machinery and reagents) led to delays in analysis and reporting times (5). Mainly during the pandemic peaks, this has inevitably caused a diagnostic slowdown, resulting in less control over the progression of the epidemic and a lower therapeutic offer for patients.

The increased demand for diagnostic tests has led several countries to use rapid antigenic tests in addition to molecular ones, according to the guidelines established by the Centers for Disease Control and Prevention (CDC) (6) and other public health institutions (7). Compared to molecular tests, antigenic tests allow to obtain a result in a shorter time (about 15-30 minutes) and reduce costs, mainly because they do not require the presence of highly trained personnel or dedicated laboratories. Point-of-care tests are diagnostic tests performed at or near where a specimen is collected; this is hardly achievable with molecular tests due to the complex infrastructure required but easily manageable with antigenic tests and their light and portable reading machines. Antigenic tests are based on identifying the Spike protein (S) or nucleocapsid peptides (N) of SARS-CoV-2 from samples taken via nasopharyngeal swabs. Antigenic tests have, on average, a higher specificity but a lower sensitivity than PCR tests. Thus, they cannot be considered an alternative to molecular tests in all situations; however, they can be instrumental in monitoring personnel working in specific risk environments, such as hospitals or schools (8).

The extraordinary health surveillance of Healthcare Workers (HCWs) is a secondary prevention measure for identifying and managing HCWs at high risk of infection (symptomatic or exposed to confirmed cases). The massive number of cases among HCWs (more than 133,000 out of about 4 million total cases in Italy when writing) supports the need for their regular monitoring (9). Surveillance objectives are the early identification and the limitation of the spread of COVID-19 in health facilities and the protection of HCWs. These objectives can only be achieved by applying specific operational protocols based on current scientific evidence provided by public health institutions like the Center for Disease Control and prevention (CDC), identifying HCWs with high and low risk of exposure (10).

In this study, we analyzed the strategies for using antigenic swabs in the extraordinary surveillance protocol of HCWs, starting from an on the field experience.

Methods

This observational retrospective study involves a population of HCWs from a large hospital in North-West Italy. A descriptive analysis of tested HCWs is given in Table 1.

The protocol for the extraordinary surveillance of HCWs, according to Legislative Decree 81/08 (the Italian legislation about Occupational Health and Safety), has been applied to the whole hospital workforce (employees, residents, fellows, contractors, temporary staff, etc.). According to the protocol, employees must compile a notification form in case of contacts with a known positive case or in case of symptoms; the form includes a brief description of the event of exposure and of the clinical status. The notification form has been built in a standardized way, comprising mainly binary answers, in order to simplify the risk assessment procedure and to reduce misclassification. The variables regarding the exposure included: (i) maximum time spent in the same place of the source of infection (if less or more

Table 1. General and occupational characteristics of tested HCWs

Sex	N.	%	Occupation	N.	%	Hospital	N.	%
Women	2855	71.37	Nurse	1144	28.60	General hospital	2314	57.85
Men	1145	28.63	Healthcare profession student	821	20.52	Trauma center	392	9.80
			Medical resident	645	16.13	University hospital	199	4.98
			Nurse auxiliary	569	14.22	Dermatological hospital	88	2.20
			Physician	313	7.83	Pediatric hospital	23	0.57
			Administrative Staff	122	3.05	OB-GYN hospital	5	0.13
			Medical technician	107	2.67	Unknown	979	24.47
			Non-medical technician	86	2.15			
			Non-medical manager	44	1.10			
			Physiotherapist	36	0.90			
			Unknown	113	2.83			

than 15 minutes); (ii) minimum distance from the source of infection (if less or more than 2 meters); (iii) last day of contact with the source of infection; (iv) PPE worn by the source of infection (facemask present or not); (v) PPE worn by the HCW (facemask or FFP2 respirator, waterproof gown, gloves or hand hygiene); (vi) breaking or misplacement of PPE; (vii) household contact.

The clinical evaluation of the HCW comprised the assessment of presence or absence of these symptoms: (i) fever; (ii) cough; (iii) dyspnea; (iv) anosmia; (v) ageusia; (vi) gastroenteric symptoms (diarrhea, nausea, vomiting); (vii) malaise and severe tiredness; (viii) sore throat; (ix) musculoskeletal pain; (x) bilateral conjunctivitis; (xi) headache; (xii) rhinorrhea. The first five symptoms (fever, cough, dyspnea, anosmia and ageusia) were considered as major and the remaining as minor symptoms.

The occupational physician, evaluating both clinical and exposure characteristics, classifies the exposure in Low, Medium or High risk based on the following criteria: (i) low risk: asymptomatic workers without close contact with a source of infection (less than 15 minutes and more than 2 meters), or with a history of close contact wearing suitable, intact and well-positioned Personal Protective Equipment (PPE); (ii) medium risk: asymptomatic workers with a history of close contact with a source of infection without suitable, intact or well-positioned PPE or workers with one minor symptom; (iii) high risk: symptomatic workers with at least one major symptom or two minor symptoms, even without a history of contact with a known source of infection.

Workers classified as low risk have not been tested but followed a self-monitoring protocol consisting of body temperature measurements twice per day for two weeks. Medium-risk workers have been tested starting from 72 hours after exposure and, while waiting for the outcome, continued their work wearing surgical masks and following the self-monitoring protocol. Medium-risk workers with a positive cohabitant were tested with a molecular test in 24 hours and then tested twice a week with antigenic tests. High-risk workers were tested with a molecular test as soon as possible and were placed in home isolation until symptoms wore off; they were then tested again right before returning to work. Workers with a positive cohabitant were classified with a specific risk class. They followed an *ad hoc* diagnostic path, including a first molecular test performed within the first 24 hours from the notification and subsequently two antigenic swabs per week until the household source of infection negativizes.

Following the protocol, rapid antigenic tests have been performed in the following cases: (i) return to work of subjects with symptoms compatible with COVID-19 but with the first negative molecular swab performed while showing symptoms; (ii) medium risks from extra-work exposure with a positive cohabitant; (iii) workers leaving COVID wards, before returning to activities in non-COVID areas; (iv) asymptomatic workers returning from foreign Countries for whom the legislation requires the execution of a nasopharyngeal swab; (v) periodic testing in wards based on risk classes (high prevalence zones like COVID wards or Emergency Rooms);

(vi) long-term positive cases; (vii) asymptomatic subjects with recent infection (in combination with a serological test).

On the other hand, molecular tests have been performed in the following cases: (i) high-risk contacts; (ii) assessment of the resolution of infection in known positive HCWs; (iii) medium risk contacts; (iv) medium risk HCWs with a known household source of infection (only the first test); (v) diagnostic confirmation after a positive antigenic test result.

Following the execution of a rapid antigenic test, a negative result is definitive, and the worker resumes or continues his/her activities. A positive test is followed by a molecular swab (pending the outcome, workers are considered positive). After that, if the result of the subsequent molecular test is positive, the result is definitive, and the worker cannot be readmitted to work. If the subsequent molecular test is negative, a second molecular swab is carried out (at least 24 hours later), but workers can resume/continue to work pending the outcome. If the second molecular test result is positive, workers are considered positive and work activities are interrupted again; if the result of the second molecular test is negative again, the worker is considered not infected (11).

From the initial implementation of antigenic testing in the health surveillance protocol, on November 1st, the Occupational Health department used only LumiraDx SARS-CoV-2 Ag Test, a rapid microfluidic immunofluorescence assay to be used with the LumiraDx Platform intended for the qualitative detection of the nucleocapsid protein antigenic of SARS-CoV-2 directly from anterior nasal or nasopharyngeal swab samples collected from individuals suspected of COVID-19 (12). The test takes 12 min to deliver a positive or negative result after the sample had been added to the test strip and inserted into the instrument with a sensitivity of 97.6 % (95 % CI: 91.6–99.3) and specificity of 96.6 % (95 % CI: 92.7–98.4) up to 12 days post symptom onset for nasal swab samples, and sensitivity of 97.5% (95% CI: 87.1–99.6) and specificity of 97.7% (95% CI: 94.7–99.0) for nasopharyngeal swab specimens (13). The predictive value of the test, positive (PPV) and negative (VPN), is influenced by the prevalence of the infection. The PPV is high in a high prevalence population, so a positive antigenic test result does not require confirmation with a molecular test; conversely, a negative result requires confirmation with a molecular test due to the low NPV. In a low prevalence population, the NPV is high at the expense of the PPV, so only positive antigenic test results require confirmation with a molecular test (14, 15). During the study period, the intra-hospital prevalence and the general prevalence in Italy had a peak around the end of November and then showed a slight but constant decline through the winter season.

The study was conducted between October 30th, 2020 and May 4th, 2021. During this period, 4,000 antigenic tests were performed (Figure 1). We have collected available data regarding HCWs (Table 1) but we could only retrieve data regarding the motivation of the swabs for 2,181 subjects; for the resulting 1,819 swabs, we could only retrieve the outcome and the tested worker's general data and working status. Based on the prevalence, we identified different groups of HCWs and demonstrated a significant difference between them using the Chi-Square test. We identified 2 main groups: the asymptomatic group (made up of HCWs without symptoms, history of recent symptoms or history of close contact) and the cohabitant group (made up of HCWs with an infected cohabitant, but without symptoms); we then created another, the not exposed group, excluding HCWs cohabitating with a positive case, HCWs with an exposure reported in the 14 days after antigenic testing from the total and symptomatic HCWs but including some tests from the previous groups. We considered HCWs with negative antigenic tests and without other risk conditions 14 days after testing as true negatives, as the CDC flow chart suggests (15).

Results

Out of 4,000 rapid swabs analyzed, 3,876 were negative and 124 positives (Table 3). For every positive antigenic test we gathered its molecular confirmation and calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) which are respectively 26.9%, 97.2%, 11.3% and 99.0% with a prevalence of 1.3% (Table 4).

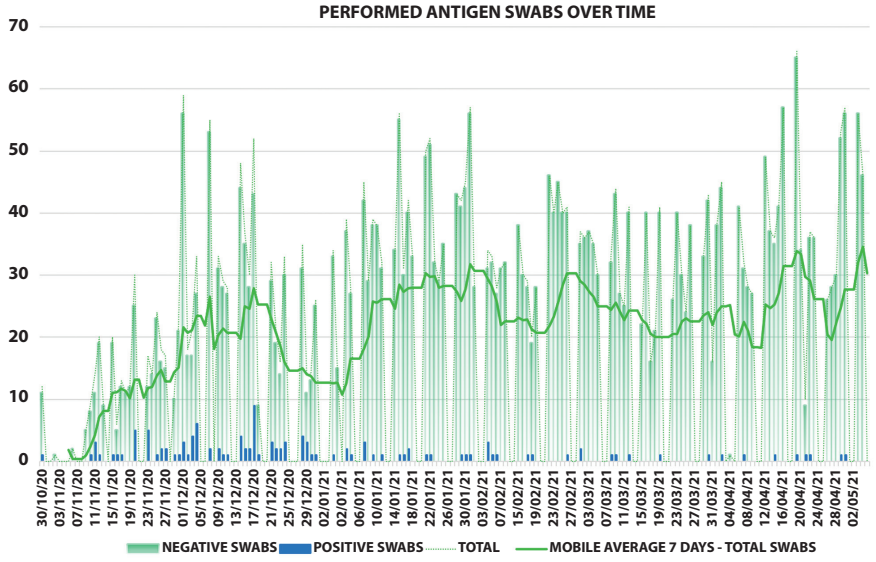

Figure 1. Daily trend of performed antigenic tests since their implementation in November 2020

Of these, 2,181 tests have been performed for a known reason (Table 2): screening (931; 23.2 %), periodic testing of HCWs with a household source of infection (547, 13.6 %) HCWs working in high-risk areas (412; 10.3 %), return to work of high-risk (symptomatic) HCWs that resulted negative to the first molecular swab or that travelled in high risk countries (189; 4.7 %), long-term positive HCWs (102; 2.5 %).

The motivated swabs were 2,181, 2,134 negative and 47 positives (Table 3). In this sample sensitivity, specificity, PPV and NPV were respectively 43.8%, 98.2%, 14.9% and 99.6% with a prevalence of 0.7% (Table 4).

Assuming a low prevalence in an asymptomatic population, we isolated 1,394 tests performed on asymptomatic subjects, of which 16 resulted positive and 1,378 negative; of the 16 positive antigen tests, only 1 was confirmed by a subsequent RT-PCR test, the other 15 were false positives. In this sample sensitivity, specificity, PPV and NPV were respectively 25.0%, 98.9%, 6.3% and 99.8% with a prevalence of 0.3% (Table 4).

Assuming a higher prevalence in HCWs with infected cohabitants, we gathered every antigen test conducted on HCWs with a positive household in the 14 days after the negative result of the initial RT-PCR test performed pursuing the surveillance protocol (90). Out of 22 HCWs that were positive at the antigenic test, 9 resulted still positive at the RT-PCR, the other 13 were false positives. Out of 68 negative antigen tests, 58 were still negative at the RT-PCR, the remaining 10 were false negatives (Table 3). Sensitivity, specificity, PPV and NPV were respectively 47.4%, 81.7%, 40.9% and 85.3% with a prevalence of 21.1% (Table 4).

In the not exposed group the number of tests was 3,653, of which 116 were positive and 3,537 negative; of those, 3,513 were true negative, 13 true positive (Table 3). Sensitivity, specificity, PPV and NPV were respectively 35.1%, 97.2%, 11.2% and 99.3% with a prevalence of 1.0% (Table 4).

Discussion

The usefulness of antigen testing in health surveillance is highly dependent on its NPV, such as in categories and groups with a low prevalence of infection, estimated or calculated, such as the asymptomatic group or the not exposed group. In these groups, NPVs were respectively 99.8% and 99.3%: a negative result can therefore be considered a true negative. The same conclusion cannot be drawn for

Table 2. Criteria for the antigenic tests in study

Test reasons	N.	%
Screening	931	23.3
Positive Cohabitant	547	13.6
HCWs working in COVID Areas	412	10.3
Return from symptoms/absence/high risk Countries	189	4.7
Long-term positive	102	2.6
Other	1,819	45.5

Table 3. Antigenic test results distributed for the various subgroups of the study

Antigenic test results		Infected	Not infected[1]	Total
Overall	Positive	14	110	124
	Negative	38	3,838	3,876
	Total	52	3,948	4,000
Motivated swabs	Positive	7	40	47
	Negative	9	2,125	2,134
	Total	16	2,165	2,181
Asymptomatic	Positive	1	15	16
	Negative	3	1,375	1,378
	Total	4	1,390	1,394
Cohabitant (matched with PCR)	Positive	9	13	22
	Negative	10	58	68
	Total	19	71	90
Not exposed	Positive	13	103	116
	Negative	24	3,513	3,537
	Total	37	3,616	3,653

[1] *We considered as "not infected" HCWs who did not develop any symptom in the subsequent 14 days from the test. For the Cohabitant group instead, we considered as "not infected" HCWs who had a negative PCR test performed within 14 days.*

Table 4. Antigenic test performances for the various subgroups of the study

	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	PPV (%, 95% CI)	NPV (%, 95% CI)	Prevalence (%)
Overall	26.9 (14.9 – 39.0)	97.2 (96.7 – 97.7)	11.3 (5.7 – 16.9)	99 (98.8 – 99.3)	1.3
Motivated swabs	43.8 (19.4 – 68.1)	98.2 (97.6 – 98.7)	14.9 (4.7 – 25.1)	99.6 (99.3 – 99.9)	0.7
Asymptomatic	25.0 (0.0 – 67.4)	98.9 (98.4 – 99.5)	6.3 (0.0 – 18.1)	99.8 (99.5 – 100)	0.3
Cohabitant	47.4 (24.9 – 69.8)	81.7 (72.7 – 90.7)	40.9 (20.4 – 61.5)	85.3 (76.9 – 93.7)	21.1
Not exposed	35.1 (19.8 – 50.5)	97.2 (69.6 – 97.7)	11.2 (5.5 – 16.9)	99.3 (99.1 – 99.6)	1.0

the cohabiting group, due to the relatively low NPV of 85.3%: such a poor result is not acceptable in a health surveillance program because of the risk of keeping up work activities of false-negative infected HCWs, that can cause a further spread of infection among HCWs or vulnerable patients.

Test performances were slightly lower compared to the manufacturer's results and to other studies on antigenic swabs (16-18); this could have happened on the one hand because this study focused only on tests performed on HCWs who were asymptomatic at the time of the test, on the other hand, because in the two main groups antigenic tests were not matched with molecular tests as necessary for meaningful comparisons among available tests (19). As for serological tests (20, 21) the predictive values of swabs strongly depend on the prevalence of infections among study subjects.

Data collected showed that about 44% of the subjects tested via antigenic swab are nurses and residents. These categories are the most represented because they are at the forefront in COVID wards and in Emergency Departments, as already observed in the first phase of the pandemic (22). Another prominent category (almost 21%) are students: even if they are not directly involved in hospital activities, their presence is needed to carry out internships. In order to protect patients and keep an in-hospital low-prevalence of infection, they have been screened with antigenic tests. Other well represented categories are auxiliary nurses and physicians (together they reach 22% of the total), mainly because of the periodic testing of personnel working in COVID wards. At last, the less represented categories are administrative staff and technicians, likely because their working activities involve less contact with potentially positive subjects.

In this study we compared the results of cohabitants who underwent both antigenic and molecular swabs. Sensitivity and specificity values (respectively 47.4% and 81.7%) were lower than expected, likely because of the high prevalence of potentially pre-symptomatic patients. Such values were much higher than those reported for a rapid lateral flow test (23). Living with a positive subject carries a major increase of probability of infection, but this group, by definition, does not include symptomatic HCWs at the time of swabbing (because symptomatic HCWs followed another diagnostic path, including a molecular test and the interruption of work activities). Given this scenario, a possible explanation of the consistent decrease in sensitivity and, most of all, specificity values is the slight change in the characteristics of the disease, frequently seen, in this group, in its early stages, in which antigenic testing is renowned to be suboptimal.

Another methodological issue could be the pairing with the actual gold standard for diagnosis of SARS-CoV-2 infection, the molecular test, that itself suffers from important gaps mainly in specificity. We have considered as true negative the HCWs who tested negative at antigenic swabbing and who in the subsequent 14 days have not reported the onset of symptoms or close contacts with sources of infection. Considering the negativity of an antigenic test as a true negative is possible in categories such as asymptomatic and not exposed groups because of their low prevalence of infection, and their subsequent high NPV. Antigenic swab is less reliable in the cohabitant group due to the high prevalence of infection among this group and the suboptimal characteristics of the test on the field. Using this type of test, the risk is to lose a large slice of asymptomatic positives.

This study has some limitations. The relatively high number of unmotivated swabs can introduce uncertainty in the overall calculation, the only one for which we used the whole number of swabs. We didn't use the unmotivated swabs in the other calculations to avoid undermining the results. The asymptomatic and not exposed groups were not matched with PCR tests, considering as true negative HCWs tested negative at antigenic test and not reporting symptoms or contacts in the next 14 days; even if the CDC algorithm allows this statement, there could have been false-negative asymptomatic HCWs or HCWs underreporting close contacts with known or unknown sources of infection.

There could have been a contact-underreporting bias also for HCWs that tested negative to a PCR swab and then positive to a subsequent antigenic swab; in some cases, there could have been an unreported (or unrecognized) contact with a positive case, invalidating the assumption of the same pre-test probability of infection for the two swab types. This last bias grew the higher was the interval between the two swabs.

Conclusions

Antigenic swabs are not to be used for every situation, but they can be very useful under certain circumstances. In selected groups of HCWs, based on the prevalence (estimated or calculated in the field), they can relieve the stress from the molecular test system while still giving relative certainty of negativity. On the other hand, testing all HCWs with molecular swabs would be suboptimal for the very high costs and the small or null increase of diagnostic power.

The use of antigenic swabs in health surveillance, assisted by in series test like the confirmation of positivity by a molecular test and parallel tests like the extraordinary surveillance of close contacts or symptomatic HCWs with molecular testing, carries an overall higher efficiency of the surveillance system, lowering costs despite a still very reliable diagnostic power. More studies should be carried out to investigate the real efficacy of antigenic testing in high prevalence subgroups.

Declaration of Interest: The authors declare no conflict of interest

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